Faculty of Engineering of University of Porto

VitalSleep: Wearable sleep device for ambulatory sleep quality monitoring

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Resumo

O sono é um processo natural, no qual ocorre uma perda gradual da consciência do ambiente externo e um aumento do relaxamento dos músculos. Devido ao papel fundamental que o sono tem no sistema imunitário e no sistema nervoso e devido ao aumento dos distúrbios do sono ao longo dos anos, a monitorização da qualidade do sono é de extrema importância. A polissonografia é o exame *standard* para a monitorização do sono e para a deteção de distúrbios de sono, no entanto tem algumas desvantagens, como o facto de ser economicamente dispendioso, não estar disponível em todos os hospitais/clínicas de sono e o facto de ser incómodo para o paciente. Com a evolução dos dispositivos vestíveis, estes surgem como uma possível solução para monitorizar o sono fora do ambiente hospitalar, de forma não invasiva, e fornecendo continuamente informações de variáveis fisiológicas.

O objetivo desta Tese de Mestrado é desenvolver um novo sistema vestível para monitorizar o sono, denominado VitalSleep. O sistema VitalSleep consiste no desenvolvimento do *hardware*, na aquisição do registo do sono em tempo real e no desenvolvimento da unidade de processamento do estadiamento do sono que consiste no pré-processamento dos sinais e no desenho e na validação do algoritmo para o estadiamento do sono. Este dispositivo será uma extensão da tecnologia VitalJacket®, um produto da Biodevices, S.A. O VitalJacket®, dispositivo médico vestível certificado, é uma t-shirt com sensores incorporados, capaz de monitorizar o sinal de eletrocardiograma, temperatura e dados de acelerómetro, de forma contínua.

O sistema VitalSleep será então capaz de monitorizar a saturação de oxigénio, os movimentos dos olhos, a temperatura, os movimentos corporais e o eletrocardiograma. Antes do desenvolvimento deste sistema foi realizado um estudo sobre o sono e as respetivas variáveis monitorizadas. De seguida, foi necessário perceber a arquitetura genérica de um dispositivo vestível e fazer um estudo aprofundado sobre o tipo de dispositivos vestíveis que existem no mercado para monitorizar o sono, bem como os sensores usados. Por fim, foi feito um estudo sobre as tendências do mercado, de forma a perceber qual seria o melhor investimento num novo dispositivo para monitorizar o sono de forma ambulatória.

Para o desenvolvimento do sistema VitalSleep foi necessário a criação e implementação de uma placa de circuito impresso (PCB) que estende a tecnologia da Biodevices. S.A, que consiste no desenho e produção do PCB usando o *software* de desenho de circuitos impressos, *Altium*, e a sua respetiva montagem. De seguida, foi desenvolvido o *firmware* usando o IDE *software* (MPLAB), baseado na linguagem C, necessário para incorporar os sensores implementados no microcontrolador. Finalmente, foi feita uma análise dos respetivos sinais utilizando o MATLAB

e a obtenção de um gráfico representativo do estadiamento do sono com base nas variáveis fisiológicas monitorizadas.

Abstract

Sleep is a natural process characterized by a gradual loss of consciousness of the external environment and by an increase relaxation of the muscles. Due to the fundamental role that sleep plays in the immune and nervous system and due to the increase of sleep disorders over the years, the sleep monitoring is extremely important. Polysomnography is the standard exam for sleep monitoring and for the detection of sleep disorders, but it has some disadvantages, such as being expensive, not available in all hospitals/clinics, and is uncomfortable for the patient. With the evolution of wearable devices, these appear as a possible solution to sleep monitoring out of medical environment, providing, continuously and in a non-invasively way, information of physiological variables.

The objective of this Master Thesis is to develop a wearable system capable of sleep monitoring, named VitalSleep. VitalSleep system consist in the development of the hardware, in the acquisition of the sleep recording in real-time and in the development of the sleep stage processing unit that consists in the pre-processing of the signals and design and evaluation of an algorithm to analyse the sleep stages. This device will be an extension of VitalJacket® Tecnhology, a product of Biodevices, S.A. VitalJacket®. VitalJacket® was the first certified wearable medical device, T-shirt, with built-in sensors, capable of monitoring, continuously, the electrocardiogram signal, temperature and accelerometer data.

The VitalSleep system will be able to monitor oxygen saturation, eye movements, temperature, body movements, and electrocardiogram signal. Before the development of this prototype, a state-of-the-art research was performed on sleep and its monitored variables. Then an in-depth study was performed on the generic architecture of a wearable device, the type of wearable devices that exist in the market to monitor sleep as well as the sensors used. Finally, market trends were analysed in order to understand the best investment in a new system to ambulatory monitoring of sleep.

For the development of VitalSleep system it was first necessary to design and implement a printed circuit board (PCB) that extends Biodevices, S.A. technology, consisting in the design and production of the PCB using the printed circuit design software, Altium, and the assembly of the PCB. Then the firmware needed to incorporate the sensors in the microcontroller was developed using the IDE software (MPLAB), which is based on C language. Finally, signal analysis was performed using MATLAB and the obtaining of a representative graph of sleep staging based on the physiological variables monitored.

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List of Acronyms

AASM	American Association of Sleep Medicine
AC	Alternating Current
ADC	Analog-to-Digital Converter
ADC_RDY	ADC Ready
AFE	Analog Front End
AHI	Apnea-Hypopnea Index
AHRQ	Agency for Healthcare Research and Quality
AIS	Athens Insomnia Scale
AR	Autoregressive Method
ASDA	American Sleep Disorders Association
BAN	Body Area Network
BP	Blood Pressure
BPM	Beats Per Minute
BSN	Body Sensor Network
CBT	Core Body Temperature
CSA	Central Sleep Apnea
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyography
EOG	Electrooculography
ESRS	European Sleep Research Society
ESS	Epworth Sleepiness Scale
FTT	Fast-Fourier Transform
HF	High Frequency
HR	Heart Rate
HRV	Heart Rate Variability
ICSD	International Classification of Sleep Disorders
IP	Impedance Plethysmography
LED	Light-Emitting Diode
LF	Low Frequency

MISO	Master Input/Slave Output
MOSI	Master Output/Slave Input
NN	Normal-to-Normal
NREM	Non-Rapid Eye Movement
OAHI	Obstructive Apnea Hypopnea Index
OSA	Obstructive Sleep Apnea
PCB	Printed Circuit Board
PDA	Personal Digital Assistant
PPG	Photoplethysmography
PSD	Power Spectral Density
PSG	Polysomnography
PTT	Pulse Transit Time
REM	Rapid Eye Movement
RERA	Respiratory-Effort Related Arousal
RIP	Respiratory Inductance Plethysmography
RX	Receive Route
SCLK	Serial Clock
SDNN	Standard Deviation of Normal-to-Normal Intervals
SEM	Slow Eye Movements
$Sp0_2$	Oxygen Saturation
SPI	Serial Peripheral Interface
SS	Slave Select
SWS	Slow-Wave Sleep
TX	Transmit Route
WBAN	Wireless Body Area Network
WSN	Wireless Sensor Network

Chapter 1

Introduction

Sleep has a strong influence on nervous and immune functions. Although it is extremely important to sleep well, many people suffer from sleep disorders and underestimate it. In many cases, these disorders are not diagnosed and/or treated. Polysomnography is the standard exam for sleep monitoring and for the detection of sleep disorders. However, because it is very invasive, expensive and unavailable in all sleep hospitals / clinics, wearable devices appear as a possible solution to monitor sleep [1], [2].

The purpose of this Master Thesis was to develop a system of a new wearable device capable of monitor sleep, named VitalSleep. The VitalSleep system is an extension of VitalJacket®. This Master Thesis was developed in the Faculty of Engineering of the University of Porto and in INESC TEC Porto with the collaboration of Biodevices, S.A., and supervised by Professor Ph.D. João Paulo Cunha.

This Master Thesis is divided in 6 chapters. Chapter 1 presents a brief introduction of what was developed during this work, the motivation to have chosen this theme, as well as the outline of the aims for the elaboration of this dissertation. The Chapter 2 approaches an in-depth study of sleep, polysomnography - the standard sleep monitoring exam - and variables monitored in this exam. A study of commercial wearable devices and prototypes that already exist to monitor sleep and a study of the market trends regarding wearable devices are presented in Chapter 3. Chapter 4 describes the development of the VitalSleep system including: design and implementation of the PCB, implementation of the firmware, the signal analysis of the variables monitored, the design of the algorithm to sleep staging and the evaluation of this algorithm using the PhysioNet Database. This database has a large archive of physiological data, including files with sleep stages annotations. Finally, Chapter 5 approaches the conclusions of this Master Thesis and future work suggestions.

1.1. Background and Context

Sleep is essential for a mental and physical recovery of the body; however, sleep disorders have been increasing and the sleep quality of the population has been decreasing over the years. Poor sleep quality affects not only the person's day-to-day, but also, may increases the risk of, for example, cardiovascular disease. It is therefore extremely important to continuously monitor sleep [1], [2].

Wearable devices can continuously monitor physiological parameters and allow to save and/or send this data in real time through wireless protocols or mobile communications. These devices can be a solution for the prevention of diseases caused by poor quality of sleep and can be a warning to improve the quality of life. There are already commercial devices for sleep monitoring, but they are mostly based on actigraphy such as watches and bracelets, which end up being uncomfortable during sleep and some of them are unfeasible [3], [4].

VitalJacket® from Biodevices, S.A. was the first certified smart medical device t-shirt, which allows to acquire and save the data of the electrocardiogram signal, and also to send this data in real time, via Bluetooth, to a mobile device [5]. Although this device has not been designed for sleep monitoring, its expansion to this area of the market is possible due to its versatile architecture that possibility the incorporation of more sensors.

This Master Thesis presents the development of a system of a new wearable device, called VitalSleep, capable of continuously monitoring sleep, through electrooculogram, oxygen saturation, electrocardiogram, temperature and actigraphy. These last three parameters already implemented in the VitalJacket®. Since VitalSleep system is a wearable device to be used at night, one of the criteria is to be small and comfortable, to not influence the results.

1.2. Motivation

Sleep quality improves mental well-being and allows the body to regenerate and recover. However, the number of people who suffer from sleep disorders is growing [1], [2].

Wearable devices have evolved over the years and have been increasingly used for continuous monitoring of physiological variables. Since the standard exam of sleep monitoring, polysomnography, is very expensive, is not available in all sleep hospitals / clinics, and is inconvenient for the patient, wearable devices have been used for ambulatory monitoring [4].

The conjunction of the area of electronics with the area of human physiology is fascinating to me, so the development of this Master Thesis theme has captured all my interest. In addition, the possibility of developing a prototype of a wearable device that could be an extension of the main board of the VitalJacket®, product of Biodevices, S.A., seemed extremely enriching.

1.3. Objectives

The goal of this Master Thesis is to develop a system able to sleep monitoring, named VitalSleep. VitalSleep system consist in the development of the hardware, in the acquisition of the sleep recording in real-time and in the development of the sleep stage processing unit that consists in the pre-processing of the signals and design and implementation of an algorithm to analyse the sleep stages. For this development it is necessary to do, initially, a study about the sleep - which variables are monitored during the polysomnography and what information they provide. Then is necessary to understand the generic architecture of a wearable device and to do a study of different types of wearable devices that already exist in the market to monitor sleep. Finally, it is necessary to study the market trend regarding wearable devices, to better define the prototype characteristics.

After performing these studies, it is necessary to design and implement the PCB using the software Altium, and assembly the PCB. Then the firmware IDE software (MPLAB) is developed to incorporate the implemented sensors in the microcontroller. The analysis of the signals in MATLAB is the following step. Finally, it is necessary to design an algorithm to sleep staging and to evaluate this algorithm using the PhysioNet Database, a database that has a large archive of physiological data, including files with sleep stages annotations.

Chapter 2

Sleep Characteristics and Physiological Variables Monitored

Sleep is defined as the recording of electrical activity of cortical neurons and muscle cells [6] and has a strong influence on nervous and immune functions [1].

More than 30 million people suffer from sleep disorders [1]. As a consequence, the mental condition decreases and the risk of cardiovascular diseases increases [2]. Therefore, it is necessary to monitor the quality of sleep to diagnose possible disorders and to do treatments or improvements in the quality of life.

Polysomnography (PSG) is the standard exam for sleep monitoring, however, it is expensive, requires specialists and is not available at all hospitals/sleep clinics. Wearable devices, although still recent and not yet mostly in the medical field, appear as a possible alternative to PSG, since they are inexpensive, do not require specialist, and the patient can perform monitoring in the comfort of their home [7],[2].

This chapter begins with a description of different stages of sleep. Then, it approaches various types of sleep disorders with more emphasis on obstructive sleep apnea (OSA) because it is very common in the population, as well as the advantages, disadvantages and the parameters monitored in the PSG standard exam.

2.1. Sleep Stages

During a normal period of nocturnal sleep of an adult – 6 to 8 hours -, occur 4 to 6 sleep cycles. Each cycle has a duration of about 90 minutes and contains different stages: REM (rapid eye movement) sleep and NREM (non rapid eye movement) sleep that is subdivided into 4 phases: stages I and II are known as light sleep and stages III and IV are known as deep sleep or slow wave sleep (SWS). It is noteworthy that American Academy of Sleep Medicine (AASM) [8] joined phases III and IV in a single phase N3. In a sleep cycle can also occurs awakenings with a

duration of about 15 seconds and excitations with a duration between 1.5 and 3 seconds [2], [6].

NREM sleep is mainly characterized by parasympathetic and cognitive activity and the REM sleep is characterized by sympathetic activity and emotional dreams [6], [9]. In NREM sleep occurs a decrease of several physiological parameters, namely, heart rate, blood pressure and muscle tone, the movements of the eyes are slow or inexistent and the cerebral activity is reduced. [9] The N1 phase is characterized by a gradual loss of consciousness of the external environment, slow eye movements, a reduction of muscle tone and the appearance of theta waves that replace alpha waves. Theta and alpha waves may also appear alternately. The N2 phase is characterized by total loss of consciousness, predominance of the activity of waves with moderate amplitude, appearance of K-complexes[1] followed by bursts of spindles[2] and the disappearance of slow eye movement. The N3 phase is characterized by the appearance of slow waves of high amplitude, delta waves, and the reduction of muscle tone [10], [11]. During REM sleep the values of heart rate, respiratory rate and blood pressure are variable, occurs rapid eye movements, brain activity is high, and occurs a complete loss of muscle tone [10], [11]. Thus, the information provided by the EEG, EOG and EMG allows to classify the different stages of sleep [11]. The Figure 2.1.1 represents the main characteristics of these signals associated to each phase [10].

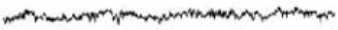
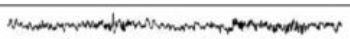
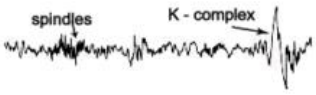
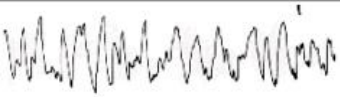
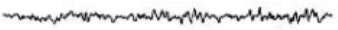
Stages	Characteristics	EEG wave patterns
Stage W	•Low voltage (10-30uV) and mixed frequency EEG activity • Alpha waves occupy more than 50 % of the epoch • Waking eye movement • EMG may be elevated	
Stage 1	•Low voltage and mixed frequency EEG activity with the highest amplitude in 2 - 7 Hz frequency range • Alpha waves occupy less than 50 % of the epoch • Slow eye movement • EMG is elevated but less than in Stage W	
Stage 2	• K complexes and sleep spindles appear • Duration of K complexes and sleep spindles should be at least 0.5 sec • Waves with amplitude above 75 uV occupy less than 20 % of the epoch • EOG is silent • EMG is mildly decreased	
Stage 3	• Waves with 2 Hz or slower • Waves with amplitude above 75 uV occupy 20 - 50 % of the epoch • EOG is silent • EMG is mildly decreased	
Stage 4	• Waves with 2 Hz or slower • Waves with amplitude above 75 uV more than 50 % of the epoch • EOG is silent • EMG is moderately decreased	
Stage REM	•Low voltage and mixed frequency EEG activity • Sawtooth wave pattern is often present • Episodic rapid eye movements • EMG is markedly decreased to absent	

Figure 2.1.1 - Characterization of each phase of sleep: stage W (wake), stage NREM (stage 1, stage 2, stage 3 and stage 4) and stage REM according to the information provided by the EEG, EOG and EMG (taken from [10])

[1] K-complexes - events with a negative wave of large amplitude followed by a slow positive wave [10]

[2] Spindles - transient episodes with frequency between 12 and 14 Hz [10]

In a normal night's sleep, – Figure 2.1.2 - the N1 phase occurs in the first moment of sleep, then the sleep becomes deeper, passing through phase N2 to phase N3. The first episode of deep sleep is long - between 20 to 60 minutes. Then, sleep progresses to a lighter sleep state (phases N2 and N1) and may occurs a transient wakefulness period before the first REM sleep. The first REM sleep appears about 90 minutes after the onset and lasts between 1 and 5 minutes. Thus, ends the first cycle of sleep. It should be noted that the REM phase increase throughout the night, contrary to the deep sleep. In addition, the periods of vigilance of short duration are very frequent at the end of the night [9]. It is also important to refer that 75% to 90% of total sleep time is NREM sleep: 3% to 5% corresponds to the N1 phase, 50% to 60% corresponds to the N2 phase and 10% to 20% corresponds to the phase N3. The REM sleep represents 10% to 25% of total sleep time [2], [6], [12].

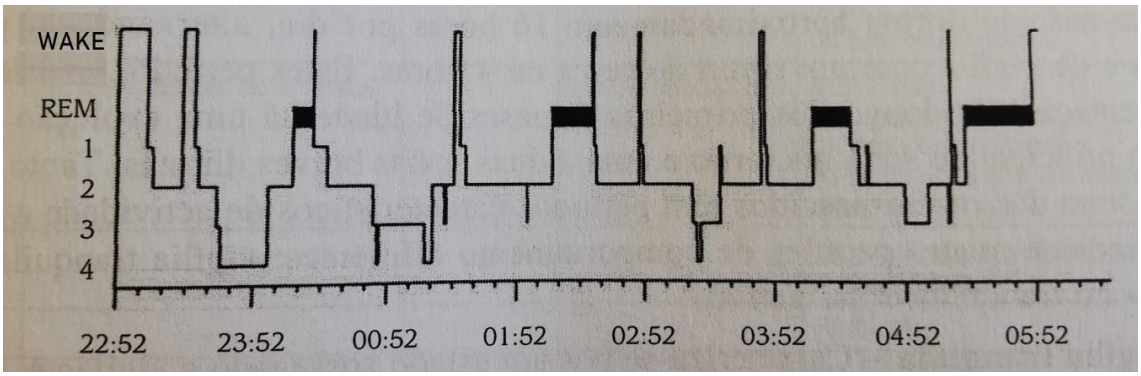


Figure 2.1.2 - Example of a normal hypnogram (taken from [9])

2.2. Sleep Disturbances

In 2002, Soldatos *et al*. [13] developed a study involving 35 327 participants from 10 countries, including Portugal, with the aim of understanding what type of sleep disorders prevail in each country and to understand the impact that poor sleep quality has in people's capabilities during the day. Participants had to respond to a standardized questionnaire and were classified through the Athens Insomnia Scale (AIS) - if the score is greater than 6 it is considered insomnia - and the Epworth Sleepiness Scale (ESS) - if the total score is between 6 and 10 is considered sleepy, if the score is between 10 and 16 it is considered very sleepy and if is over 16 it is considered dangerously sleepy. The results of this study showed that 24% of the participants had poor sleep quality; 31.6% had an AIS score higher than 6, considered as insomnia; 11.6% had an ESS score higher than 10, considered very sleepy. This study showed that sleep-related problems are underestimated, noting that 91.6% of participants who reported that slept poorly had an AIS score of at least 4 indicating sub-threshold insomnia and 77.8% had a score corresponding to insomnia. Among the 24% of the participants who considered that slept poorly, only 30.7% reported that they had visited a physician (55.5% were Portuguese) and 31.4% reported that they had token sleeping medication (45.7% were Portuguese).The study also showed that sleep habits and sleep duration are similar in the 10 countries [13].

This study showed that many people considered sleep disorders insignificant, however, when untreated they may be associated with hypertension, memory loss, strokes, type 2 diabetes and cardiac problems. Sleep disorders are classified in insomnia, parasomnia, circadian rhythm sleep-wake disorders, sleep-related breathing disorders, sleep-related movement disorders, central disorders of hypersomnolence and other sleep disorders according to International Classification of Sleep Disorders (ICSD) [14], [15].

- Insomnia is characterized by the difficulty that a person has in sleeping, whether in falling asleep or staying asleep [10], [14].
- Parasomnia is characterized by undesirable events that occur at onset, during sleep or during waking up [10], [14].
- Circadian rhythm sleep-wake disorders are characterized by changes in the circadian system that may affect sleep regulation and can be classified in delayed sleep-wake phase, advanced sleep-wake phase, irregular sleep-wake rhythm, non-24-hour sleep-wake rhythm, shift work and jet lag [10], [14].
- Sleep-related breathing disorders are characterized by disturbances in breathing while the person is sleeping. Can be obstructive sleep apnea (OSA), central sleep apnea (CSA), hypopnea, respiratory-effort related arousal (RERA) sleep-related hypoventilation disorders, chronic snoring, upper airway resistance syndrome and sleep-related hypoxemia disorder [10], [14], [16].
- Sleep-related movement disorders are characterized by movements during sleep and are classified in sleep-related movement disorder due to a medical disorder, sleep-related movement disorder due to a medication, propriospinal myoclonus at sleep, benign sleep myoclonus of infancy, sleep-related rhythmic movement disorder, sleep-related bruxism, sleep-related leg cramps, periodic limb movement and restless leg syndrome [10], [14].
- Central disorders of hypersomnolence are characterized by sleepiness during the day [10], [14].

One of the most common disorder is sleep apnea, which affects about 40 million people in the US [17]. It is characterized by a stop of breathing for 10 or more seconds, and it can be repeated more than 20 times in an hour. There are two types of sleep apnea: CSA and OSA. CSA occurs when the brain does not transmit signals to the muscle to breathe [1] and OSA occurs when the upper airway is blocked [18] and is identified through increased respiratory effort [16], [2]. OSA is the most common sleep apnea and undiagnosed OSA affects 15% of the middle-aged population [19]. Variations of heart rate and body movements during sleep are characteristic in OSA. [18] This disorder is also known to increase the risk of cardiovascular disease and to cause impaired concentration, excessive sleepiness and snoring. Snoring is caused by the vibration of the upper airway' structures and is a common breathing disorder that affects about 20% to 40% of the population [2], [16].

2.3. Polysomnography

Polysomnography (PSG) is the standard exam for sleep monitoring and for the diagnosis of sleep disorders, such as apnea [1], [19]. In this exam are monitored several parameters: electroencephalogram (EEG), electromyogram (EMG), electrooculogram (EOG) electrocardiogram (ECG), airflow, thoracic and abdominal movements, oxygen saturation (SpO_2), temperature and body position, with video and audio recording. PSG requires a specialist who places the sensors

correctly on the patient, is time consuming, expensive, and is not available in all hospitals/sleep clinics. In addition to these disadvantages, the fact that this exam is performed outside the comfort of the patient's home, the use of so many sensors and the low freedom of movement created by wires that connect the electrodes to the equipment can negatively influence the quality of the patient's sleep, altering the results [1], [2], [19].

2.4. Physiological parameters

The parameters monitored in PSG are EEG, EMG, EOG, ECG, SpO_2, airflow, thoracic and abdominal movements, temperature, body position and blood pressure. The EEG is characterized by rhythmic activities and transient events and can detect different stages of sleep. The EOG allows to detect eye movements and can distinguish between wake, REM sleep and NREM sleep. The EMG allows to distinguish between wake, REM sleep and NREM sleep, through the detection of muscle activity. The ECG, which detects cardiac activity, can also distinguish between wake, REM sleep and NREM sleep. Breathing monitoring allows to detect sleep-breathing disorders, such as apnea. The monitoring of oxygen saturation can detect oxygen supply failures during respiratory events such as apnea and through the monitoring of blood pressure it is also possible to detect apneas. Through the body movements it is possible to distinguish if the person is awake or asleep. Lastly, the monitoring of temperature can distinguish between REM sleep and NREM sleep and allows to know when the onset of sleep occurs.

The following sub-chapters will present the various parameters more exhaustively.

2.4.1. Electroencephalogram

Electroencephalogram (EEG) is able to monitor the electrical activity of the brain and is essential to identify different stages of sleep. The standard method for this monitoring is according to the International 10-20 System [2], [20]. Nevertheless, according to the AASM criteria, 3 EEG channels, such as F4-A1, C4-A1 and O2-A1, must be used [21]. It should be used Ag/AgCl or gold electrodes with low impedance. The Figure 2.4.1 shows the placement of the electrodes according to the 10-20 system [16], [22].

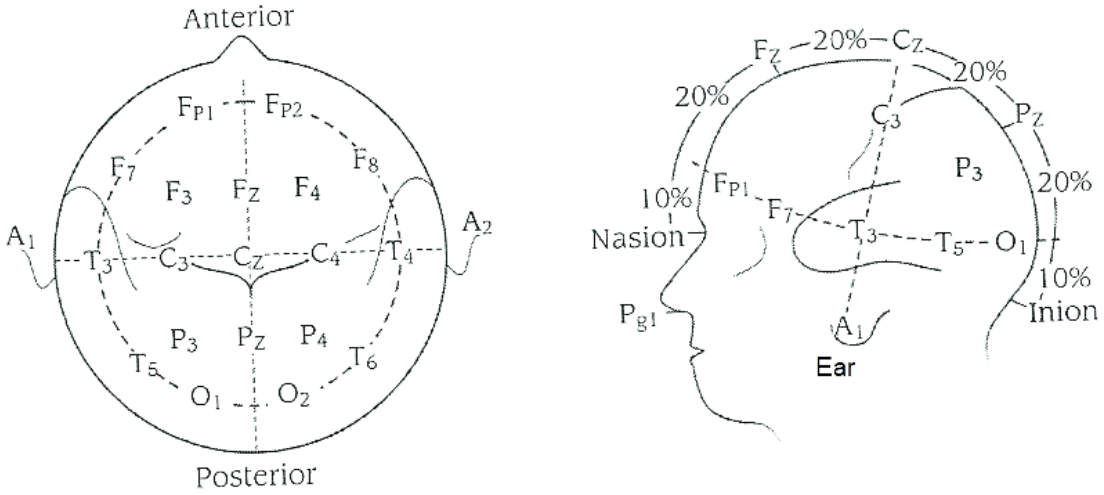


Figure 2.4.1 - Placement of the electrodes to measure EEG according to the 10-20 system (adapted from [18])

The EEG signal consists of rhythmic activities, characterized by delta, theta, alpha, beta and gamma waves, and by phasic activities, characterized by transient events such as K-complexes, spindles, apex tips and sawtooth waves. Alpha waves (8-13 Hz, with a variable amplitude of 10-120 μV) appear during the wake phase only with eyes closed. As sleepiness increases - beginning of the N1 phase - the frequency and amplitude of the alpha waves decrease. The amplitude of these waves increases when an eye open in the state of drowsiness. These waves also appear in micro-awakenings [2], [22].

During N1 phase occurs a transition from alphas waves to theta waves (3-8 Hz, with amplitude less than 75 μV). [3] Theta waves are abundant not only during the N1 phase, but also in the N2 phase, disappearing as sleep progresses to deeper phases and reappearing in the REM phase. The N1 phase is also characterized by apex tips (4-6 Hz, with an amplitude that must be twice as wide as the previous 5-second amplitude) which are mono or biphasic waves, with a negative component preceded by a positive component. In the case of biphasic, the positive component should be greater than 50% but less than 100% of the negative component [15], [22].

During phase N2, besides the appearance of theta waves, also occurs the appearance of K-complexes [2] which are events with a large negative wave amplitude followed by a slow positive wave. The duration of the initial peak must be less than the next peak and the amplitude should be twice as high as the previous 5 minutes with the amplitude of the positive component at least, 50% of the amplitude of the negative component. The minimum duration of the K-complex is 0.5 seconds. This type of transient event has a lower incidence with age, dysthymia, alcoholism and abnormal sleep. Also, during this phase occurs the appearance of spindles that are outbreaks waves (12-14 Hz), with a duration of more than 0.5 seconds, with a minimum amplitude of 10 μV, fusiform morphology and may appear 3 to 8 times in a minute. Spindles may suggest the existence of a cortical or thalamic structural lesion when there is a persistent asymmetry in both amplitude and frequency [15], [16], [22], [23].

N3 phase is characterized by delta waves (0.5-2 Hz, with an amplitude greater than 75 μV) [2].

Beta and gamma waves not provide information about sleep staging but are clinically important: beta waves (14-30 Hz) are visible in adults who are medicated with psychoactive drugs and toxic-dependent; gamma waves (25-100 Hz) are associated to the conscious perception [22].

During REM phase, in addition to the appearance of theta waves, there can also appear sawtooth waves (2-6 Hz), which are outbreaks waves characterized, as the name implies, by a sawtooth morphology, with a duration of 10 seconds and with a progressive increase of amplitude (20-100 μV) followed by a steep descent [22]. Different stages of sleep can be observed in the Figure 2.1.1.

EEG is very important in sleep staging; however, it is inconvenient because many electrodes are glued on the scalp.

2.4.2. Electrooculogram

The EOG signal has a range of frequency between 0.1 Hz to 20 Hz and a range of amplitude between 50 μV to 3500 μV [24], [25]. EOG can record, noninvasively, the movement of the eyes through electrodes placed around the eye. This recording is possible due to the potential difference between the retina, which is electrically positive, and the cornea, which is electrically negative,- corneoretinal potential [22], [26]. Thus, when there is no eye movement, the potential is approximately equivalent in both directions and when there is movement, the potential changes depending on the direction of the movements [26].

Regarding the placement of the EOG electrodes, for detection of horizontal motion which provides a binocular recording, one electrode is placed 1 cm out and up the outer corner of one eye and the other electrode is also placed 1 cm out but down from the other eye. The electrodes may also be placed 1 cm below the outer corners of the eyes. The reference electrode can be placed in the contralateral ear or on the middle of the forehead. The Figure 2.4.2 shows the different placements of the electrodes [21], [22], [26].

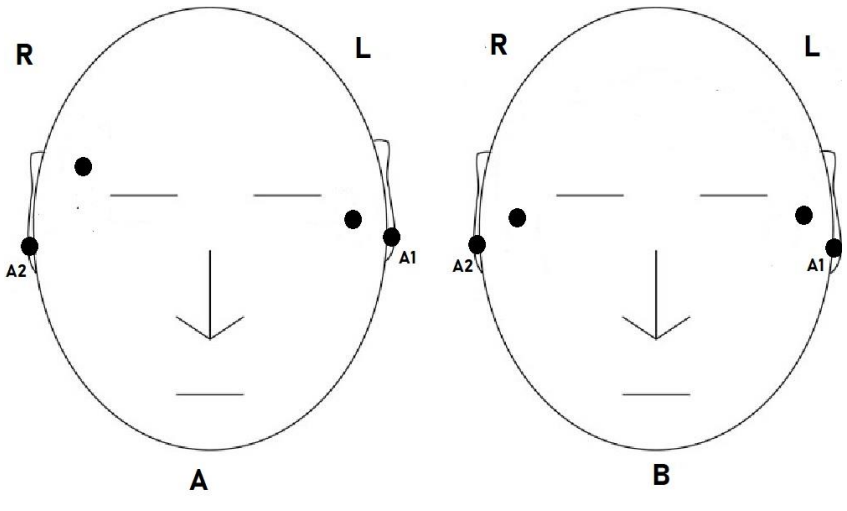


Figure 2.4.2 - Placement of the electrodes to measure EOG. In the left image is possible to observe one electrode placed 1 cm out an up the outer corner of the eye and other electrode placed 1 cm out and down from the other eye. In the right image is possible to observe the placement of electrodes 1 cm below the outer corners of the eyes. A1 and A2 represent the reference electrodes, R represents the right ocular and L represents the left ocular (adapted from [22], [26])

There are several types of eye movements: rapid eye movements, slow eye movements and blinking movements. Rapid eye movements (> 0.6 Hz) are present during wakefulness and REM phase and are characterized by being irregular, with sharp edges and with an initial deflection of less than 500 milliseconds. Slow eye movements (0.2-0.6 Hz) are present in N1 phase [23] and are characterized by being regular, with sinusoidal contours and with an initial deflection greater than 500 milliseconds. Blinking movements (0.5-2 Hz) occur during wakefulness and are characterized by vertical conjugate eye movements [22].

The signal acquired can be influenced by changes in illumination, by movements of the head and eyelids and by the placement of the electrodes [26].

2.4.3. Electromyogram

The EMG can measure the muscular activity in the chin region. According to the AASM, three electrodes should be used: one electrode in the midline 1 cm above the lower edge of the mandible, another electrode 2 cm below the lower edge of the mandible and 2 cm to the right in relation to the midline and the third electrode should be placed the same as the previous one, but 2 cm to the left in relation to the midline. Nevertheless, it may be necessary to monitor the EMG in other places, for example in the masseters to detect episodes of bruxism, in the anterior tibia to detect periodic movements of the lower limbs and in the extensor of the fingers or toes. In Figure 2.4.3 is possible to observe the placement of the EMG electrodes in different parts of the body [22].

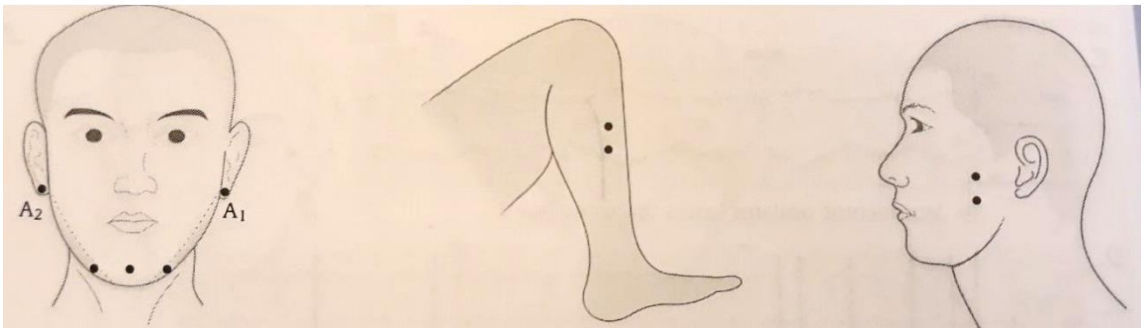


Figure 2.4.3 - Placement of the electrodes to measure EMG. In the image to the left it is possible to observe the placement of electrodes in the area of the ment. In the central image it is possible to observe the orientation of the electrodes in the anterior tibial zone and in the right image in the masseter zone. A1 and A2 represent the reference electrodes. (taken from [20])

Muscle activity is higher during wakefulness, decreases with sleep depth, and is lower or absent during REM sleep [20].

2.4.4. Electrocardiogram

The ECG is able to detect heart rate (HR) changes and can provide a HR standard that can detect OSA. The analysis of the variation of heart rate provide information about the circadian rhythm of sleep.

The normal range of heart rate among adults is 60-100 beats per minute (bpm), being an indication of disease if its value is outside this range, namely bradycardia for lower values, or

tachycardia for higher ones. The ECG waveform can be observed in the Figure 2.4.4 [22] and the heart rate variation during sleep can be observed in the Figure 2.4.5 [27].

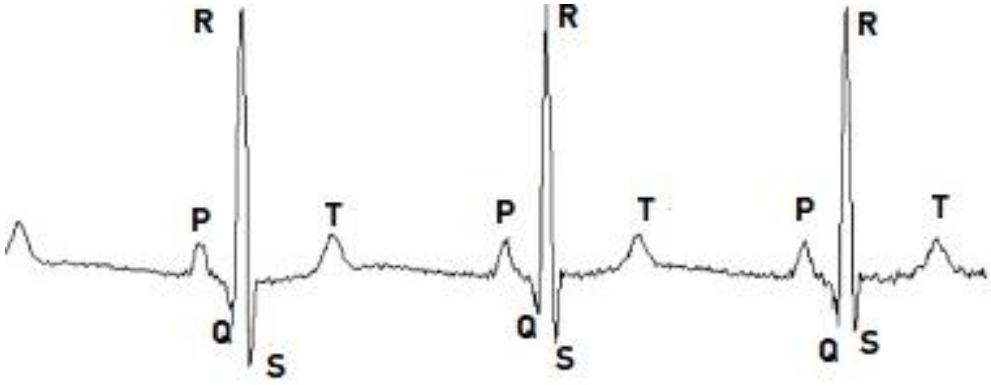


Figure 2.4.4 - The ECG waveform (adapted from [22]).

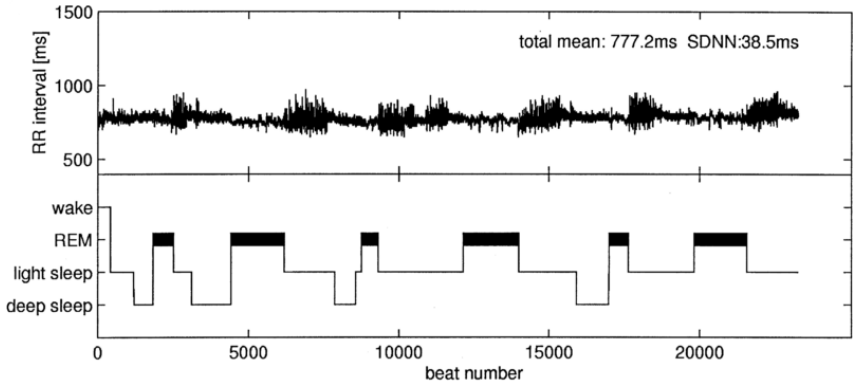


Figure 2.4.5 - Variation of the heart rate throughout the different stages of sleep (taken from [27])

One important parameter that can be extracted from the ECG signal is the heart rate variability (HRV). The HRV allows to evaluate the autonomic nervous state through the variations between consecutive heartbeats and has a frequency domain and a time domain. With the frequency and time domain variables it is possible to perform a sleep staging.

Through the time domain method it is possible to calculate the mean NN interval and the standard deviation of the NN interval (SDNN)[28], which are the most common time domain variables used to described the sleep stages according to Jiang et al. [29] Vigo et al., [30] showed that the mean NN interval was lower during wake time than during sleep time and was greater during deep sleep than during REM sleep. Kesek et al., [31] showed the same differences as the previous article in the mean NN interval and add that SDNN is higher during wake time than during sleep time, and deep sleep has lower values compared to other phases. Regarding the heart rate, Trinder et al., [32] and Ako et al., [33] showed that is higher during the wake time than during sleep time, being lower in the NREM phase compared to the REM phase.

Through the frequency domain method it is possible to evaluate the cardiac system during sleep since the spectral power in specific band frequencies is related to the activity of the

sympathetic and parasympathetic nervous system: the spectral power in high frequency (HF, 0.15-0.4 Hz) is associated with the activity of the parasympathetic nervous system and the spectral power in low frequency (LF, 0.04-0.15 Hz) is associated with the activity of the sympathetic and parasympathetic nervous system. Versace et al., [34], Kesek et al., [31] and Opavsky et al., [35] showed that the LF component is higher in the REM phase compared to the NREM phase, and in this last phase the LF component is lower in the deep sleep. Relatively to HF component, they showed that is lower during wake time than during sleep time, being higher during NREM sleep (light sleep) than during REM sleep. Finally, they also showed that the ratio between low frequency and high frequency is higher during REM sleep than during wake time and is lower during deep sleep. In the Table 2.4.1 it is possible to verify the sleep staging based on the time and frequency domain variables.

Table 2.4.1 - Sleep staging based on the time and frequency domain variables. '+' represents that the variable is lower in that sleep stage and '++++' represents that the variable is higher in that sleep stage. [31], [34], [35]

Time and Frequency domain variables	WAKE	NREM Phase		REM Phase
		Light Sleep	Deep Sleep	
Mean NN interval	+	++++	+++	++
SDNN	++++	++	+	+++
LF component	+++	++	+	++++
HF component	+	++++	++	+++
LF/HF	+++	++	+	++++

Respiration can also be derived from the ECG, an important parameter for detecting apneas and other respiratory disorders. That detection is possible due to cardiac electrical axis changes during respiration, with periodic attenuation of the ECG amplitude with the respiratory effort or through periodic changes that occur in the RR interval: during inspiration, intrathoracic pressure decreases, venous return increases, HR increases and consequently RR interval decreases; during expiration, frequency decreases and RR interval increases [2].

2.4.5. Respiration

Breath monitoring during sleep can detect sleep-breathing disorders such as apnea. Nasal pressure and/or airflow, respiratory effort and oxygen saturation are the respiratory parameters recorded during PSG [22].

Plethysmography and pneumotachography are standard methods for detecting sleep events, however, both methods are not suitable for use in PSG. Since, in the plethysmography exam, the patient must be in a chamber suitable for that purpose, and in pneumotacography exam, a face mask is used to measure pulmonary volume, which is considered intrusive. Regarding the measurement of respiratory effort, esophageal pressure is the most reliable method because can record oscillations of intrathoracic pressure during apnea due to respiratory effort, however, it is a very invasive and complex method [2], [22], [36].

Thus, there are other methods that can be incorporated in the PSG, such as thermistors or thermocouples, nasal cannula pressure transducers, respiratory inductance plethysmography

(RIP), impedance plethysmography (IP) and piezoelectric sensors. Thermistors and thermocouples detect differences of temperature and therefore can detect inspiration and expiration, since the air is hotter during the expiration and cooler during the inspiration, however, they do not provide quantitative measurements of the airflow, not being able to detect hypopneas. Nasal cannula pressure transducers provide a linear approximation of airflow but cannot accurately distinguish apnea from hypopnea. The RIP can measure, through the self-inductance, changes in the thoracic area, providing a measurement of the tidal volume, however, in apnea situations this measurement becomes less correct, so it is not often used. The IP can measure changes in chest volume due to respiration through changes in electrical resistance. And, finally, there are piezoelectric sensors embedded in straps that measure the circumference of the chest and abdomen, however these sensors are sensitive to artefacts [2], [22], [36].

Expiratory carbon dioxide is an important parameter that should be monitored since it provides information about the carbon dioxide concentration and can indicate if airways are obstructed. Nevertheless, there are some disadvantages, namely the need for a mask and the fact that it is not possible to measure it during apnea. Infrared sensors are used to record this parameter [22].

Although the airflow and respiratory efforts are easy to monitor and apply, they can be affected by the movement of the body, so this is a parameter that must always be taken into account [18].

2.4.6. Blood Gases

Monitoring oxygen saturation (SpO_2) is of paramount importance as it allows the detection of oxygen supply failures during respiratory events such as apnea. Oxygen desaturations of more than 2-5% are considered indicator of OSA [2].

The oximeter is an optical-electronic device that is generally used to monitor SpO_2 [22], through the difference in light absorption of two different wavelengths, [37] that is, the oximeter measure the absorption of the specific wavelength in oxyhemoglobin (which transport the oxygen) and compare with the absorption of the specific wavelength in deoxyhemoglobin (without oxygen). Through the difference between oxyhemoglobin and deoxyhemoglobin it is possible to calculate the amount of oxygen contained in the blood [38]. This type of device is based on photoplethysmography (PPG), a non-invasive optical method. Its signal is constituted by the AC component that provides information about the absorption due to the pulsatile arterial blood and, consequently, provides information about heart rate since the arterial blood volume is synchronous with the heartbeat, and by the DC component that provides information about tissue and mean blood volume. The DC component may suffer variations due to vasomotor activity, vasoconstriction waves and respiration [39]. The figure 2.4.6 represents a PPG waveform.

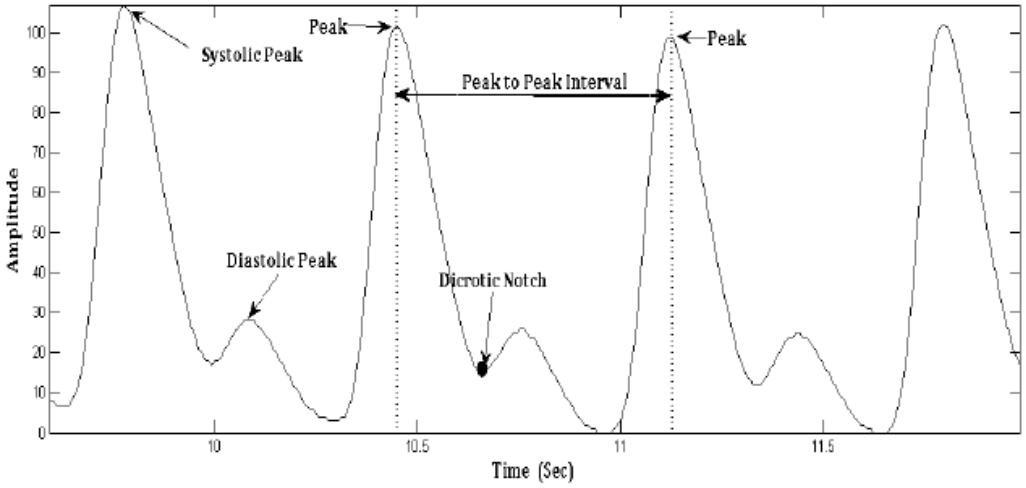


Figure 2.4.6 - Representation of a PPG waveform (taken from [116])

There are two types of PPG: reflectance and transmittance. In both are needed two light emitting diode (LED), and a light detector, which is usually a photodiode. One LED emits infrared light (940 nm) which is absorbed by the oxyhemoglobin and other LED emits red light (660 nm) which is absorbed by deoxyhemoglobin. The amount of light absorbed by the oxyhemoglobin is proportional to the concentration of oxyhemoglobin in the blood vessel and each oxyhemoglobin absorbs some of the light, thus, more oxyhemoglobin absorbed more light, according to the Beer's Law. The photodiode measure the detected light and convert it into an electrical voltage. [38] In reflectance, the source and the light detector are placed on the same side of a peripheral part of the body, such as fingertip, earlobe and foot, in the transmittance they are placed on the opposite side of any part of the body, usually on the forehead [39].

During systole occurs an increase of oxyhemoglobin in the tissue that will absorb the infrared light, and consequently, reduces the amount of light that is detected by the photodetector [38].

When the source emits light for one part of the body, part of the light is absorbed, another is transmitted, and another is reflected. In the case of reflectance, the photodetector detects reflected light [39] and in the case of transmittance, the photodetector will detect the transmitted light [37].

Oximeters can provide false results due to movement artefacts and poor contact between the sensor and the skin surface [2]. Furthermore, results may also not be correct since dyshemoglobinemias may not be detected and desaturations may not occur during an apnea situation [22].

2.4.7. Arterial Pressure

The blood pressure (BP) is an important parameter that should be monitored because many people with hypertension are asymptomatic [3]. The BP changes during sleep and apnea, increasing during the REM phase and during apnea. Although there are some methods for monitoring BP, none is ideal for the record during sleep: one method is through an inflatable armband; however, it disturbs sleep, it does not make a continuous recording and not detect sudden alterations; the other method is through an intra-arterial catheter that despite providing a continuous record, is invasive [22].

To minimize the discomfort during sleep caused by these methods, the BP can be estimated using pulse transit time (PTT). The PTT can be defined as the time between the ECG R peak and the corresponding maximum slope of PPG wave [3]. For each R peak of the ECG, the nearest maximum slope of the PPG is detected and, then, the PPT value is calculated, which can only be validated if it is within 20 % to 70 % of the RR interval [40].

2.4.8. Peripheral Pulse

The peripheral pulse wave is created during systole, when blood is ejected from the heart. [41] The peripheral pulse can be extracted through oximetry, through the reflectance or transmission of IR and Red light. It can detect changes in the volume of peripheral tissue [41], and can provide information on peripheral vasodilation and RR intervals [22].

2.4.9. Body Position and Movements

The movement and the position of the body are also important factors in assessing sleep quality. Actigraphy is a non-invasive and inexpensive method that use the accelerometer to detect the movements while the person is sleeping. Through this detection it is possible to predict whether the person was sleeping or awake. The position of the body is an important parameter, since the severity of OSA varies according to the position of the person while sleeping. A study by Ozeke *et al*. [42] showed that sleeping in the supine position causes a higher Apnea Hypopnea Index (AHI) and sleeping on the left side has a higher AHI compared to sleeping on the right side. To evaluate this parameter, a study by Kesteren *et al*. [43] used two position sensors, one placed in the centre of the forehead and the other in the trunk, since the supine position of the head and trunk influence the AHI in OSA. The position sensors used in the study by Kesteren *et al*. [43] were created by Sleepsense, St. Charles, IL, USA, and provide a signal which is directly related to sleeping position.

2.4.10. Core Body Temperature

Core body temperature (CBT) occurs as a combination between production and heat loss: when the heat production is greater than its loss, the CBT increases and when the heat production is lower than its loss, the CBT decreases [44].

The circadian rhythm of CBT is related to the sleep period: at the beginning of sleep, CBT decreases markedly with an increase in blood flow and, consequently, occurs a loss of heat through the transfer of heated blood to blood vessels, especially to the ones located in the distal areas of the skin, such as in the hands, since they have a faster heat loss; and at sleep interruption, CBT increases [44], [45]. It should be noted that the onset of sleep occurs 5-6 hours before the minimum value of CBT, and the awakening occurs 1-3 hours later [44]. A study by Burgess *et al*. [46] showed that the decrease of the CBT is related to the NREM sleep, in the transition between the NREM sleep to REM sleep a slight increase occurs and decreases again in the transition from the REM sleep to the NREM sleep [46], [47].

When the rhythm of CBT is delayed or advanced relative to the period of sleep, can occur difficulties in falling asleep - insomnia - or in maintaining the sleep. This happen because, under these conditions, the rhythm of the CBT may coincide with the time at which the onset of sleep is delayed, 6-9 hours before the minimum value of CBT, causing difficulties in falling asleep.

Or may coincide with the associated height upon awakening that occurs in the morning, 4-7 hours after the minimal value of CBT, causing problems in maintaining the sleep [44].

2.4.11. Skin Temperature

The circadian rhythm of the skin temperature is also related to the sleep period. It varies according to the ambient temperature and is inversely related to the CBT rhythm [44].

Some studies showed that the increase in skin temperature may be related to the onset of sleep. Van den Heuvel *et al*. [48] showed that the increase in temperature of the hands and feet (distal temperate) is related to the onset of sleep. Lack *et al*. [49], showed a rapid increase in finger temperature before sleep onset and, consequently, a decrease in CBT. Taking these studies into account, Raymann *et al*. [45] have shown that increasing distal temperature, particularly in the foot, in young adults, may increase the ease of falling asleep. Older individuals have a lower ability to raise distal temperature. A study by Roy et al. [50], goes further and shows that for people without sleep problems, the increase of distal skin temperature increases REM sleep and suppresses light sleep, and the increase of proximal skin temperature (such as the abdominal area) increases deep sleep and suppresses wakefulness.

In conclusion, the increase of skin temperature is related to sleep onset and the manipulation of the distal and proximal skin temperature can improve the sleep.

Chapter 3

Wearable Sleep Devices

Wearable devices collect sensors data, continuously and non-invasively, on a specific and small part of the body. These sensors can be placed in different parts of the body or can be inserted in the fabric of the garment, which makes the monitoring of vital signs more comfortable [3] The use of this type of device during sleep allows a simpler and less disturbing monitoring comparing to PSG, and since it is a continuously monitoring, can be a method of intervention, allowing for a quick intervention if necessary.

These devices must be low power consumption, comfortable, easy to use, light weight, should be safe to use, the sensors should work for long periods of time and the system implemented in the device must guarantee security and confidentiality in the collected data [18], [51].

This chapter presents the description of a generic architecture of a wearable device and a study of some commercial devices and prototypes devices used to monitor sleep.

3.1. Device Architecture

The generic device architecture is mainly constituted by three modules. The first one is constituted by sensors that capture the vital signs of the user, for example, motion, pressure, biometric and temperature sensors. This first module is defined as the Body Area Network (BAN), which is a network with the sensors around the body. Then, the electrical signals are sent to a central unit, where signal processing takes place (amplification, filtering and conversion of the analog to digital signal through an A/D converter). This is the second module. The processed signals can then be stored in the central unit or can be sent to other device for offline or real-time analysis, respectively – third module. Figure 3.1.1 shows the different components of the generic architecture of a wearable device.

In the following sub-chapters the Body Area Network (BAN) and the central unit will be described in more detail in order to clarify the architecture of a wearable device, as well as the differences between real-time and offline monitoring.

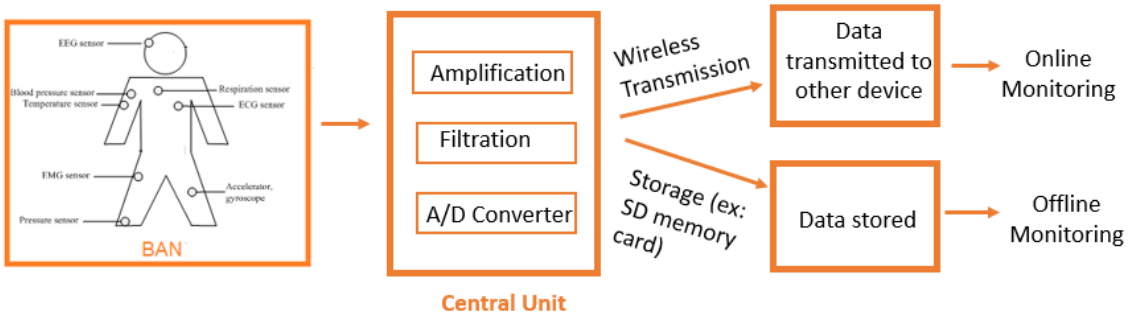


Figure 3.1.1 - Wearable device architecture (adapted from [55], [56])

3.1.1. Body Area Network

The term Body Area Network (BAN) is sometimes mistaken with the terms Body Sensor Network (BSN) and Wireless Sensor Network (WSN). These three terms can be used in different types of wearable devices architecture, but they do not have the same meaning, so their respective definitions will be clarified next.

The BAN is a network that connect all the sensors, which are placed around the body, to a main unit. The term BSN is used when each node from the connecting network contains a medical device or a sensor with a sensing unit, with more than just the sensor. The term WSN is defined as a large number of low-power, low-cost and tiny sensor nodes and each node has a set of components, such as sensors, microcontroller, and memory. Besides that, each node has the capacity of sensing, computing, storage and communication [52]–[54].

3.1.2. Central Unit

The vital signs collected by the sensors are usually transmitted to the central unit through wires, making the wearable device cheaper and simpler. This type of transmission is short-range and can affect the free movement of the user due to the loose wires. One possible improvement is the use of conductive wires that transmit the information provided by sensors embedded in clothing [52], [53]. The signal processing occurs in the central unit and includes amplification and/or filtering and conversion of the analog signal to digital. The signal processing can also be made in other device after the transmission of data.

The data in the central unit can be stored through, for example, an SD memory card for later analysis or through a wireless transmission. The central unit can also receive data from online monitoring devices, allowing the storage of these data [51], [55], [56]. This transmission is due through wireless communication. Examples of wireless connection channels are Bluetooth, Wi-Fi and ZigBee [3], [54], [55]. Bluetooth enables a short-range radiofrequency connection between portable and/or non-portable devices. It is low-cost and low-power consumption (consumes about 350 mW). The ZigBee [55] is a low-cost and ultra-low power consumption technology (about 100 mW) that consumes less power compared to Bluetooth, but instead has a lower data transfer rate. It also has the disadvantage of short-range communication. Wi-Fi allows a higher data transfer rate, however, it is the most energy-consuming, about 4 W [3], [10].

3.1.3. Real Time Monitoring *versus* Offline Monitoring

Real-time monitoring of the user's vital signs allows the user to not need to be in a hospital/health center confined to a machine which perform the monitoring. The data collected by the sensors are then transmitted by wireless to a user's portable device giving him information about his status and alert him to possible anomalies. The data collected can also be sent to the medical center. This type of monitoring enables an immediate real-time response to an action [24].

In offline monitoring, the vital signs data is stored, for example, on an SD memory card for later analysis by the user or by the medical center. Contrary to real time monitoring, offline monitoring provides a slower response to a given action [24] and does not allow for an early detection of disease.

3.2. Wearable Sleep Devices - State of Art

Wearable sleep devices have been used as an alternative for PSG since are less expensive and can monitor the user's sleep in his comfort of house. According to American Sleep Disorders Association (ASDA) devices which can do a portable monitoring are classified in type II, III or IV since type I device is the standard PSG and is consider the reference to the other devices. Table 3.2.1 represents the ASDA classification of the four types of devices according to their respective sleep records, taking into account the following parameters: have or not have supervision, presence or absence of EEG channels, the number and type of variables monitored and their respective function [16], [18], [19], [57]. According to the Agency for Healthcare Research and Quality (AHRQ), devices which do not have the characteristics to be type III devices are consider type IV [57].

Table 3.2.1 - Classification of different types of devices to monitor sleep (adapted from [16], [18], [19], [57])

	Type I Standard PSG	**Type II Comprehensive portable PSG**	**Type III Portable sleep apnea testing**	**Type IV Continuous recording of parameters**
Parameters monitored	EEG, EOG, EOG, chin and tibia EMG, ECG or heart rate, airflow, respiratory effort and oxygen saturation	EEG, EOG, EOG, chin and tibia EMG, ECG or heart rate airflow, respiratory effort and oxygen saturation	Minimum of four channels, including respiratory movement or effort, airflow, ECG or heart rate and oxygen saturation	Minimum of one channel, mainly oxygen saturation
Supervision	Yes	No	No	No
Function	Calculation of total sleep time; Identification and quantification of different stages of sleep; Detection of sleep disturbances	Calculation of total sleep time; Identification and quantification of different stages of sleep; Detection of OSA, leg movements, awakenings and respiratory abnormalities	Detection of sleep apnea;	

The high technical complexity and the low technical reliability led to the limited use of these devices. It is therefore necessary that ambulatory sleep monitoring devices be simple and technically reliable so that they can be used for possible diagnosis [19].

3.2.1. Commercial Devices

The actigraphy has been used for ambulatory monitoring, since it is an easy and cheap method to measure the duration of sleep, through the movements. However, this type of device cannot measure parameters such as heart rate and breathing, and is conditioned to acceleration measures, so it can induce some classification errors in activities with little movement, such as reading [58]. Fitbit Flex is an example of a commercial device that uses the method of actigraphy through an accelerometer on a bracelet that records movements of the body. It can detect when the user is awake or sleeping, records total sleep time and sleep latency but not extract more information about sleep staging [59]. Like FitbitFlex, UP3 from Jawbone is a bracelet which can measure the movements of the body through an accelerometer but can also records respiration and heart rate through a bioimpedance sensor, galvanic skin response and body temperature. This device can detect wake, REM, light sleep and deep sleep, although it is not very comfortable because the bracelet has to be tightest in order to be able to measure the physiological parameters and is not very precise [60], [61]. Another device that can detect wake, REM, light sleep and deep sleep is a watch named Basis Peak from Intel. It has an accelerometer to measure the movements of the body, an optical sensor to records heart rate, a galvanic skin response sensor and a body temperature sensor. Although this device has a good

battery life and could detect sleep stages, it was withdrawn from the market in 2016 by reports of overheating of the watch [60], [62].

BodyMotion Inc. has developed a wearable device SenseWear Pro2 Armband which consists of a 2-axis accelerometer, a skin temperature sensor, a heat flux sensor and a galvanic skin response sensor [63]. This device was subsequently tested to verify if it could estimate the total sleep time of users with obstructive sleep apnea and was found that its estimative agreed with the results of the PSG. Has also been found that, because the device is used on the arm, it is less affected by wrist movements that can lead to false results. However, this device cannot detect sleep phases [64], [65].

In order to measure other signals that are correlate with sleep quality, such as heart rate variability and respiration, there are some commercial devices, for example, Equivital system [66] and Hexoskin smart t-shirt [67]. The first one is a belt around upper chest that measures a respiration effort through a strain gauge, a two-lead ECG, 3-axis acceleration and skin temperature [58]. Hexoskin smart t-shirt incorporate two magnetic sensors to measure breathing rate, one-lead ECG and 3-axis accelerometer. Both devices can distinguish between wake and sleep and between light sleep and deep sleep, can detect disruptions in breathing, movements and positions during sleep [68]. There is a commercial t-shirt named Somnus Sleep Shirt from Nyx Device [69] which can detect if the user is awake or sleeping and can detect the phase of sleep – REM, light sleep and deep sleep – only with the measurement of the respiration through three capacitive sensors – two of these sensors are placed in the abdomen and one in the chest. [70] In the Figure 3.2.1 it is represented the commercial wearables devices described above: Fitbit Flex, UP3, Basis Peak, SenseWear Pro2 Armband, Equivital System and Hexoskin Smart T-Shirt.

Figure 3.2.1 - Commercial wearable devices. (A) Fitbit Flex [59], (B) UP3 [61], (C) Basis Peak [62], (D) SenseWear Pro02 Armband [63], (E) Equivital System [53] and (F) Hexoskin Smart T-shirt [67].

Another type of commercial device is patch. One example is the VitalPatch [71] from Vital Connect which is worn on chest and has a duration of more than 4 days. This adhesive patch records heart rate with ECG electrodes, respiratory rate, skin temperature with thermistor and body movements with 3-axis accelerometer. This device can distinguish wake, sleep, REM and NREM sleep, however it does have some disadvantages such as the patch may peel off and the sensor battery may suffocate if the patient sleeps in a prone position [72], [73].

NeuroOn Open [74] is a sleeping mask that has a 3-axis accelerometer which records body movement, temperature sensor, EOG and EEG sensors and a pulse oximetry sensor. This sleeping mask can sleep track through the EEG and can detect apnea through the pulse.

SmartSleep from Philips is a headband recently released in the market (2017). It uses an EEG to detect deep sleep (N3), and when N3 phase is detected, SmartSleep delivers optimized sound to enhance this stage. This device was designed to improve sleep efficiency ideally for people who sleep less than 7 hours per day and wake up tired but not have problem falling asleep or staying asleep. This product should not be used by hearing impaired, since the volume of this device does not exceed 80 dB [75]. The devices described above are type IV devices according to the AHRQ [57].

There are some commercial type III devices, for example, APV2, Sleep Scout from Cleveland Medical and ApneaLink by ResMed. APV2 can diagnose obstructive sleep apnea through the measurement of oxygen saturation and heart rate with a pulse oximeter, orinasal air flow and snore with a pressure cannula, respiratory effort in thorax and in abdomen with accelerometer and strain gauge, respectively, and body position with an accelerometer. This device although limited by the number of channels, is easy to use and has a good technical reliability [19]. ApneaLink [76] can report apnea, hypopnea, flow limitation and snoring through the measurement of nasal airflow with a cannula, respiratory effort and heart rate with a belt around the chest and oxygen saturation with an oximeter. However, it has been reported that this device can overestimate the Obstructive Apnea Hypopnea Index (OAHI) probably because it scores obstructive events that would not be scored on PSG, for example, events during wakefulness. Therefore it was important that this device has a sensor to detect wake and sleep time, such as actigraphy [77]. Sleep Scout [78] records thoracic and abdominal effort, body position, airflow, snore, pulse oximetry, ECG and EMG [51].

AlicePDx from Philips Respironics is a type II-III device which records respiratory effort with chest and abdominal belts, airflow and pressure with the cannula and thermistor, oxygen saturation with an oximeter and body position, and can also records EEG, EOG, EMG and ECG. This device is easy to use and has a code of colours around the device that indicate where to connect the various sensors. In relation to the data recordered, it is stored on a storage card, but the device can also be connected directly to a computer so that the data can be viewed in real time. AlicePDx can detect different stages of sleep and can report sleep apnea and sleep-disordered breathing [10], [79]. Embletta X100 from Embla is a type II device that measures EEG, EOG, EMG, ECG, respiratory effort with abdominal and thoracic bands, airflow with nasal cannulas, oximetry and body position [19]. This device can monitor different stages of sleep. Park *et al.*, demonstrated that the Embletta X100 scoring system does not provide an acceptable and accurate OSA diagnosis. [80] Another example of a type II commercial device is Somté PSG from Compumedics [81] which records six EEG channels, two EOG channels and two chin EMG channels, ECG, airflow through the pressure transducer, snore, respiratory effort with abdominal and chest bands, body position and oxygen saturation with oximeter [57] . Figure

3.2.2 represents the following commercial wearable devices: SmartSleep, VitalPatch, NeuroOn Open, Sleep Scout, ApneaLink, AlicePDx, Embletta X100 and Somté PSG

Figure 3.2.2 - Commercial wearable devices. (A) Embletta X100 [19], (B) NeuroOn Open [74], (C) SleepScout [78], (D) ApneaLink [76], (E) Somté PSG [81], (F) AlicePDx [79], (G) VitaPatch [71] and (H) SmartSleep [75]

The Table 3.2.2 classifies the described commercial devices according to the ASDA classification. As can be seen in the table, about 57% of the analysed commercial devices are type IV because they have fewer sensors and are easier to monitor compared to other types of devices.

Table 3.2.2 - Classification of different commercial devices according to the ASDA classification

Type			
II	**II/III**	**III**	**IV**
Somté PSG	Alice PDx	APV2	Fitbit Flex
			UP3
		SleepScout	Basis Peak
			SenseWear PrO_2 Armband
		ApneaLink	Equivital System
			Hexoskin Smart T-Shirt
		Embletta X100	Vital Patch
			NeuroOn Open
			SmartSleep

3.2.1.1. Vital Jacket®

VitalJacket® is the first certified wearable medical device, designed and developed at the University of Aveiro and licensed by the company Biodevices, S.A. that combines knowledge in the area of textile and microelectronics, in order to allow the monitoring of vital variables. This system is a T-shirt with built-in sensors, developed for various clinical situations, either in hospitals or at home, for people who require frequent or continuous monitoring of vital signs, such as electrocardiogram, heart rate, activity and posture, and body temperature. The t-shirt is washable, easy to use and has disposable electrodes. The data acquired by this device is transmitted via Bluetooth, which enables real-time monitoring, and can also be stored on a SD memory card for offline monitoring [5].

Although the VitalJacket® is not specified for sleep monitoring, it has sensors such as electrocardiogram, 3-axis accelerometer and temperature sensor, which can be used for this type of monitoring. In addition, this device can be adapted to acquire other vital signs, such as oxygen saturation and electrooculogram. Due to these characteristics, it will be possible to develop a prototype of a wearable device that will extend the VitalJacket®, named VitalSleep. The Figure 3.2.3 represents the VitalJacket® wearable device.

Figure 3.2.3 - VitalJacket® commercial device [5].

3.2.2. Prototype Devices

Some type IV devices have been developed over the years, examples of that are the following devices. Sukuzi *et al.*, [82] developed a watch (Prototype 1) that records wrist movements with a 3-axis accelerometer and pulse wave through photoelectric sensor. It can detect wake, REM and NREM sleep and has the advantage that the prototype can be small and simple due to the signals that it measures. Although, it cannot detect apnea and the algorithm only applies to healthy individuals. Lee *et al.*, [83] also developed a wrist shaped device (Prototype 2) that records heart rate through photoplethysmography and movement using an actigraphy. This device can only detect wake and REM sleep phase. Chang *et al.*, [84] developed a wearable device to be placed on the chest (Prototype 3) with a 3-axis accelerometer and ECG to detect the sleeping position, sleep stages and sleep disorders such as obstructive sleep apnea. In order to detect obstructive sleep apnea, Rofouei *et al.*, [85] created a wearable neck-cuff (Prototype 4) which records oxygen saturation and heart rate through an oximetry connected to the earlobe, respiratory sounds with a microphone, body movements and head position with a 3-axis accelerometer. The use of a microphone to records respiratory sounds has the disadvantage of only providing a relative value. Wongdhamma *et al.*, [86] developed a type III device: a shirt (Prototype 5) incorporated with 3-lead vectorcardiogram, 12-lead ECG, an oximetry and a phonocardiography transducer which capture cardiac sounds and respiratory sounds, such as snoring. This device can detect obstructive sleep apnea and cardiovascular diseases. The use of a phonocardiography has the same disadvantage that had already mentioned in the wearable neck-cuff device. Oh *et al.*, [1] also developed a type III device (Prototype 6). This prototype can monitor sleep apnea and records ECG signal, body position with a gyroscope, respiratory effort with piezoresistive sensors, nasal airflow with pressure transducers and oxygen saturation with an oximetry. The Table 3.2.3 classifies the described prototypes devices according to the ASDA classification. Like commercial devices, most of the prototypes of the analysed devices are also type IV.

Table 3.2.3 - Classification of different prototypes devices according to the ASDA classification

Type	
III	**IV**
Prototype 5 [86]	Prototype 1 [82]
	Prototype 2 [83]
Prototype 6 [1]	Prototype 3 [84]
	Prototype 4 [85]

The use of many sensors provides more data and increases the reliability of the sleep quality examination; however, it can harm the patient while sleeping and, consequently, can influence the results.

Through the analysis of existing wearable commercial devices and prototype devices it is possible to conclude that type IV devices are the most common. That is because they have few sensors, are easy to monitor and easy to use. Also through that analysis it is possible to conclude that the most common parameters monitored on that wearable devices are the body movement, ECG signal and breathing [3].

3.3. Market and Trends

The concern of daily monitoring of health status has been increasing. Thus, several devices have been developed for real-time monitoring [87].

Developments in small devices and in mobile computing have increased the interest in wearable technology. Wearable devices are comfortable, easy to use, non-invasive and allow continuous monitoring during a long period of time, for these reasons they have been growing in the economy [4]. It is estimated that in 2025 there will be about 3 billion wearable sensors [51]. And it is estimated that by 2022 the wearable technology market will reach $ 57,653 million, almost 3 times more than in 2016 [88]. Figure 3.3.1 shows a graphic with the estimated growth of revenue from wearable devices from 2015 to 2016 [89].

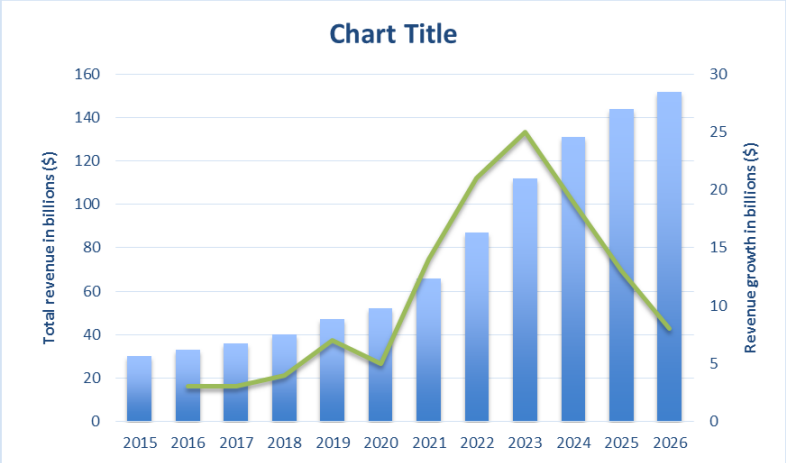


Figure 3.3.1 – Estimated growth of revenue from wearable devices between 2015 and 2016 (taken from [89]

The global smart textiles market has also increased, with an estimated $1500 million in 2020, more than $1000 million compared to 2012 [90].

Specifically in the sleep area, a study by Légel et al., showed that 25.6 million people in Japan, 82.3 million people in Western Europe and 131.3 million people in the USA suffered from sleep problems [91]. It is estimated that millions of Americans suffer from sleep disorders that are undiagnosed or untreated, for example, about 40 million suffer from sleep apnea and many of these people have this disorder undiagnosed [17].

The PSG can monitor the sleep quality; however, it is expensive, invasive and is not available in all hospitals/health centers. At least 2 300 PSG per 100 000 people must be made in USA, however, only 425 PSGs are made [92]. Thus, wearable devices appear as a possible solution for ambulatory sleep monitoring. In 2014, the global market for sleep testing at home reached about $36.8 million [17]. In 2017 it was estimated that the revenues reached $3 115 million only considering the US [93].

Through the analysis of these statistics, it is possible to conclude that the use of wearable devices will increase. Advances in the textile area and in mobile computing make this type of healthcare technology cheaper, simpler, smaller, more comfortable and with more reliable results. In addition, it is notable the large number of people who suffer from both diagnosed

and undiagnosed sleep disorders. Therefore, the investment in the development and improvement of wearable devices to ambulatory sleep monitoring should continue.

Chapter 4

VitalSleep: A wearable sleep system

VitalSleep is a new concept of a wearable technology to monitor sleep. VitalSleep system consist in the development of the hardware, acquisition of the sleep recording in real-time and the development of the sleep stage processing unit that comprises signal analysis, design of an algorithm to analyse the sleep stages and the evaluation of the algorithm.

To better understand which are the essential signals to monitor sleep, a study of physiological parameters measured in the polysomnography was made as can be seen in the Chapter 2 “Sleep Characteristics and Physiological Parameters Monitored”. With this study it was concluded that the EEG signal has more information to monitor sleep. ECG and EOG are two signals that can also monitor sleep, although not so complex and with less information comparatively to EEG signal. Oxygen saturation is also an important parameter in sleep monitoring, because can detect oxygen supply failures during respiratory events such as apnea. Another study was made to understand what type of physiological variables are often monitored in commercial sleep wearable devices, as can be seen in Chapter 3 “Wearable Sleep Device – State of Art” and it was concluded that the main variables monitored are the ECG signal, body movements and breathing. Considering the time to do this work and the complexity of all signals, it was chosen the ECG and the EOG signals, because despite giving less information of sleep monitoring comparatively to the EEG, are less complex to analyse, ensuring that it is possible to do the development of the hardware and the signals analysis in the time agreed. The oxygen saturation was also a variable selected since it can detect sleep respiratory disorders. The actigraphy is the most common parameter used in sleep commercial wearable devices and since actigraphy and temperature are included in the VitalJacket® technology it will also be considered in the VitalSleep system. After chosen the physiological parameters, it was study what kind of wearable device could incorporate all these variables, ensuring that it is comfortable and easy to use. It was concluded that a headband could incorporate these sensors and, at the same time, is easy to use and comfortable.

4.1. VitalSleep System Architecture

VitalSleep system is constituted for the following units: hardware of the prototype wearable device that is subdivided in the hardware of Biodevices S.A. board and the hardware of prototype board; acquisition platform that enable to visualize, in real-time, the data of physiologic variables monitored, save and import data; and the sleep stage processing unit that is subdivided in the pre-processing and analysis of the signals acquired, design of an algorithm to sleep staging and posterior evaluation using the MIT-BIH Polysomnographic Database, a database of PhysioNet that has a large archive of physiological data, including files with sleep stages annotations. In Figure 4.1.1 it is possible to observe a schematic of the VitalSleep system.

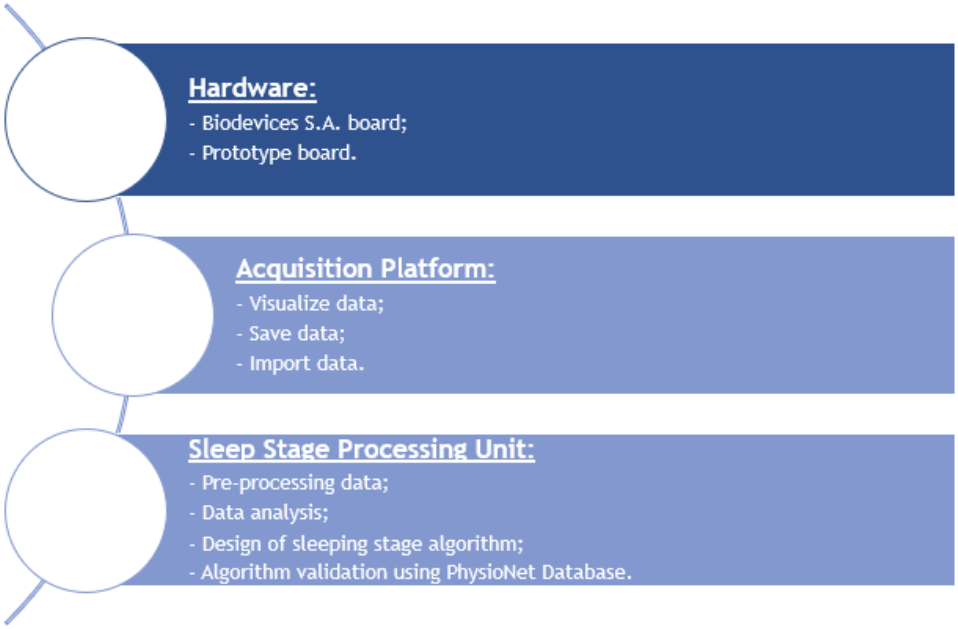


Figure 4.1.1 - Schematic of the VitalSleep system.

VitalSleep prototype is a headband that incorporate the following sensors: electrooculogram, electrocardiogram, oxygen saturation, actigraphy and temperature. The first VitalSleep prototype is presented in Figure 4.1.2.

Figure 4.1.2 - First prototype of the wearable device developed during the Master Thesis. In this figure it is represented the VitalSleep extension board prototype, the main board of Biodevices, S.A., the battery and the following sensors: accelerometer, oximeter, temperature, EOG and ECG.

4.2. Hardware Development

The hardware of VitalSystem is constituted by the prototype board and the VitalJacket® maian board. To extend the prototype board to the Vital Jacket® main board it was necessary to connect the hardware board to Biodevices, S.A board (main board) through the Vital Jacket® connector, enabling the use of Biodevices, S.A board microcontroller. So, first it was made an electronic prototype board that could connect the VitalJacket® connector in one side of the board and a flat cable in the other side to connect with Biodevices, S.A. board. This allows that the signals acquired by the prototype board were sent to the main board where the signals from the VitalJacket® are also being acquired.

For the development of the hardware of the prototype board it was necessary to, initially, implement the circuit to acquire the horizontal movement of the eyes, since the other sensors are already implemented [94]. After the validation of the EOG circuit, the design of the PCB of the VitalSleep prototype board using the *Altium* software was made and tested.

In the Figure 4.2.1 it is possible to observe a component diagram that represents the interaction between the prototype board and the Vital Jacket® main board.

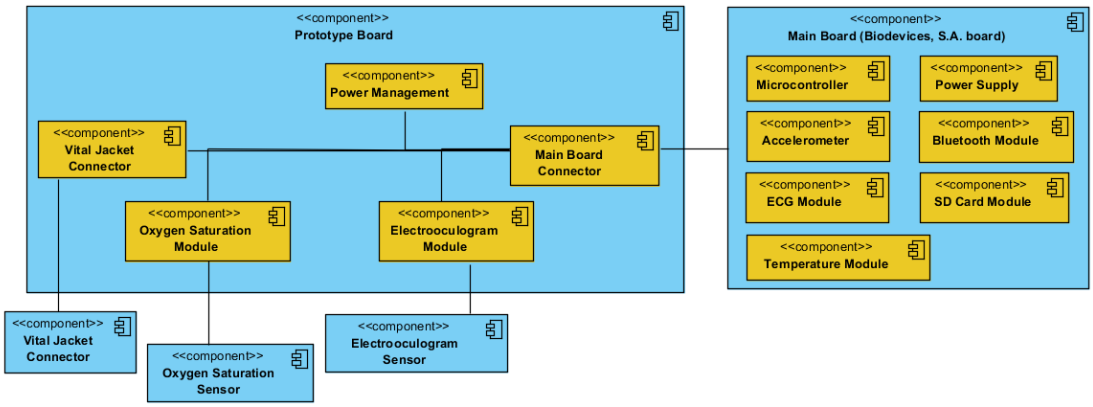


Figure 4.2.1 - Component diagram of VitalSleep prototype.

VitalSleep prototype board is divided into the Electrooculogram module, the oxygen saturation module and the power management module. Each of these modules will be further discussed. The Vital Jacket® T-shirt connector and the connector to the Biodevices, S.A main board allows the access of ECG, EOG, oxygen saturation, temperature and actigraphy to the main board and the SPI communication between the developed schematics modules.

The SPI communication allows a synchronized communication between a master and one or more slaves, through Serial Clock (SCK), Master Out Slave In (MOSI), Master In Slave Out (MISO), and Slave Select (SS) lines. The SCK channel allows the synchronization of data between the master and the slave, and depending on the configuration of the microcontroller, when this channel goes high or low, a bit is transferred to the slave; the MOSI channel allows the transmission of data from the master to the slave; the MISO channel allows the transmission of data from the slave to the master; and the SS channel is unique for each slave and selects which slave will be in communication with the master.

In Figure 4.2.2 it is presented the schematic representation of the develop prototype hardware architecture and the SPI communication between schematic modules.

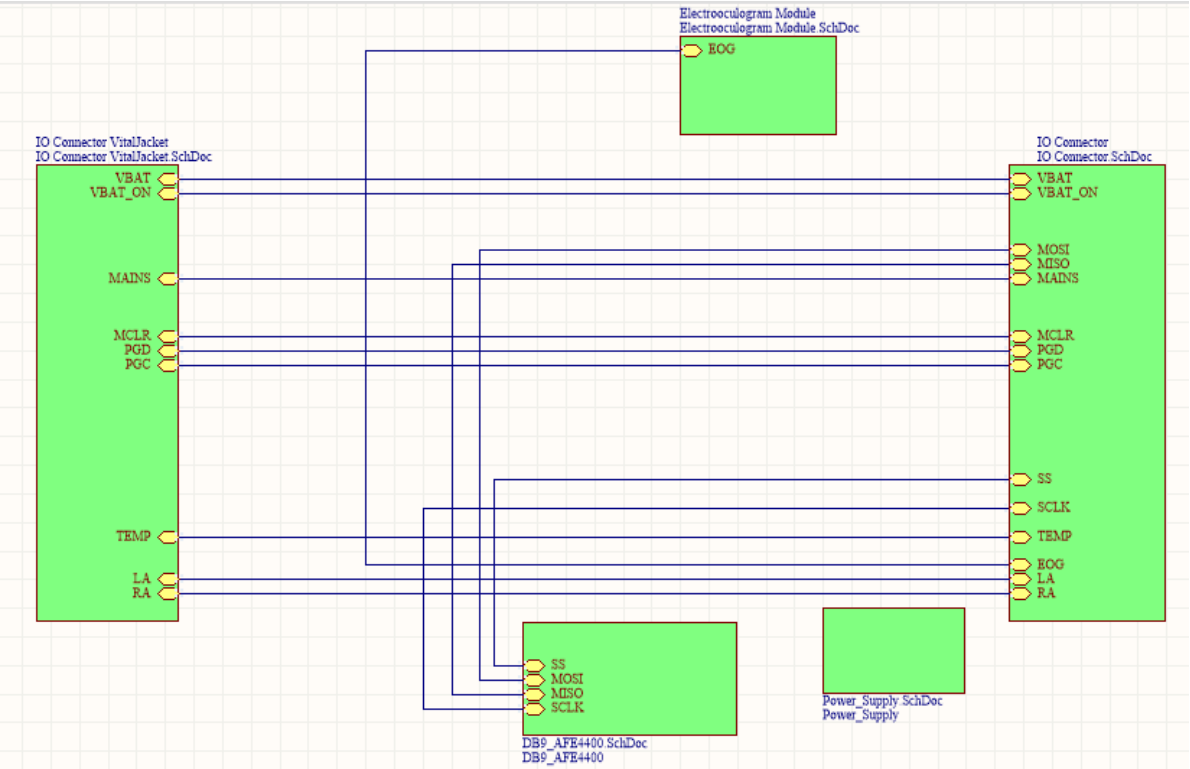


Figure 4.2.2 - Schematic of the VitalSleep prototype board, which are divided into the Electrooculogram module, the AFE4400 module, the power management module, the VitalJacket® connector and the connector of the Biodevices, S.A. main board, and the SPI communication between them.

In the following sub-chapters, it will be described the electronic circuits schematics of the VitalSleep prototype.

4.2.1. Electrooculogram Module

The EOG signal has a range of frequency between 0.1 Hz to 20 Hz and a range of amplitude between 50 µV to 3500 µV [24].

The ADC of the Biodevices, S.A. board has a sampling frequency of 500 Hz, a resolution of 8 bits and a range of -3.3 mV to 3.3 mV.

Since the potential difference of horizontal eye movements is very small, it was used an AD620 instrumentation amplifier to amplify this small amplitude. The AD620 was chosen because is a monolithic instrumentation amplifier based on a modification of three op amp approach, is easy to use, has a gain range of 1 to 10 000, has a wide power supply range (± 2.3 V to ± 18 V), higher performance than 3 op-amp approach, low noise and higher CMRR [95].

To have an input signal in the range of the EOG signal and taking into account the baseline fluctuations, it was used a gain of 494. The AD620 requires an external resistance, RG, to define the gain. The expression of the gain, G, is given by Eq. (5.1),

$$G = \frac{49.4\ k\Omega}{RG} + 1\ , \tag{5.1}$$

where RG has a value of 100Ω.

During the amplification of the signal, the output voltage of the amplifier can be amplified with noise in the range of 49 Hz to 51 Hz. In addition, this signal can be easily contaminated with electrodes artefacts, power line noise and muscle movements artefacts [96]. In order to remove this noise and considering the frequency of interest to analyse the EOG signal during sleep, a low pass RC filter with a cut-off frequency of 4.82 Hz was applied. The general expression of the cut-off frequency of the low pass filter, Fc, is given by Eq. (5.2),

$$Fc = \frac{1}{2\pi RC}\ , \tag{5.2}$$

where R corresponds to the resistance and C to the capacitor.

The Figure 4.2.3 shows the schematic of the Electrooculogram module.

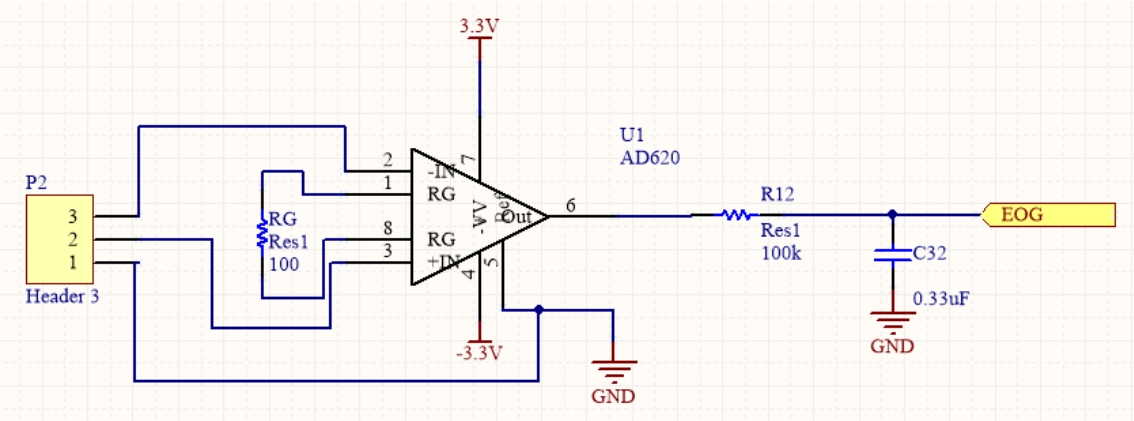


Figure 4.2.3 - Schematic of the Electrooculogram Module.

Regarding the placement of the electrodes, it was used three electrodes to monitor eye movements: one is placed 1 cm above the outer corner of the right eye, the other is placed 1 cm below the outer corner of the left eye, and the reference electrode is placed 1 cm above the bridge of the nose. This arrangement of the electrodes was suggested by Rechtschaffen and Kales [96].

To validate this circuit, it was built in a breadboard – Figure 4.2.4. The sensors were placed as already mentioned. It was verified that if the electrode connected to the pin 3 (+IN) of the AD620 was placed in the outer corner of the left eye, when the person looked to the right side, a negative peak appeared in the wave of the signal and when looked to the left side it appeared a positive peak in the signal wave. The Figure 4.2.5 shows these results.

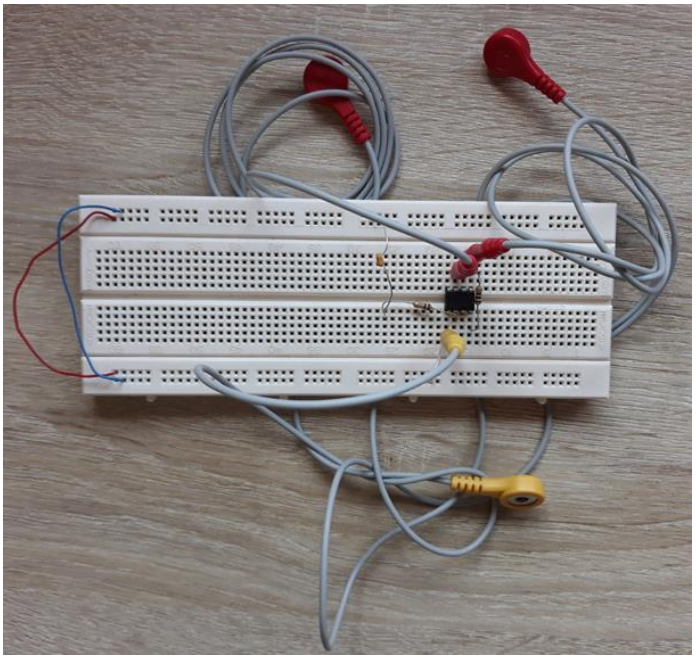


Figure 4.2.4 - EOG circuit implemented on a breadboard for monitoring horizontal eye movement. In this circuit three electrodes are used: one (rede) is placed 1 cm above the outer corner of the right side of one eye, the other (red) is placed 1 cm below the outer corner of the left side of the other eye and the reference electrode (yellow) is placed 1 cm above the bridge of the nose.

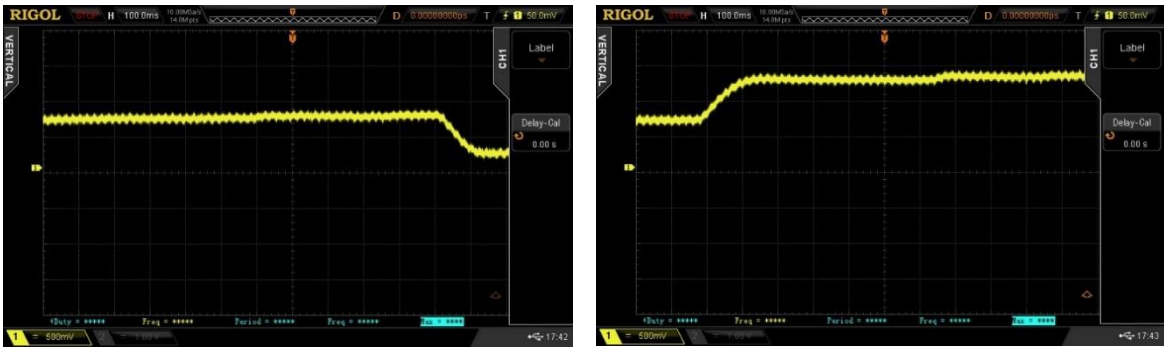


Figure 4.2.5 - Monitoring of horizontal eye movements through the implemented EOG circuit on a bread-board. If the electrode connected to the pin 3 (+IN) of the AD620 was placed in the outer corner of the left eye, when the person looked to the right side, a negative peak appeared on the signal - left image. When the person looked to the left side, a positive peak appeared on the signal - image on the right.

After the validation of the EOG circuit, the schematic of the Electrooculogram module was design in Altium software. In this schematic was used a connector for the three electrodes that capture the signal of the horizontal movement of the eyes.

4.2.2. Oxygen Saturation Module

This module allows the acquisition of oxygen saturation signal. For the oxygen saturation sensor, it was used an Analog Front-End (AFE), AFE4400, developed by Texas Instruments. It was chose this type of AFE since it was specially designed to pulse oximetry and allows to convert analogue readings into a digital output according to the master-slave communication protocol, Serial Port Interface (SPI) [97].

The AFE4400 has several routes: Transmit Route (TX), Receive Route (RX) and SPI route communication. Both TX and RX have two routes: a cathode route to connect to the oxygen oximeter sensor LED and an anode route to connect to the photodiode [97].

The AFE turns on the LED in the oximeter sensor using the TX route and then turns off the LED and collects the received intensities in the photodiode sensor using the RX route to convert the analog input to digital using the ADC converter. This process is made four times: twice for the determination of the oxygen saturation which requires the sample of the red-light wavelength and the sample of the infrared light wavelength, and the others two times to acquire the ambient light with a more accurate result. Figure 4.2.6 shows when each step of each cycle starts and ends. When a complete reading cycle is made, and the digital output is ready to be read, the ADC ready pin (ADC_RDY) gets high during a short period of time and then turns low. The AFE4400 can subtract the ambient light sample to the corresponding LED value, this occurs in the last ADC conversion, and can be read in the SPI output [97].

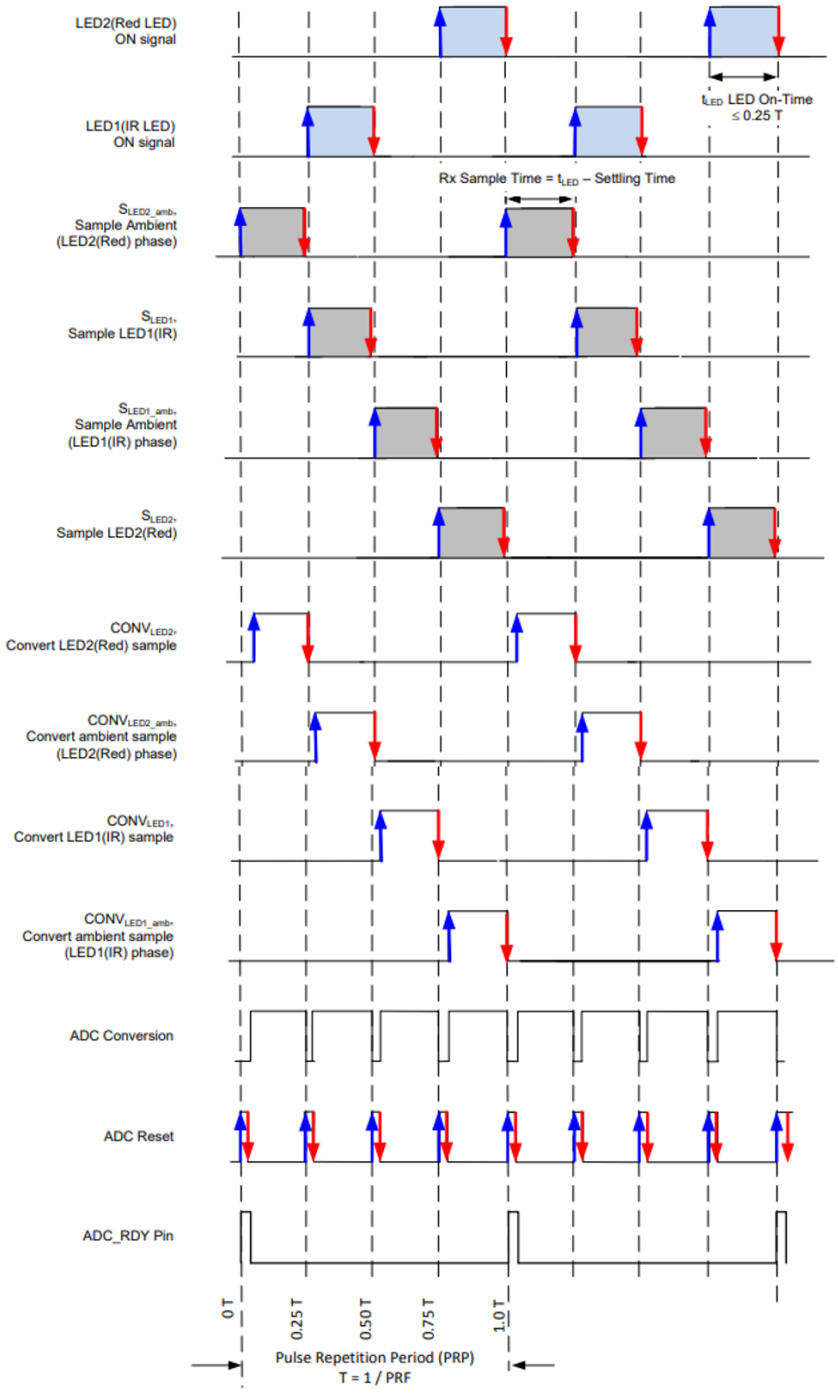


Figure 4.2.6 - Representation of the sampling cycles of AFE4400. In this figure it is possible to observe two complete cycles of acquisition and ADC conversion (taken from [97]).

One of the main features of the AFE4400 is the possibility to program the timings of when each action occurs. These timings have a common reference time that is also programmable and is directly correlated to an external crystal clock of 8 MHz in the clock route. The AFE4400 acquire the oscillation of the crystal and convert it to a 4 MHz frequency that is used as AFE pacemaker.

Furthermore, two connectors were design in the PCB (one for the emitter sensor and the other for the detector sensor) to allow the communication between the oxygen saturation sensor and the prototype board.

The schematic of this module is present in the Figure 4.2.7 and was based on the recommended circuit in the datasheet of the AFE4400 Texas Instruments [97].

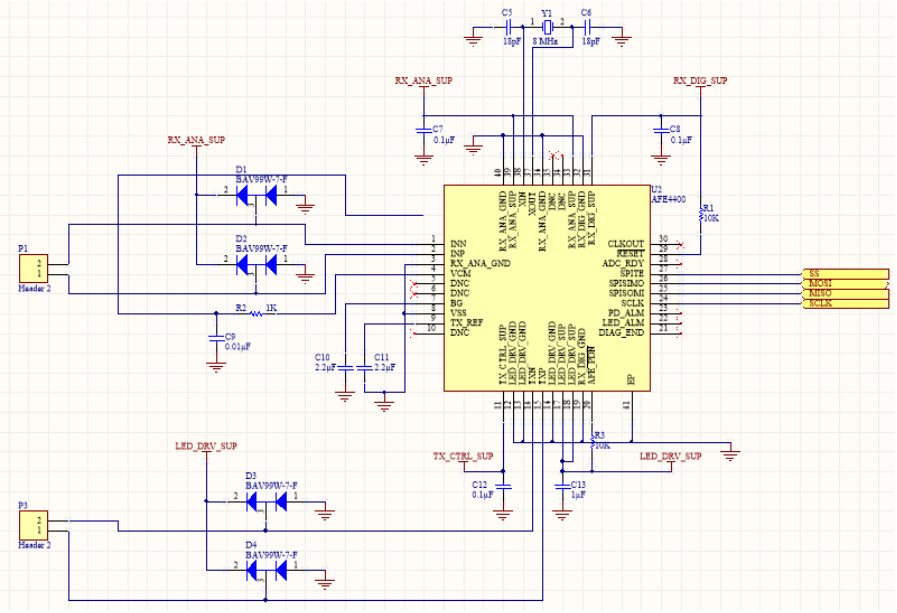


Figure 4.2.7 - Schematic of the oxygen saturation module based on the recommended circuit by the Texas Instruments [79].

4.2.3. Power Management Module

The AFE4400 has three types of supplies: the RX supplies, which can be between 2.0 V to 3.6 V; the TX supplies, which can be between 3.0 V to 5.25 V; and the LEDs supplies, which can also be between 3.0 V to 5.25 V. In order to simplify the AFE4400 power supply and according to the recommendations by Texas Instruments, [97] the voltage used in TX route is the same used in LEDs. Thus, the AFE4400 power supply has only two different voltages. The power management is represented in Figure 4.2.8 and is based on the recommendations by Texas Instruments [98].

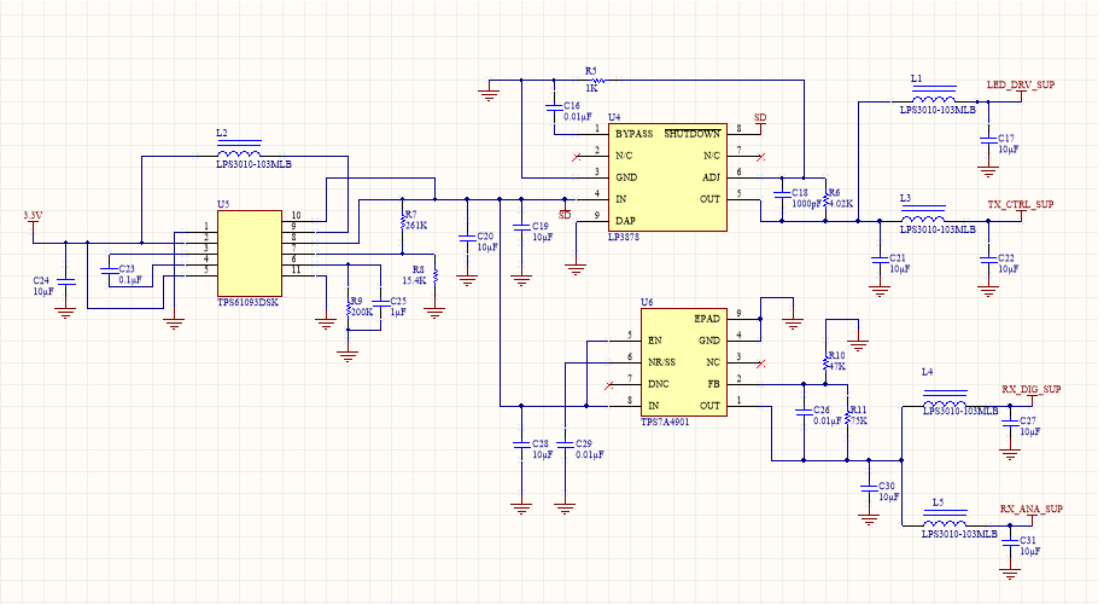


Figure 4.2.8 - Schematic of the power management module based on the recommended circuit by the Texas Instruments [79].

4.2.4. Printed Circuit Board Design

After design all the schematics needed for the prototype board, it was possible to design the PCB of VitalSleep prototype board, using the software *Altium*, the same software used for schematics design. To make the PCB, it was necessary to design the specific footprint of each component, which consists in drawing the pads of the components that will be soldered to the board. Finally, to create a 3D representation of the board, it was necessary to associate the corresponding 3D model of the component to each footprint. These 3D models were imported from the 3D ContentCentral page, an OpenSource.

In this PCB two layers were used: top and bottom – Figure 4.2.9. It is noteworthy that to make the prototype more comfortable, one of the requirements was to make it small. The final size was 33 mm x 40 mm.

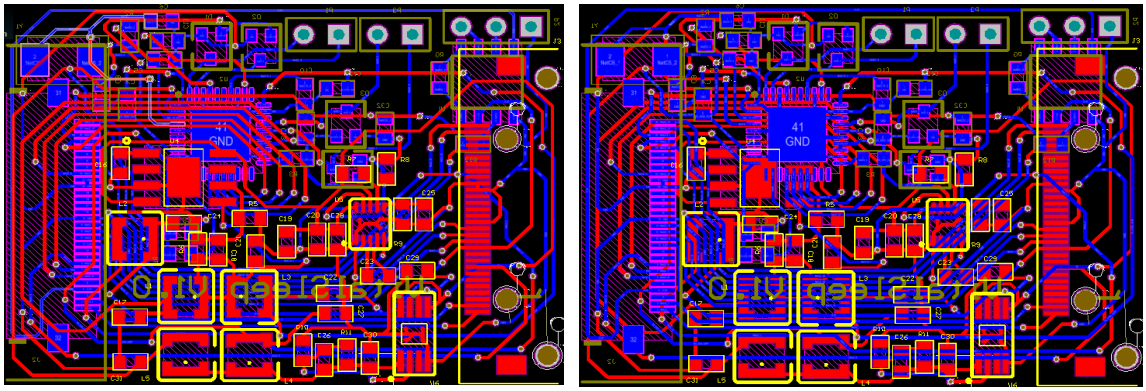


Figure 4.2.9 - PCB design of VitalSleep prototype board. Top layer (left image) and bottom layer (right image).

In Figure 4.2.10 it is possible to observe the 3D model of VitalSleep prototype board.

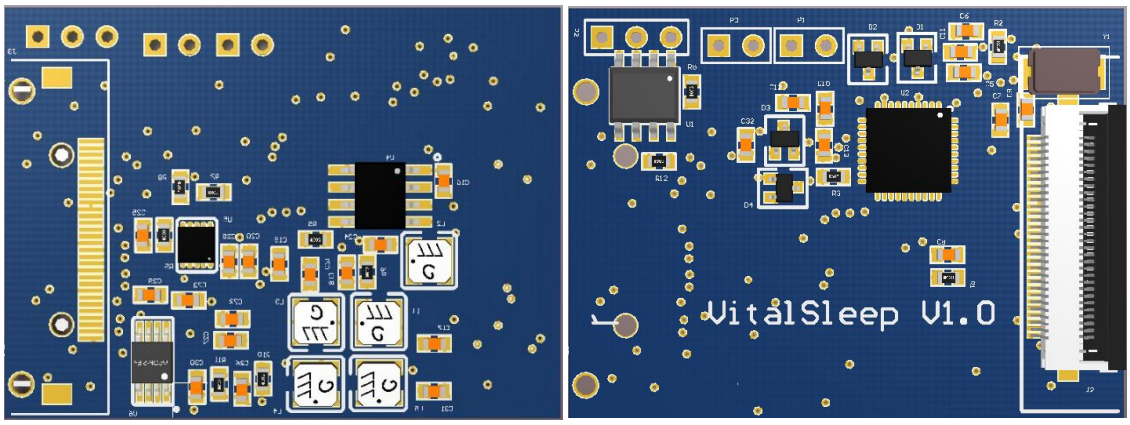


Figure 4.2.10 - 3D model of VitalSleep extension board prototype. The left image shows the top view and the right one shows the bottom view.

4.2.5. Prototype Extension Assembly

The production of the PCB is the next step. For this, it was necessary to generate Gerber files with the design of the layers and with the drills that are necessary to make in the PCB fabrication. To verify if the PCB is exactly as it was designed, a Gerber design generated by the producer was verified. After this process some errors were detected, such as a bad union between vias and/or between a via and a route. These errors were corrected, and the process was repeated until agreed with the design of the PCB. Finally, the PCB was ordered to be produced and the components needed were purchased. In Figure 4.2.11 it is possible to observe the produced PCB of the VitalSleep prototype.

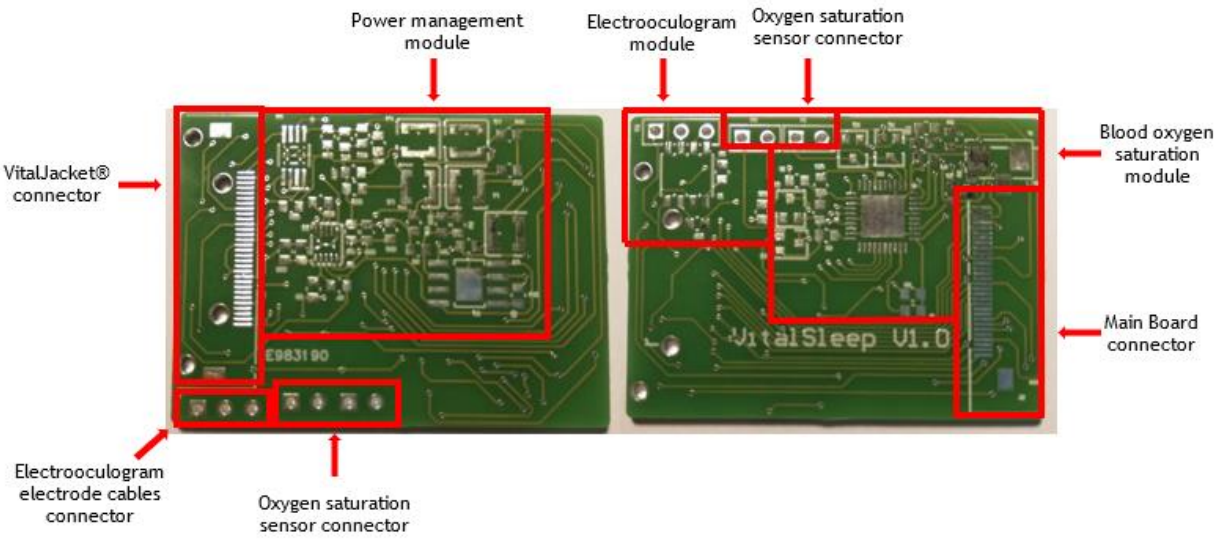


Figure 4.2.11 - Top layer (left image) and bottom layer (right image) of the produced PCB of the VitalSleep prototype board with the identified modules and connectors.

When all the components and the PCB were received, is was necessary to learn how to solder the components to the board. After the prototype board assembly It was necessary to test the board, more specifically, the ECG, EOG, oxygen saturation and temperature signal.

Regarding the oxygen saturation test, the AFE4400 power supply was evaluated. The values of the TX and RX roots supply were measured, 5,34 V and 1,36 V, respectively. It was verified that the measured value of the TX route was within the range of expected values of the power management circuit developed however the measured value of the RX route was significantly lower than the range of expected values. After some experiments and resoldering the value of the RX route it was not still in the range of expected values, maybe due to some components' failure. After all tries and taking into account the time to developed the rest of the work that includes the test of the other signals, the acquisition of sleep recording using VitalSleep prototype, signal analysis, the design of the algorithm to sleep staging and posterior evaluation using the PhysioNet Database, it was decided to continue the VitalSleep prototype development without considering the oxygen saturation sensor.

For the EOG signal test, it was verified if the voltage was corrected: 3.3 V and -3.3 V, and for the ECG and temperature signal test, it was verified the conductivity between the ECG electrode cables and the prototype board and between the temperature sensor and the prototype board, respectively.

The next and last step of the hardware development was the incorporation of the EOG electrode cables in the prototype board and the connection between the prototype board and the Biodevices. S, A. board. That is described in the next sub-section.

4.2.6. Wearable Prototype Assembly

The last step of the hardware development was the incorporation of three electrode cables for the monitoring of the movement of the eyes. For this, some tests were done to understand the best way to incorporate them considering that they would have to be soldered to the PCB. Two attempts were used: soldering the filament and the mesh or soldering only the filament, dispensing the mesh. It was found that soldering only the filament had less interference. Then, heat shrink sleeve was used to make the cables more stable and less sensitive to external interference. To finalize, the connection between the VitalSleep prototype and the main board was made through a flat, as it can be seen in the Figure 4.2.12.

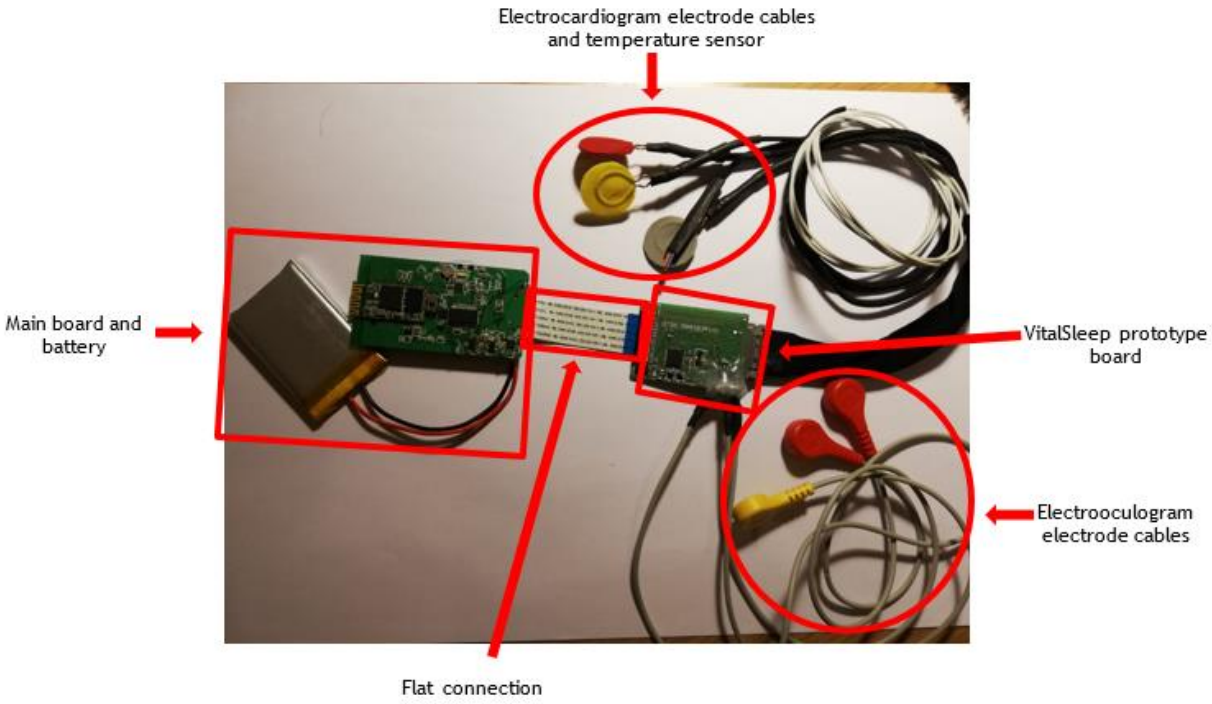


Figure 4.2.12 - Connection between the VitalSleep prototype board and the main board and the incorporation of the EOG and ECG electrode cables and the temperature sensor.

First acquisitions showed some problems in the EOG signal that could derive from electrodes gel or electrode cables. Acquisitions with different types of gel electrodes were made and the differences were almost insignificant. The second alternative was to change electrode cables to gold electrode cables and insulate them with heat shrink sleeve – Figure 4.2.13. This solution had more significant improvements, however, the best solution would be to have connectors on the PCB to connect electrode cables without the need to strip and solder them to the board.

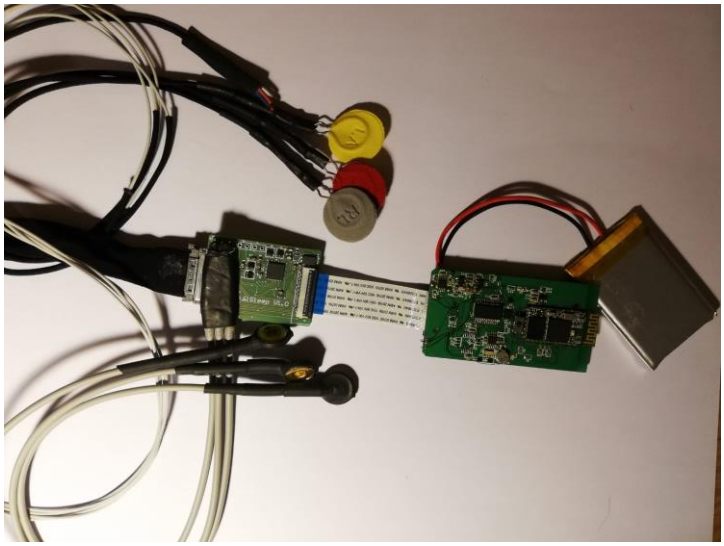


Figure 4.2.13 - Incorporation of gold electrode cables.

The Figure 4.2.14 shows the VitalSleep prototype with the electrode cables, the VitalSleep prototype board and the Biodevices, S.A. main board incorporated in the headband.

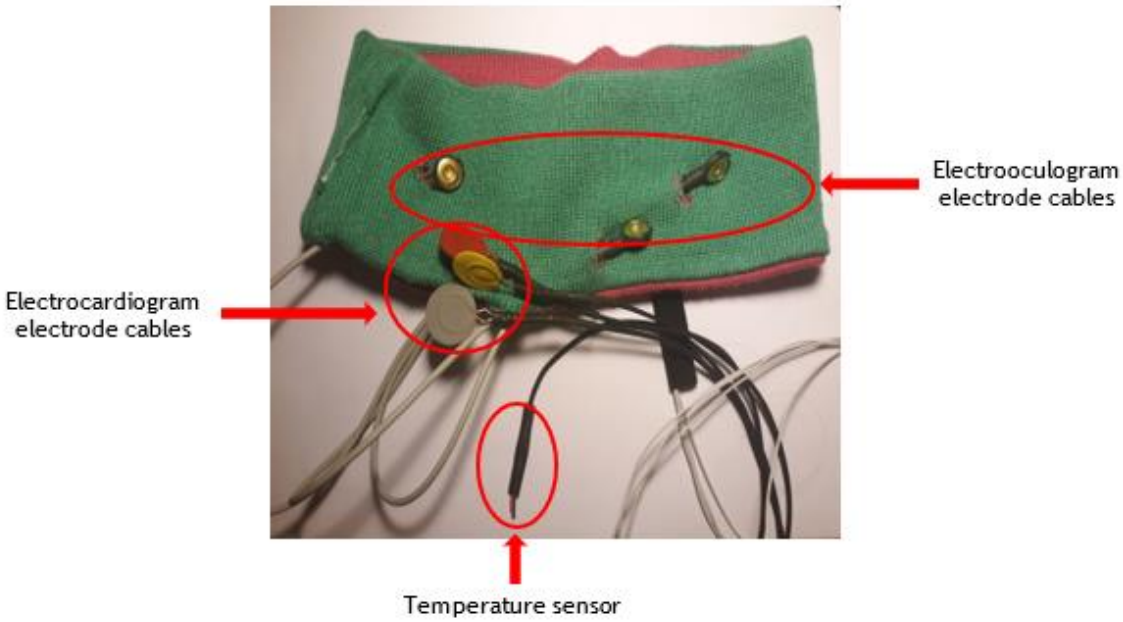


Figure 4.2.14- VitalSleep Prototype. Incorporation of electrode cables, VitalSleep prototype board and Biodevices, S.A. main board in the headband.

4.3. Firmware Development

The development of the firmware was made using a software named MPLAB X IDE. With this software it is possible to implement through C programming language the firmware for a specific Microchip microcontroller such the one that is used in the main board, which cannot be specified because it is Biodevices. S, A. property. The MPLAB X IDE has a plug-in tool named MPLAB Code Configurator that allows to generate automatically the code for the initialization and control of the microcontroller pins, more specifically, allows to select and setup the peripherals, to select the pins of the microcontroller, to set up the input/output pin configurations and to select their functions. After these configurations, the MPLAB Code Configurator create a peripheral driver code with functions automatically developed for each peripheral that is open sourced and editable [99]. Figure 4.3.1 shows a window of MPLAB Code Configurator.

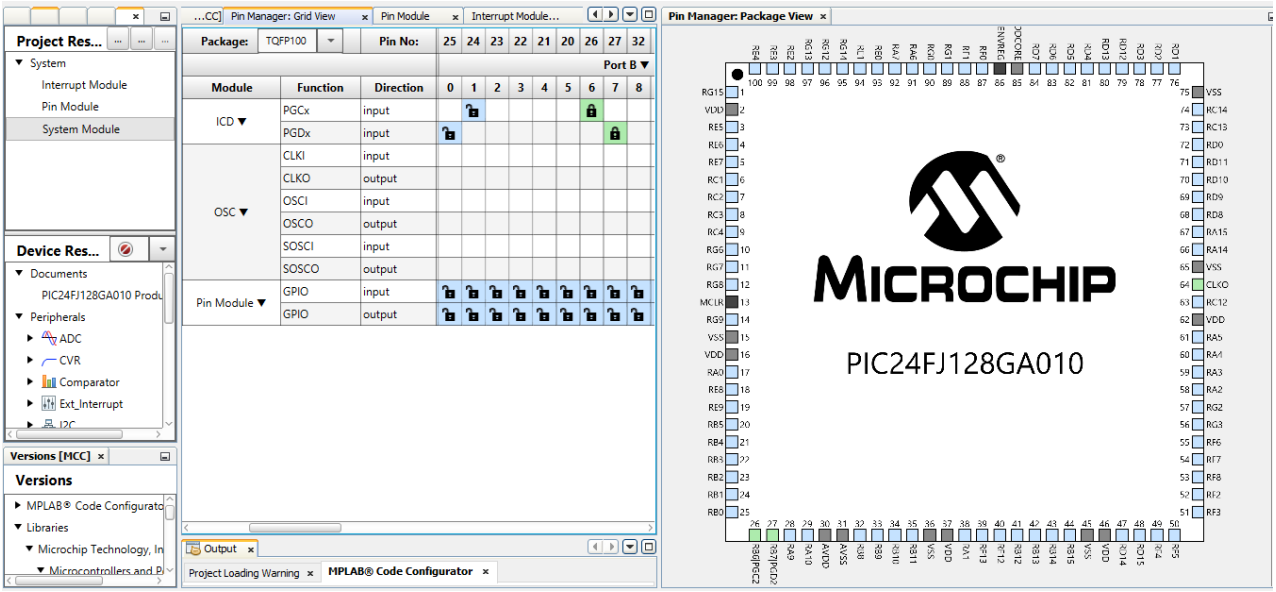


Figure 4.3.1 – Window of MPLAB Code Configurator

After generating the code using the MPLAB Code Configuration it was made the remaining code for the oxygen saturation sensor, electrooculogram sensor and for the SPI communication to allow to send and receive bits from a selected slave. The microcontroller used in this work has an 8-bit architecture, so the communication is in groups of 8-bit. These groups of 8-bits are named as register and can contain until 8 bits to identify what is the address of the respective register, the remain bits contains the information about that register. As example, to define some setting in a slave it is necessary to send the address of the register that contain the wanted setting and then it is necessary to set high or low bits according to the specification. The datasheets of the components have a list of the registers and the respective description relatively to the address and the setting that each bit defines.

For the development of the AFE4400 firmware it is first necessary to initialize the slave pins. Then it is necessary to initialize the AFE4400, which consist in the following steps: reset of all registers; check if the AFE4400 has any fault, returning a certain number of bits to inform its status; send twenty seven timing control registers to set when each operation starts and ends; and send five register related to the AFE4400 operation mode to define crucial configurations.

After the reset and initialization, it is necessary to implement the reading and writing functions to allow the communication between the microcontroller and the AFE4400. Each register of the AFE4400 has 32 bits where the first 8 bits indicate the address of the register that is being sent and the remaining 24 bits corresponds to the information about that register. Taking this into account, for the writing process in AFE4400 the microcontroller sends 32 bits, divided in groups of 8 bits. For the reading process, the AFE4400 must be set in the reading mode by sending a specific register with a bit to active the reading mode. When the reading mode is active it only can be turned off if the same register is sent with the opposite value of the same bit. In this case, the reading mode is inactivated, and the writing mode is activated. To get a register from AFE4400, the reading mode must be active, and it is necessary to send the 8 bits that contains the register address that is going to be read. After receiving the register address,

the AFE4400 writes the information of the requested register in the next 24 clock cycles. That information is read and saved.

Due to the hardware problem of the oxygen saturation module as mentioned in the subsection “4.2.5 Prototype Extension Assembly”, it was not possible to progress with the AFE4400 firmware. The next step would be read the oxygen saturation sensor values.

For the EOG firmware it was necessary to initialize the selected pin and to do an ADC conversion.

After this the firmware was integrated in the Biodevices. S.A VitalJacket® firmware.

A first acquisition of EOG, ECG, temperature and actigraphy signals was made to verify if they were being acquired correctly. The visualization of these signals in real time was made through an application of Biodevices, S.A. that contains the EOG signal, besides the variables already implemented by Biodevices, S.A. technology.

The next steps were the analysis of the variables in MATLAB, including the pre-processing of the signals and the extraction of essential characteristics for sleep staging, the design of the algorithm for sleep staging and the evaluation of the algorithm using the PhysioNet Database, as it will be described in detail in the next section.

4.4. Sleep Stage Processing Unit

In this section it will be presented the signal analysis made for the four variables implemented in the VitalSleep prototype – electrocardiogram, electrooculogram, temperature and accelerometer. The algorithm designed for sleep staging was also be described.

In order to evaluate the algorithm developed, the results of the algorithm will be evaluated using the MIT-BIH Polysomnographic Database, a database of PhysioNet, [100] that contains polysomnographic exams classified by a specialist in the different stages of sleep: wake/REM/deep sleep/light sleep. The variables that are monitored in these exams are EEG, EOG, respiration, oxygen saturation and EMG. So, neither the temperature nor the body movements - variables included in the VitalSleep prototype - were monitored in these exams.

Different algorithms will be design, implemented and evaluated using the PhysioNet Database: one algorithm only based on the ECG variables, other only based on the EOG variables and another based on the combination between the ECG and EOG variables. For the temperature and actigraphy signals, the algorithms were not evaluated because the PhysioNet Database do not have these signals.

4.4.1. PhysioNet Database

PhysioNet is a research resource that provides free web access to a large number of recorded physiological signal and is subdivided in three components: PhysioBank that contains a large number of recording physiological data; PhysioToolkit that has a large library of software that allows, for example, signal processing and analysis; and PhysioNetWorks for members of PhysioNet that allows the development of data and software resources that can be incorporated in PhysioBank and PhysioToolkit [100]–[102].

Regarding the PhysioBank it contains about 90 000 recordings organized in 80 databases – over 4 terabytes of physiological signals. The database used to evaluate the developed algorithms was the MIT-BIH Polysomnographic Database that has recordings of multiple physiological signals during sleep. This database includes 18 records of subjects that were monitored in Boston's Beth Israel Hospital Sleep Laboratory. All recordings include an ECG signal, an EEG signal, a respiration signal and an invasive blood pressure signal, and are annotated with respect to sleep stages and apnea, if it was the case. The recordings with six and seven channels, include a respiratory effort signal, some include an EOG and an EMG signals, and the remaining recordings include a cardiac stroke volume signal and an earlobe oximeter signal [100], [102].

Only 2 of the 18 recordings were recorded from subjects without sleep disorders, and both recordings include EOG and ECG signals but not include temperature and actigraphy signals. For this reason, only the algorithm design based on the ECG and EOG variables can be evaluated using the MIT-BIH Polysomnographic Database [100], [102].

4.4.2. Electrocardiogram Analysis

The heart rate variability (HRV) is an important parameter that can be extracted from the ECG signal. It allows to evaluate the autonomic nervous state through the variations between consecutive heartbeats and has a frequency and time domain. Through the variations of the frequency and time domain variables it is possible to perform a sleep staging, as described in the sub-section "2.4.4. Electrocardiogram".

The HRV is obtained from ECG signal and can be derived from intervals between consecutive R peaks. It is important to enhance that all RR intervals were named normal-to-normal (NN) intervals because the acquisition of the ECG signal was made during a rest position – sleep – and has a good quality has it can be observed in Figure 4.4.1.

The NN intervals were extracted through the QRS wave using the Pan Tompkins implementation. This implementation will be explained in this sub-section and is also represented in the workflow of the Figure 4.4.2 [103].

The first part of the Pan Tompkins algorithm consists in the preprocessing of the signal. More specifically, the signal can be influenced by many types of noise, such as, power-line interference. To reduce this noise, it is implemented a bandpass filter with 5-15 Hz – frequency band to maximize the QRS energy. Then it is used a derivative filter to provide the information about the QRS complex slope and the signal is squared to enhance the dominant peaks and to restrict false positives caused by T waves which have higher spectral energy than normal. A moving window integrator is applied to smooth close-by peaks [103].

After the preprocessing of the signal it is necessary to do some decision rules to correctly detect QRS complex. In an initial phase the threshold of the signal and the noise peaks are detected. Then two heartbeats indicate the average of the NN interval and NN interval limit. It is necessary to highlight that the thresholds are adjusted periodically to adapt the characteristics of the signal. This algorithm uses two threshold values to classify each peak as either signal or noise: if the sample is higher than the threshold of the signal then it is identified a possible QRS complex; if the sample is higher than the threshold of the noise and less than the signal threshold then it is considered a noise peak. In addition, this algorithm does not accept QRS complexes that occurred within 200 ms after a previously detected QRS complex. If the possible QRS complex occurs after the 200 ms but within 360 ms of the previous QRS complex,

the algorithm detects if it is a possible QRS complex or if it is an abnormal T wave, through the mean slope of the waveform at that position: if the slope is less than one half of the previous QRS complex then it is a T wave [103]. In Figure 4.3.2 are shown the described steps of the Pan-Tompkins algorithm implemented on the ECG signal.

After the detection of all QRS complex, the NN intervals between successive heartbeats were determined to characterize the HRV. The analysis of the HRV can be divided into time-domain or frequency-domain [28].

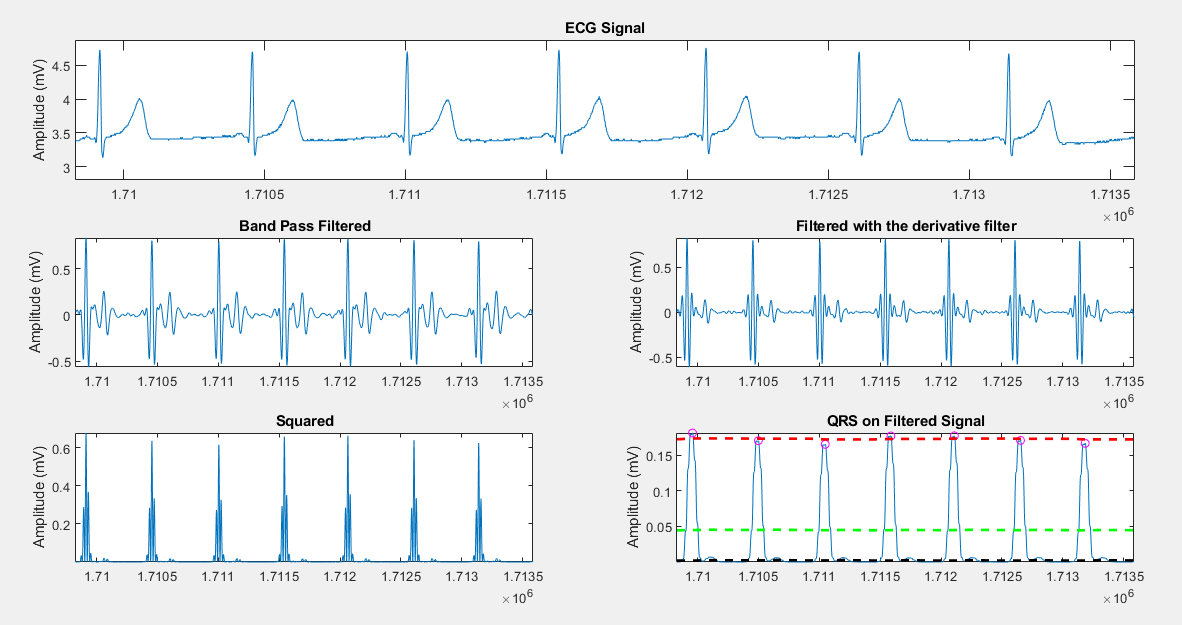


Figure 4.4.1 - Implementation of the Pan-Tompkins algorithm. In this figure it is possible to observe a segment of an ECG signal without any pre-processing (superior image), subject to a bandpass filter (middle image on the left side), subject to a derivative filter (middle image on the right side), subject to a squared signal (lower left corner image), and, finally, the detection of the QRS complex (lower right corner image). The black line represents the noise, the green line represents the adaptive threshold, the red line represents the signal level and the pink circles represent the QRS adaptive threshold.

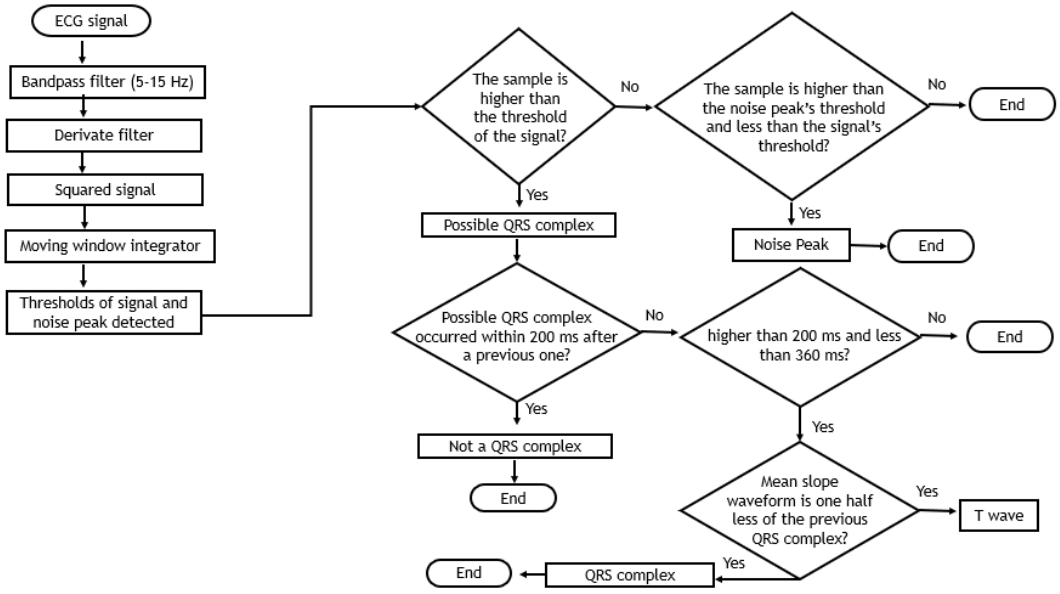


Figure 4.4.2 - Workflow of the implementation of the Pan-Tompkins algorithm [103].

4.4.2.1. HRV - Time Domain Method

The time domain method is one of the simplest methods to measure heart rate variations through the intervals between successive normal QRS complexes.

According to [28] and a study by Jiang et al., [29] the most common variables that can be calculated and used to described the sleep stages are the mean NN interval, which is the interval between successive QRS complexes and the standard deviation of the NN interval (SDNN). The SDNN is calculated through the square root of variance so it reflects the cyclic components responsible for the variability. The SDNN is relatively insensitive to small errors, although is not a well-defined statistical variable, since it depends on the length of the registration period. Thus, in order to compare SDNN measurements of several records, their duration should be standardized [28]. In Figure 4.4.3 are represented the different variables measured using the time domain method: NN intervals, mean NN intervals and SDNN.

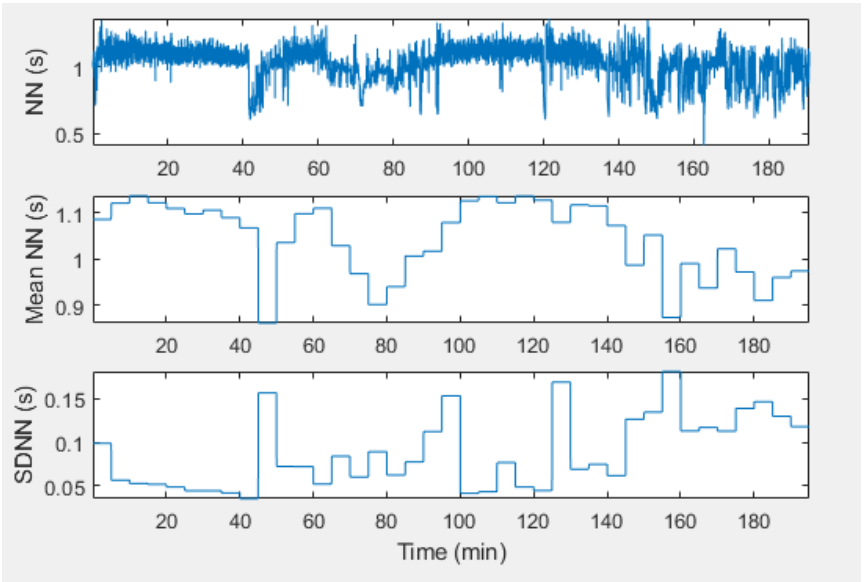


Figure 4.4.3 - Time domain variables: NN intervals (s), mean NN intervals (s) and SDNN (s).

4.4.2.2. HRV - Frequency Domain Method

The spectral analysis of the NN intervals is often used to evaluate the cardiac system during sleep since the spectral power in specific band frequencies is related to the activity of the sympathetic and parasympathetic nervous system, more specifically, the spectral power in high frequency (0.15-0.4 Hz) and the spectral power in low frequency (0.04-0.15 Hz) are associated with the activity of the parasympathetic nervous system and the activity of the sympathetic and parasympathetic nervous system, respectively. [34], [104] Studies have shown, through this type of analysis, that the parasympathetic tone is higher during sleep than during the awake state, being higher in the NREM phase compared to the REM phase and also showed that there is a small decrease in the sympathetic tone from awake state to NREM phase and an increase during REM phase.[105], [106].

The method chosen for spectral analysis was the power spectral density (PSD) as it provides basic information on how power is distributed as a function of frequency. Standard methods for estimating PSD include Fourier Transform and autoregressive methods (AR) that operate in time series with uniform intervals between samples. Thus, to apply one of these methods to the time series of heart rate, it is necessary that these series be resampled at uniform intervals. This process can attenuate the high frequency components. Furthermore, if there are discontinuities in the series of NN intervals, due to, for example, the presence of ectopic beats and noise, these methods require the discard of these data, which leads to the possibility of introducing bias in the HRV analysis, or the replacement of these data by estimating probably values, which may lead to a change in frequency content. For these reasons, the method chosen to calculate the spectral frequency domain was the Lomb-Periodogram, since it does not require resample or sample replacement. [107]

For the spectral analysis, it was first necessary to extract the heart rate from the ECG signal (methodology already explained in subsection “4.4.2 Electrocardiogram Analysis”). Then, the Lomb-Periodogram method was applied. Using this method, it is possible to calculate the two main frequency components that are associated with autonomic nervous system activity: low frequency, LF (0.04-0.15 Hz), and high frequency, HF (0.15-0.4 Hz). Finally, the power average was calculated for every 5 minutes of the LF component and the HF component. This measurement is usually made in absolute values of power (ms^2) and then transformed into logarithmic values [28], [108] The choice of 5-minute intervals is due to the fact that frequency domain analysis requires stationarity, that is, it requires that the mean and variance of the signal do not change significantly at different stages of recording. In this way the choice of a short period of time tends to satisfy this condition. The ratio of LF/HF was also calculated every 5 minutes as it is often used to assess changes in autonomic function between sleep stages [109]. In Figure 4.4.4 are represented the different variables measured using the frequency domain method: HF, ratio LF/HF and the Lomb-Periodogram of all signal.

A study by Versace et al showed that the mean HR is higher in the REM phase than in the NREM phase. It also showed that the LF is slightly higher in the REM phase compared to the NREM phase, contrary to the HF that is higher in the NREM phase than in the REM phase, however, this latter difference decreases over the cycles [34].

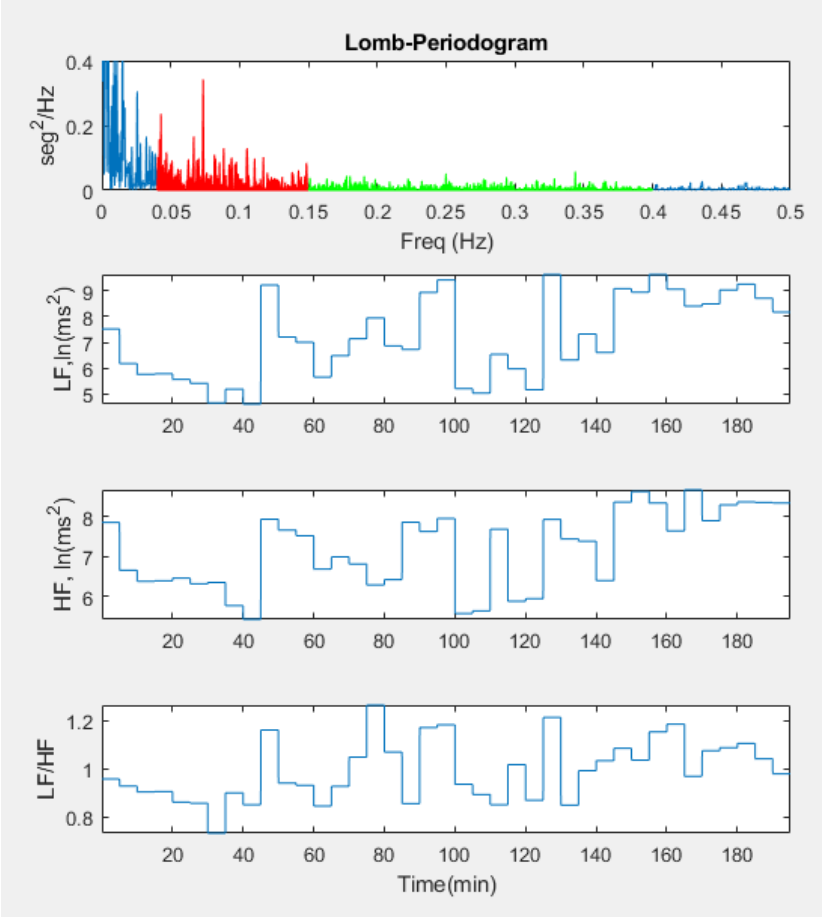


Figure 4.4.4 - Frequency domain variables: LF, HF, ratio LF/HF and the Lomb-Periodogram of all signal. The red colour represents the low frequency and the green one represents the high frequency.

4.4.2.3. Development of Sleep Staging Algorithm based on Frequency and Time Domain Variables of the HRV

To perform a sleep staging based on frequency and time domain variables of the heart rate variability, it was necessary to understand which variables predominate in each phase of sleep.

In early studies it was proposed that the autonomic nervous system has related to the sleep and that sleep stages were related with changes in this system: the REM phase is associated with an increase of sympathetic activity and the NREM phase is associated with an progressive increase of parasympathetic activity (from stage 1 to stage 4) [110].

As already described in the subsection “2.4.4 Electrocardiogram”, for the variation of time domain variables, studies showed that the mean NN interval was lower during wake time than during sleep time and was greater during deep sleep than during REM sleep. The SDNN is higher during wake time than during sleep time, and deep sleep has lower values compared to other sleep phases [30]–[33]. For the variation of frequency domain variables, studies showed a higher LF component during the REM phase compared to the NREM phase, and in this last phase the LF component is lower in the deep sleep. The HF component is lower during wake time than during

sleep time, being higher during NREM sleep (light sleep) than during REM sleep. The ratio between low frequency and high frequency is higher during REM sleep than during wake time and is lower during deep sleep [31], [33], [35].

Considering the predominance of different variables in different stages of sleep, an algorithm was developed in MATLAB, based on the method implemented by Kesper et al. [111]. Figure 4.4.5 represents the workflow of the developed algorithm.

Initially, the signal was classified as light sleep since during the night about 50% of sleep is light sleep. Then the frequency domain variables classified sleep phases into Wake/REM/deep sleep. For the HF and LF components, the difference between the maximum value and the minimum value of the respective component was first calculated and divided by 4, since these two components can differentiate the WAKE, REM sleep, light sleep and deep sleep. These values will be called 'a' and 'b', respectively. For the ratio between LF and HF, the difference between the maximum value and the minimum value was calculated and divided by 3, since this ratio can differentiate the WAKE, REM sleep and deep sleep. This value will be called 'c'. Taking this into account, it is considered REM phase if it reunited the following conditions: the HF component has a value superior to the sum between the minimum value of HF component and 50 % of the 'a' value but inferior to the sum between the minimum value of HF component and 70 % of the 'a' value; the LF component is higher than the sum between the minimum value of LF component and 75 % of the 'b' value; and the ratio LF/HF is higher than the sum between the minimum value of the ratio LF/HF and 66 % of the 'c' value. It is considered Deep sleep if: the value of the HF component is higher than the sum between the minimum HF component and 25 % of the 'a' value but inferior to the sum between the minimum HF component and 50 % of the 'a' value; and if the value of the LF component is inferior to the sum between the minimum LF component and 25 % of the 'b' value and if the value of the ratio LF/HF is inferior to the sum between the minimum LF/HF and 33 % of the 'c' value. It is considered Wake if the value of the HF component if inferior to the sum between the minimum HF component and 25 % of the 'a' value; if the value of the LF component is superior to the sum between the minimum LF component and 50 % of the 'b' value and 75 % of the 'b' value, and if the value of the LF/HF ratio is superior to the sum between the minimum LF/HF value and 33 % of the 'c' value and inferior to the sum between the minimum LF/HF value and 66 % of the 'c' value. Then, the segments classified as REM sleep were verified through the NN intervals, since this time domain variable presents large variations of NN intervals during the final period of REM sleep [112]. So, if the REM sleep corresponds to the time when one of the 6 maximum differences between the maximum and the minimum NN interval occurs, then it is considered REM phase, if not it is considered Light Sleep. It was calculated the 6 maximum differences between the maximum and the minimum NN interval because it was considered that during a normal night occur six REM phases – one REM phase per sleep cycle [9]. This variable was also calculated during 5 minutes.

SDNN and mean NN intervals were used to reclassify the light sleep segments in wake time, since the values were very different from one another and because in the literature it is refer that the differences between the sleep phases are more visible in the spectral analysis [113]. So it was considered that during the first 5 minutes, the values would be the basis to consider the signal classification in wake time.

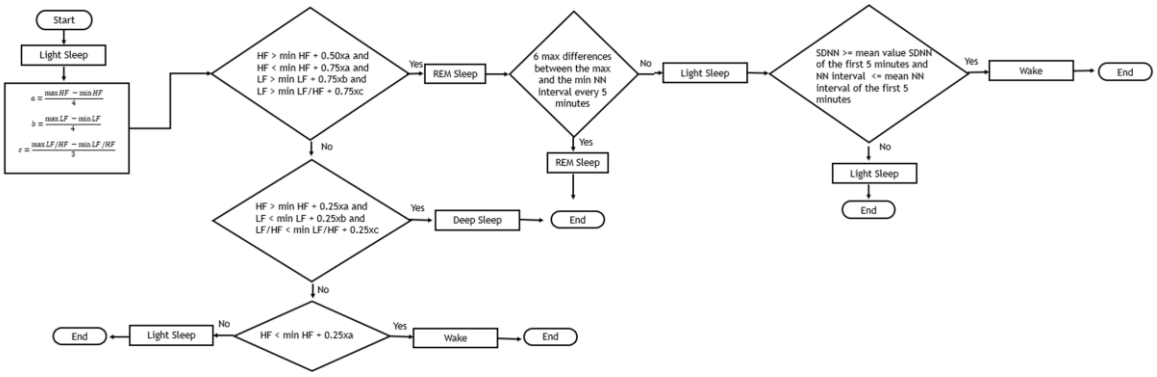


Figure 4.4.5 – Workflow of the developed sleep staging algorithm based on the frequency and time domain variables of the HRV

After the development of the sleep staging algorithm based on frequency and time domain variables of the HRV it was necessary to evaluate it. For that, it was used the PhysioNet Database that provides the NN intervals and the annotations of the respective sleep staging. The algorithm was then evaluated using the NN intervals of two exams provided by PhysioNet, as already mentioned in subsection "4.4.1 PhysioNet Database". The results of sleep staging were compared to the sleep staging annotations of the Database. This evaluation can be seen in Figure 4.4.6.

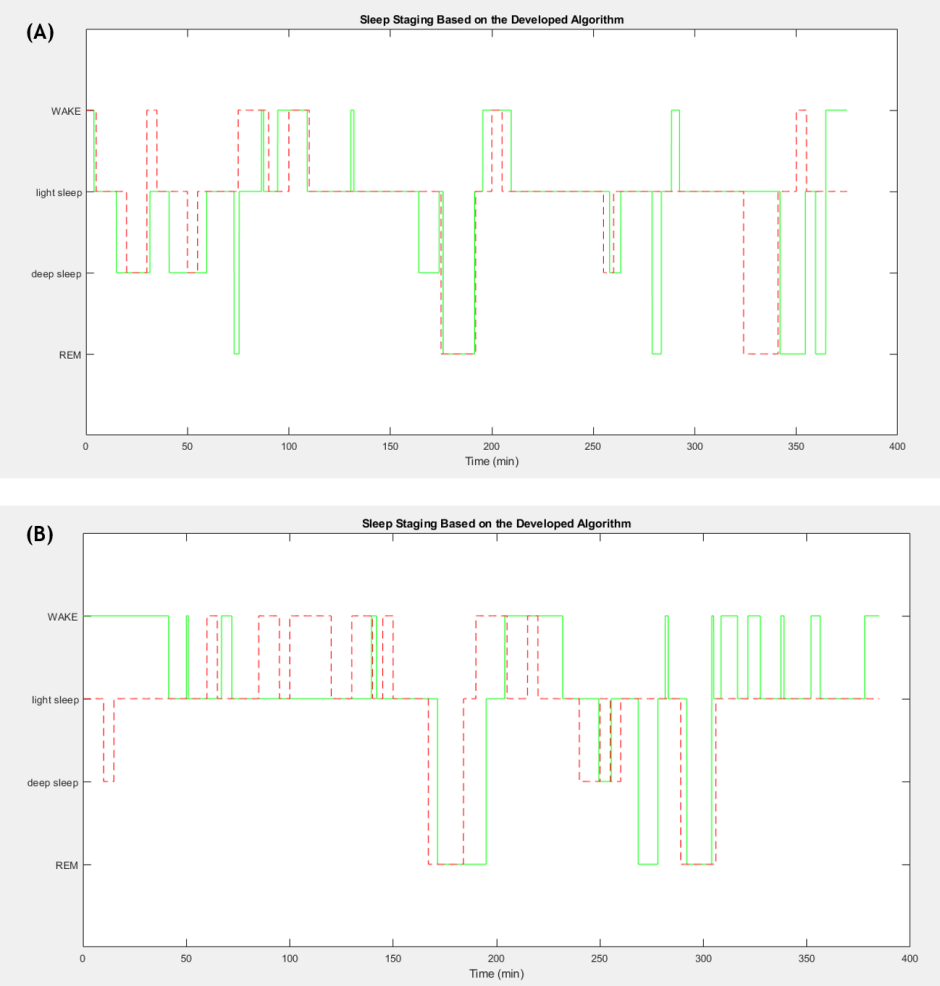


Figure 4.4.6 – Evaluation of the developed sleep staging algorithm. The sleep staging based using the developed algorithm (discontinuous red line) and the sleep staging provided by PhysioNet Database (green line) – (A) Exam 1 and (B) Exam 2.

The sensitivity, specificity and accuracy were calculated for the different phases of sleep of both exams -Table 4.4.1

Table 4.4.1 - Sensitivity, Specificity and Accuracy of the developed algorithm based on ECG variables for sleep staging

		Wake	Light Sleep	Deep Sleep	REM
Exam 1	**Sensitivity (%)**	38,3	88,0	33,7	38,7
	Specificity (%)	92,0	41,3	99,1	94,3
	Accuracy (%)	84,9	67,2	90,3	88,5
Exam 2	**Sensitivity (%)**	6,1	64,2	16,7	54,5
	Specificity (%)	77,1	27,1	95,0	97,2
	Accuracy (%)	57,3	49,0	93,8	92,2

Analyzing the Table 4.4.1 it is possible to observe that the algorithm can easier detect the light sleep and the REM sleep comparatively to wake and deep sleep. Regarding the fact that the algorithm detects light sleep more easily compared to the other variables, it may be because in the implemented methodology it was considered initially that the whole signal is light sleep since light sleep occurs in more than 50% of one night sleep. Regarding the detection of REM phase, the fact that a high variability in heart rate occurs in the final or after the REM, is a good indicator for this phase, however, it is not defined in the literature the exact time of the REM phase when occurs higher variability. The low percentage of wake time sensitivity may be because the time domain variables have a very large range of values, being difficult to define the average of each variable in different phases.

It should be noted that to calculate the spectral analysis, an average of the frequency domain variables was made every 5 minutes. This requires that each phase has at least 5 minutes, and analyzing the signals provided by PhysioNet Database, it is verified that there are phases with a duration shorter than this time.

It should also be referred that after the analysis of the results some readjustments of the variables was made in order to have better results, namely, for the classification of the REM phase using the variable NN intervals, since, as it was already mentioned, it is not defined the exact time of the REM phase when occurs higher variability.

4.4.3. Electrooculogram Analysis

The EOG signal has a range of frequency between 0.1 Hz to 20 Hz and a range of amplitude between 50 μV to 3500 μV [25]. As already described in subsection “2.4.2 Electrooculogram”, rapid eye movements (> 0.6 Hz) are present during wakefulness and REM phase and are characterized by being irregular, with sharp edges and with an initial deflection of less than 500 milliseconds and slow eye movements (0.25 Hz - 0.6 Hz) are present in N1 phase [23] and are characterized by being regular, with sinusoidal contours and with an initial deflection greater than 500 milliseconds [22].

Considering the characteristics of rapid eye movements and slow eye movements, the frequency of eye movement and the duration of the sharpest slope of peaks were extracted from the EOG signal and used to design the sleep staging algorithm that will be described in the next sub-subsection.

Initially, the EOG signal was preprocessed through a low pass filter with a cut-off frequency of 15 Hz to eliminate high-frequency and through a high pass filter with a cutoff frequency of 0.3 Hz to eliminate low-frequency noise from the amplified signal [114]. In Figure 4.4.7 is represented the EOG signal without and with pre-processing.

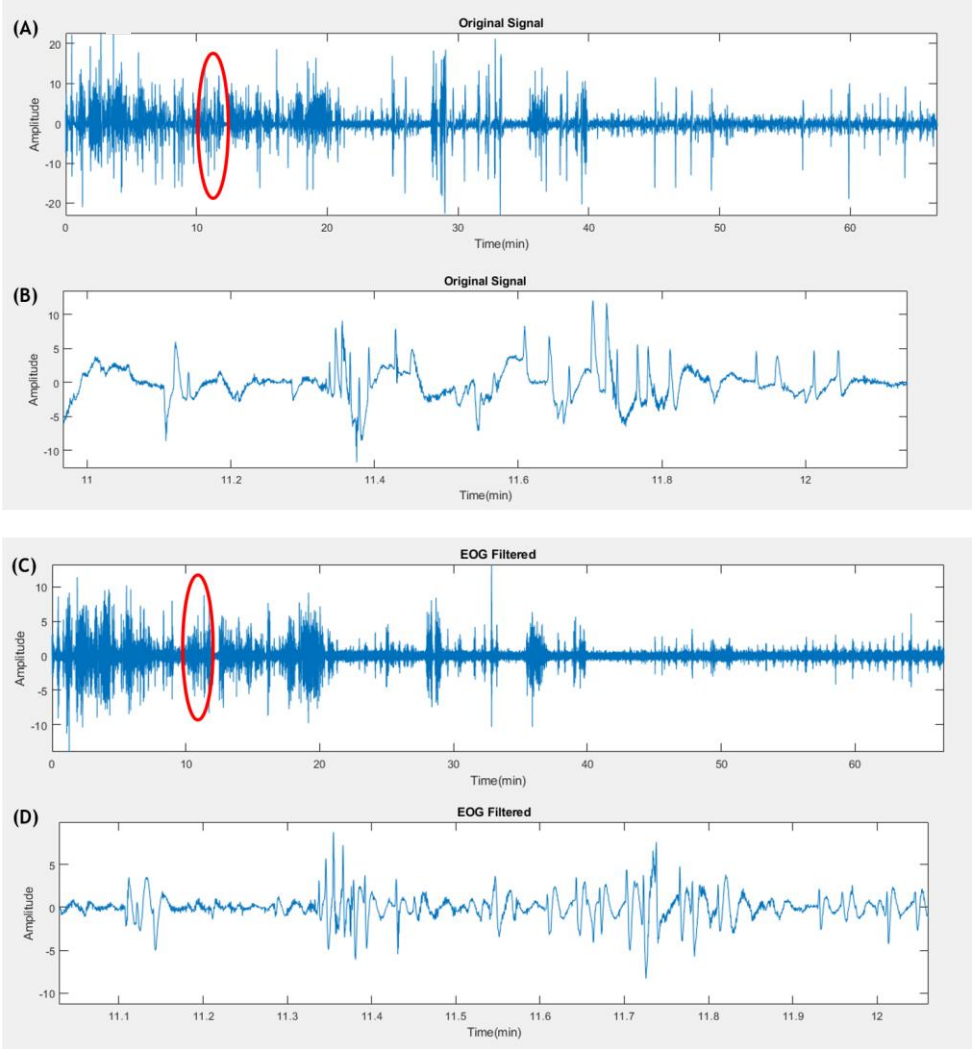


Figure 4.4.7 - (A) Example of one EOG signal extracted from the Physionet Database without pre-processing (original signal) and (B) one segment of the EOG without pre-processing. (C) EOG signal pre-processed (signal filtered) and (D) one segment of EOG signal with pre-processing.

To calculate the duration of the sharpest slope of the peaks, it was necessary to detect the maximum peaks of the signal and to subtract by the closest zero. The mean sharpest slope duration was then calculated in periods of 1 minute [115]. The maximum peaks were detected using the *findpeaks* function. In this function it was define that the maximum peaks must have an amplitude superior to 0.05 mV and a distance to each other more than 5 seconds, according to the maximum duration of SEM. The frequency of eye movement was calculated in periods of 1 minute [115], using the Fourier Transform. In Figure 4.4.8 it is possible to observe the detection of the maximum peaks, the mean sharpest slope duration and the frequency of the movements of the eyes both in periods of 1 minute.

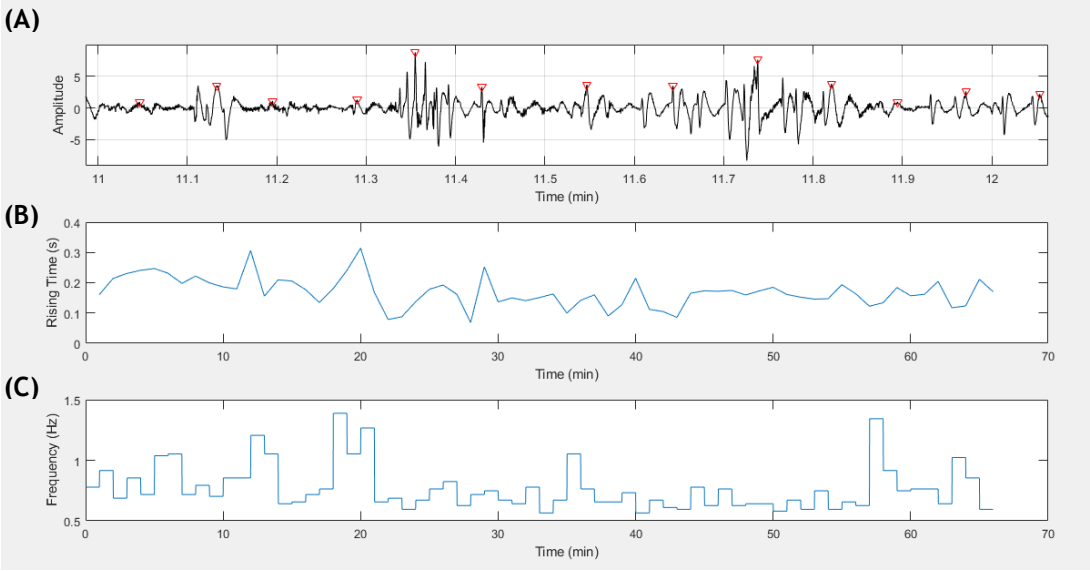


Figure 4.4.8 - (A) Example of the detection of the maximum peaks in a segment of the EOG signal, the maximum peaks are represented with a red triangle. (B) The mean sharpest slope duration in periods of 1 minute and (C) the frequency of the movements of the eyes also in periods of 1 minute.

4.4.3.1. Development of Sleep Staging Algorithm based on EOG variables

With the two variables describe above, according to the literature it is possible to differentiate wake/REM sleep from NREM sleep, since NREM phase is characterized to do not have any ocular movements, except for phase 1 of NREM (light sleep), which is characterized by slow eyes movements: the frequency of the slow eyes movements is between 0.25 Hz and 0.6 Hz and the sharpest slope of each movement has a duration more than 500 ms [101]. Wake and REM phase are characterized with a frequency of eye movements higher than 0.6 Hz and the sharpest slope of each movement has a duration less than 500 ms [22]. Figure 4.4.9 represents the workflow for the development of this sleep staging algorithm.

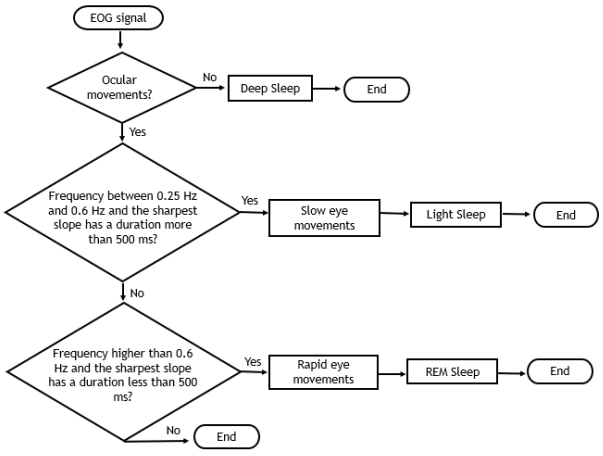


Figure 4.4.9 – Workflow of the sleep staging algorithm based on the EOG variables

For the evaluation of this algorithm, the EOG signal from both exams were extracted from the PhysioNet Database. It is important to refer that they only provide 1 hour of EOG signal record.

In Figure 4.4.10 it is represented the evaluation of the sleep staging algorithm based on the two variables of the EOG signal for the Exam 1(A) and for the Exam 2 (B).

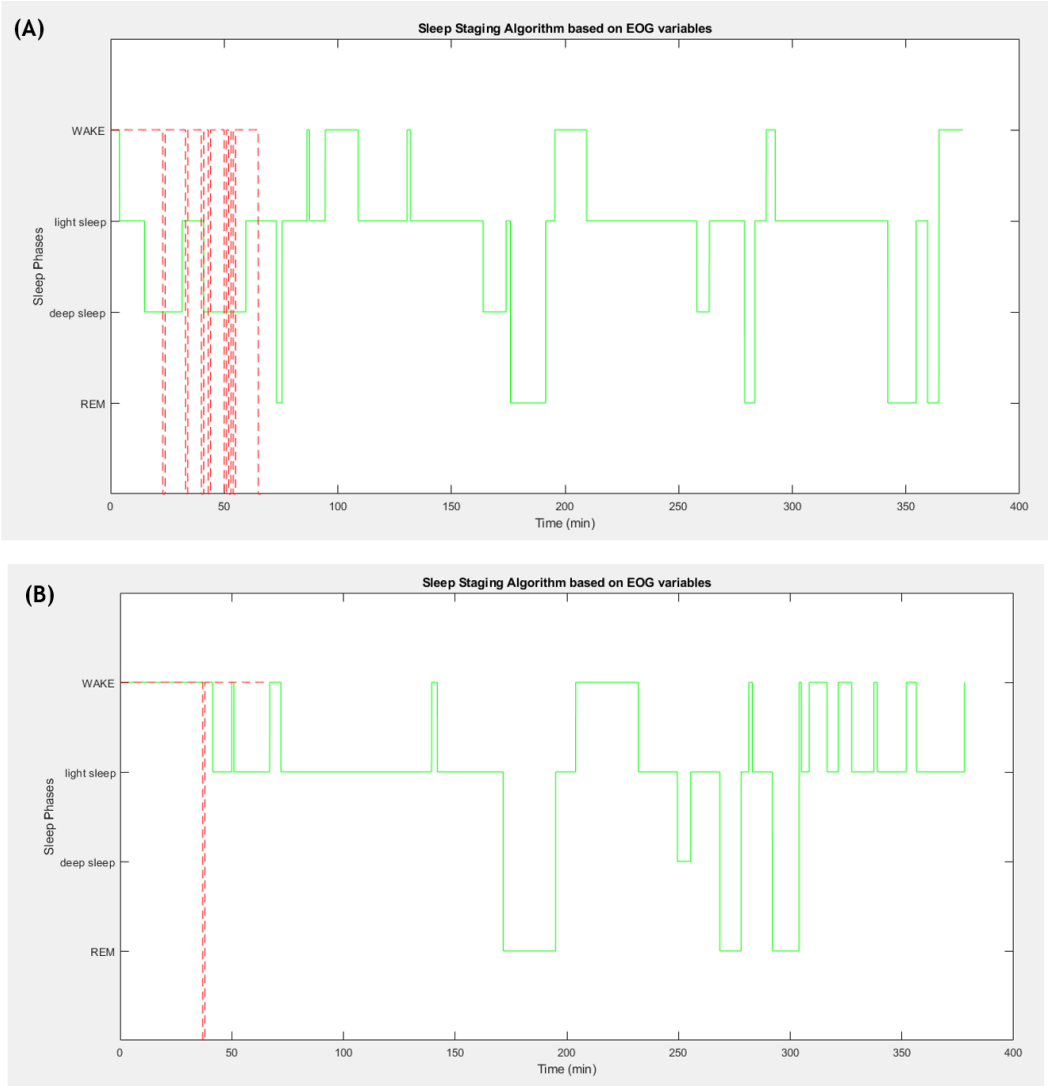


Figure 4.4.10 – Evaluation of the sleep staging algorithm based on the frequency of eye movements and based on the duration of the sharpest slope, using the Exam 1 (A) and Exam 2 (B) provide from PhysioNet Database. The sleep staging based on the developed algorithm is represented with a discontinuous red line and the sleep staging provided by PhysioNet Database is represented with a continuous green line.

Analysing the Figure 4.4.10 it is possible to observe that the developed algorithm does not have good results compared to the sleep staging provided by PhysioNet Database. A possible reason for this is because the determination of the duration of the sharpest slope is not very rigorous, since for this calculation, the maximum peak of the ocular movements is subtracted from the nearest zero. Due to that, in the algorithm it will not be considered this characteristic of the EOG signal and it only be considered the frequency of eye movement. The Figure 4.4.11 represents the evaluation of the new sleep staging algorithm based only on the frequency of eye movement for the Exam 1(A) and for the Exam 2 (B).

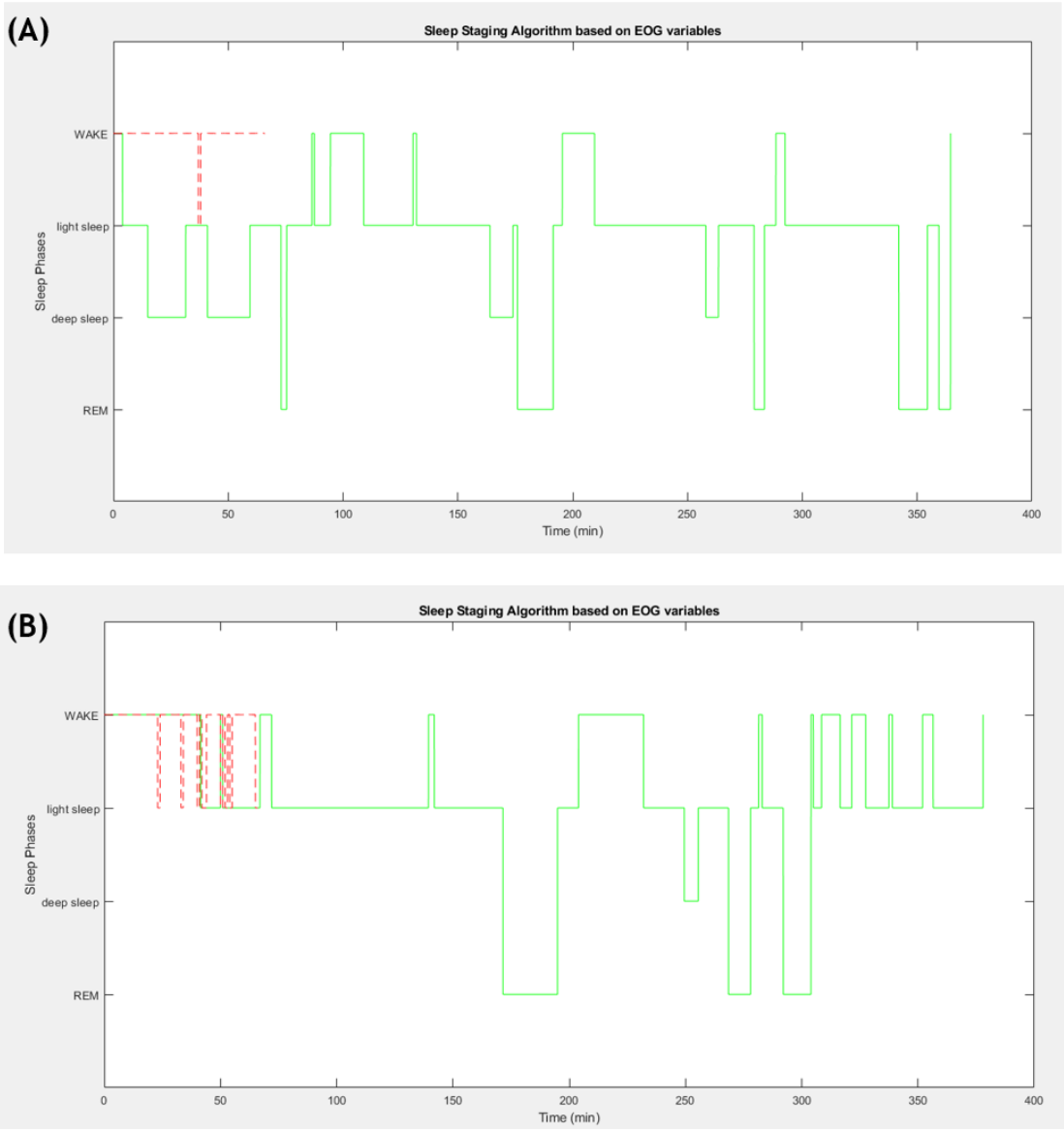


Figure 4.4.11 - Evaluation of the sleep staging algorithm only based on the frequency of eye movements, using the Exam 1 (A) and Exam 2 (B) provide from PhysioNet Database. The sleep staging based on the developed algorithm is represented with a discontinuous red line and the sleep staging provided by Physio-Net Database is represented with a continuous green line.

The sensitivity, specificity and accuracy were calculated for the different phases of sleep for both exams -Table 4.4.2

Table 4.4.2 - Sensitivity, Specificity and Accuracy of the developed algorithm based on the EOG variables for sleep staging

		Wake/REM	Light Sleep	Deep Sleep
Exam 1	**Sensitivity (%)**	100	3,7	0
	Specificity (%)	52,0	100	100
	Accuracy (%)	63,8	60,7	47,0
Exam 2	**Sensitivity (%)**	90,6	21,3	0
	Specificity (%)	78,1	90,6	100
	Accuracy (%)	82,3	65,9	100

Analyzing the Table 4.4.2 and the Figure 4.3.11 it is possible to verify that the developed sleep staging algorithm detect mostly the Wake phase. Although the literature reports that the frequency of rapid eye movements is greater than 0.6 Hz and the frequency of slow eye movement ranges from 0.25 Hz to 0.6 Hz [26], [106] , it is possible to verify that the sleep staging by taking into account these values are not in agreement with the sleep staging provided by the PhysioNet Database. In this way, it was made a readjustment and it was considered that the frequency of slow eye movements ranges from 0.25 Hz to 0.62 Hz and the frequency of rapid eye movements is greater than 0.62 Hz. So, the frequency of eye movement is a characteristic that should be further studied.

To make this algorithm more accurate, a possible solution would be the evaluating of other characteristics of the signal, such as the determination of the curvature time of REM waves and slow eyes movements (SEM) waves, since one of the characteristics that distinguishes them is the fact that the REM waves have contours pointed and SEM waves have sinusoidal contours.

4.4.4. Development of Sleep Staging Algorithm based on Electrocardiogram Variables and Electrooculogram Variables

To understand if the combination between ECG variables – frequency and time domain variables of the HRV - and the EOG variable – frequency of eye movements - provide better accuracy than the last two sleep staging algorithm described in the previous sub-subsections, an algorithm was developed based on these variables. In Figure 4.4.12 it is represented the workflow of the algorithm developed.

For the development of this algorithm, it was first considered the sleep staging based on the algorithm developed in the sub-subsection "4.4.2.3 Development of Sleep Staging Algorithm based on Frequency and Time Domain Variables of the HRV". For segments that were staged as light sleep, if the algorithm developed based on the frequency of eye movement detected that segment as wake, then it would be considered wake.

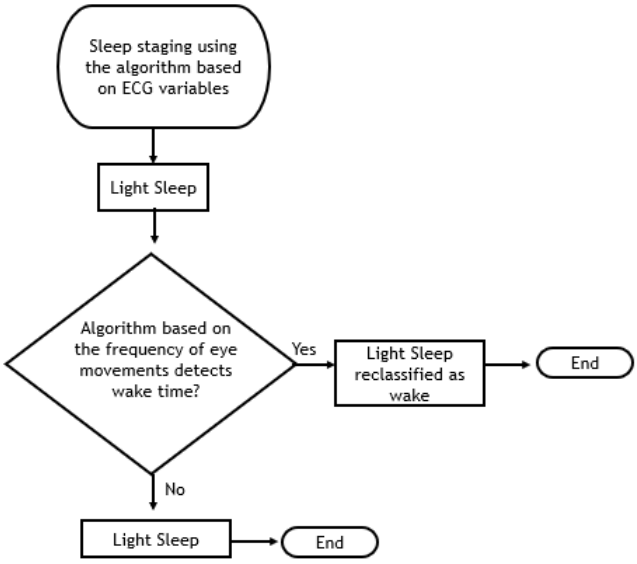


Figure 4.4.12 – Workflow based on the combination between the ECG variables and the EOG variable

In Figure 4.3.13 it is possible to observe the evaluation of sleep staging algorithm for the Exams 1 (A) and 2 (B) provided by PhysioNet Database. The sensitivity, specificity and accuracy were calculated for the different phases of sleep of both exams -Table 4.4.3

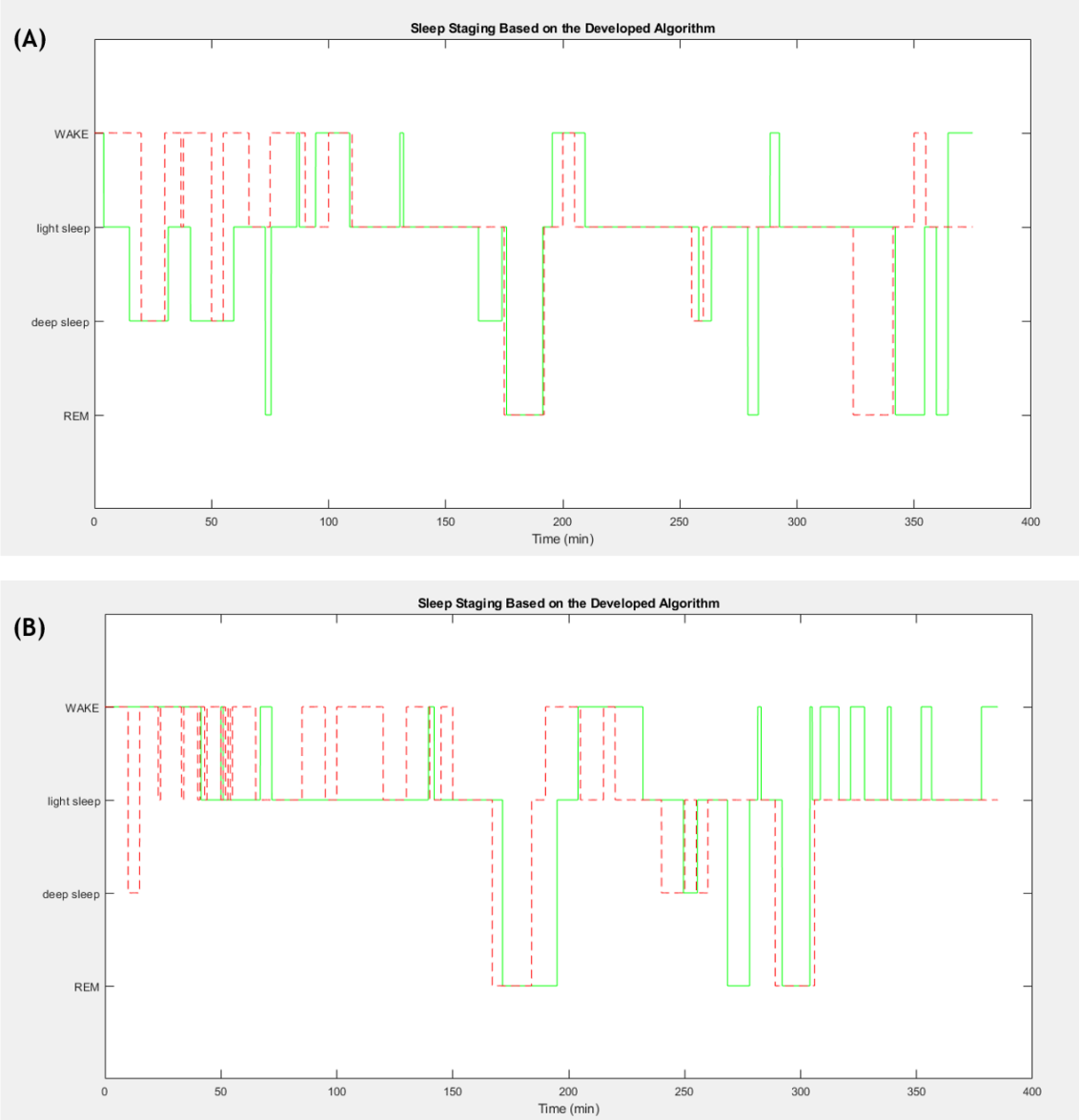


Figure 4.4.13 - (A) Evaluation of sleep staging algorithm using the Exam 1 and (B) of the Exam 2 provide by Physionet Database. The sleep staging based on the developed algorithm is represented with a discontinuous red line and the sleep staging provided by PhysioNet Database is represented with a continuous green line.

Table 4.4.3 - Sensitivity, Specificity and Accuracy of the developed algorithm for sleep staging

		Wake	Light Sleep	Deep Sleep	REM
Exam 1	Sensitivity (%)	45,3	73,4	33,7	38,8
	Specificity (%)	80,1	54,6	99,1	94,5
	Accuracy (%)	74,2	66,4	90,2	88,5
Exam 2	Sensitivity (%)	38,0	57,8	16,7	54,5
	Specificity (%)	71,9	48,6	94,9	97,2
	Accuracy (%)	62,2	53,9	93,8	92,2

Comparing the results of the algorithm developed based on the variables extracted from the ECG signal and the variable extracted from the EOG signal, with the results of the other two algorithms developed it is possible to observe that the sensitivity of the wake phase is better when the EOG variable is added. This shows the importance of monitor EOG signal.

It is important to mention that, during the development of the algorithms, some changes were made to improve the accuracy. Since the dataset is small, doing readjustments in the algorithms can influence the results. A larger dataset would be needed for a better evaluation of the algorithms.

4.4.5. Skin Temperature: Development of Wake/Sleep Staging Algorithm

As already mentioned above, the temperature is a variable that is not included in the PhysioNet database. In this way, it was not possible to evaluate it. However, the monitoring of this parameter is important because allows to know when the sleep onset occurs, since the skin temperature increases, and when the wake time occurs, the skin temperature decreases [48], [50].

To analyze the temperature signal it was necessary to make a signal acquisition using Vital Sleep prototype. This acquisition was done under normal ambient temperature conditions and during 200 minutes. After 195 minutes the person was awaked by an alarm. Then, the temperature data was extracted from the VJ Holter Reader software from Biodevices, S. A. The temperature is monitored each 1 minute – condition of Biodevices, S.A.

Based on the literature [48], [50] it is possible to know when the sleep onset occurred and when the wake time occurred. Figure 4.4.14 represents a workflow for the developed algorithm based on temperature.

The sleep onset occurred when the temperature reaches its maximum, so for that it was necessary to determine the time when the maximum temperature occurred. Relatively to the moments when wake time occurred, it is known that when it happens the temperature decrease, although in the literature it is not stated how much the temperature decreases. Therefore, it was considered that the wake time occurred when the minimum temperature occurred.

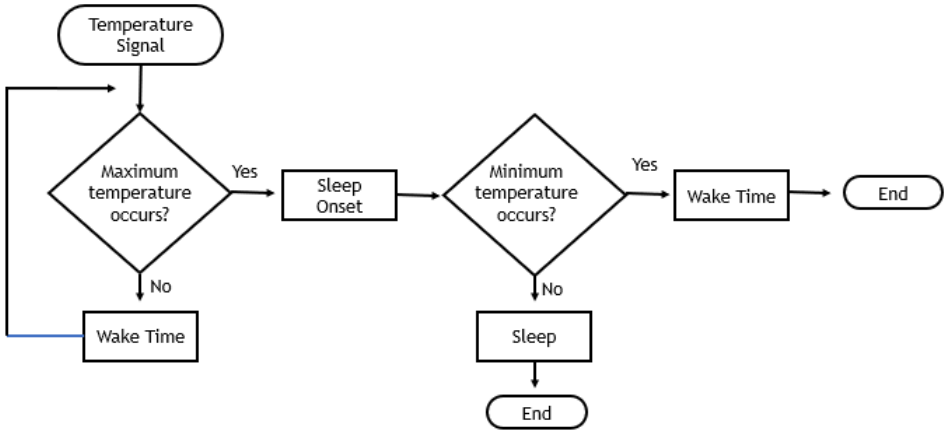


Figure 4.4.14 – Workflow of the development of the algorithm based on temperature.

In Figure 4.4.15 (A) it is possible to observe the variation of the temperature in a sleep recording using VitalSleep prototype and in Figure 4.4.15 (B) it is possible to observe the sleep staging – sleep onset and wake time – based on the temperature variations.

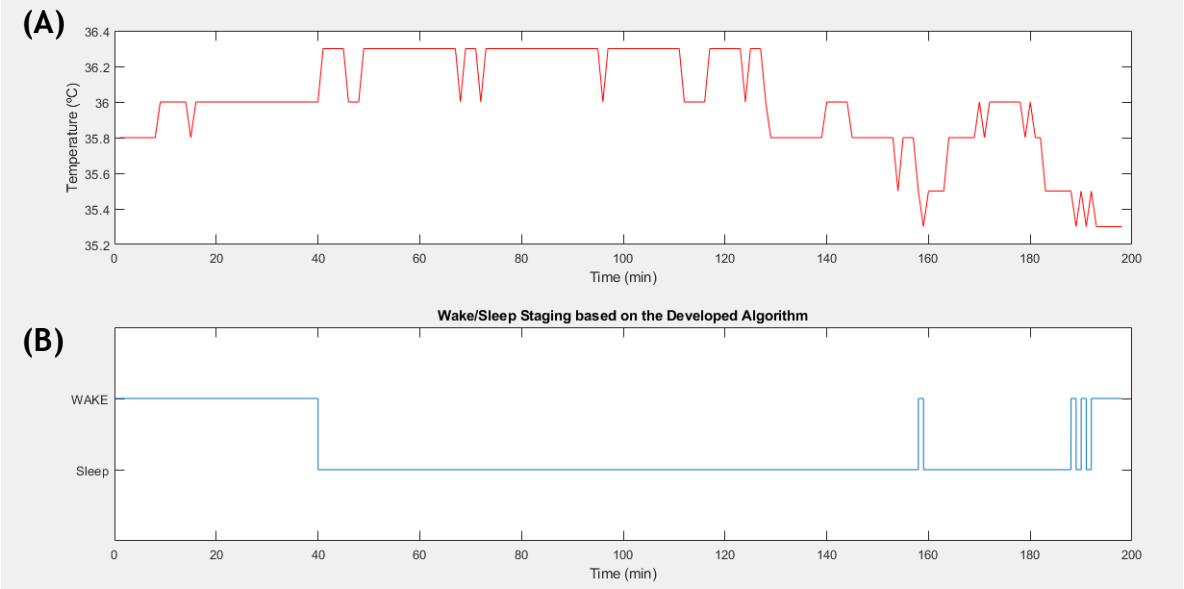


Figure 4.4.15 - (A) Variation of the temperature during a sleep recording using VitalSleep prototype and (B) sleep staging based on that variation.

Analyzing the Figure 4.4.15 it is possible to verify that the sleep onset starts around the minute 41, which corresponds to the first maximum, and wake time occurs in the last minutes of recording which corresponds to the minimum values. The person who was subjected to this monitoring reported that took some time to fall asleep, which may justify the 41 minutes to fall asleep. Relatively to the time when wake occurs, it is possible to observe that it corresponds near the minute 195, when the alarm clocked. However, with this algorithm it is not possible to ensure that do not occurred more wake times, since it was only considered the time of the minimum temperature.

Without a database to evaluate this algorithm, more acquisitions must be made. It is also be enhance that the skin temperature depends on the temperature that the body receives, for example, through the clothing of the body. So, this variable must also be considered.

4.4.6. Accelerometer: Development of Wake/Sleep Staging Algorithm

As noted for temperature, accelerometer monitoring is also not covered in the PhysioNet Database, so it is not possible to evaluate the algorithm. However the movements of the body is a good indicator to detect wake time, since there are more movements in this phase [108].

To analyze the actigraphy signal it was necessary to make a signal acquisition using Vital Sleep prototype. This acquisition was done at the same time when the temperature was acquired, so was done under normal ambient temperature conditions and for 200 minutes. After 195 minutes, the person was awaked by an alarm. Then, the actigraphy data was extracted from the VJ Holter Reader software from Biodevices, S. A.

After that, and based on a study made by Hayano et al., [108] it was necessary to extract the values on the x, y and z axis as well as the time when these values occurred. The magnitude of the movement was calculated through the root of the values on the x, y, and z axis squared. At each 3 minutes the difference between maximum value and minimum value was calculated, then all differences that were greater than 1 were considered wake time, since this phase is characterized by more movement. [108] In Figure 4.4.16 it is represented the workflow of the algorithm developed for wake/sleep staging based on actigraphy data.

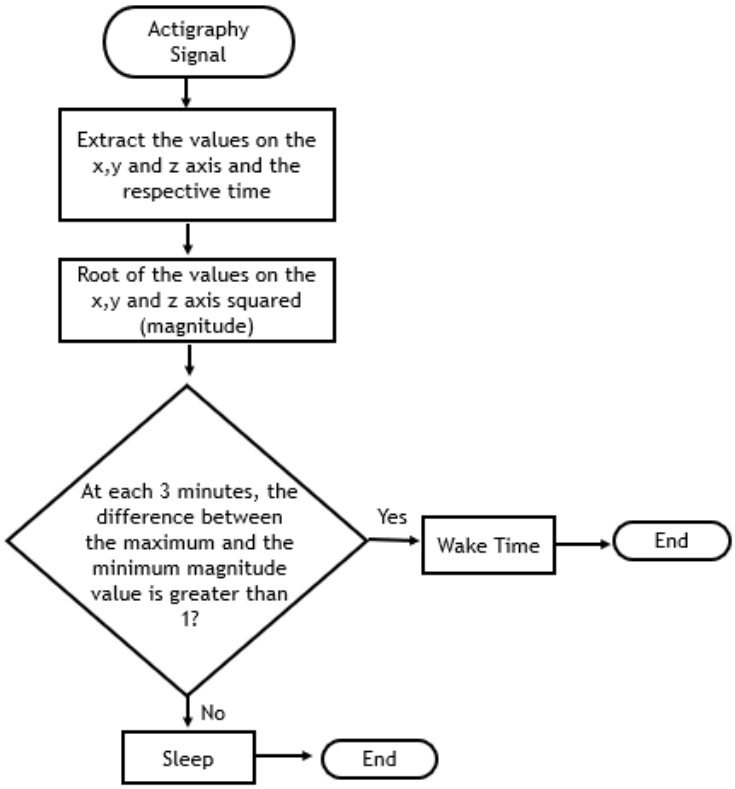


Figure 4.4.16 – Workflow of the developed algorithm for wake/sleep staging based on actigraphy data

In Figure 4.4.17 (A) it is possible to observe the variation of the magnitude of body movements and (B) the wake/sleep staging based on that variation.

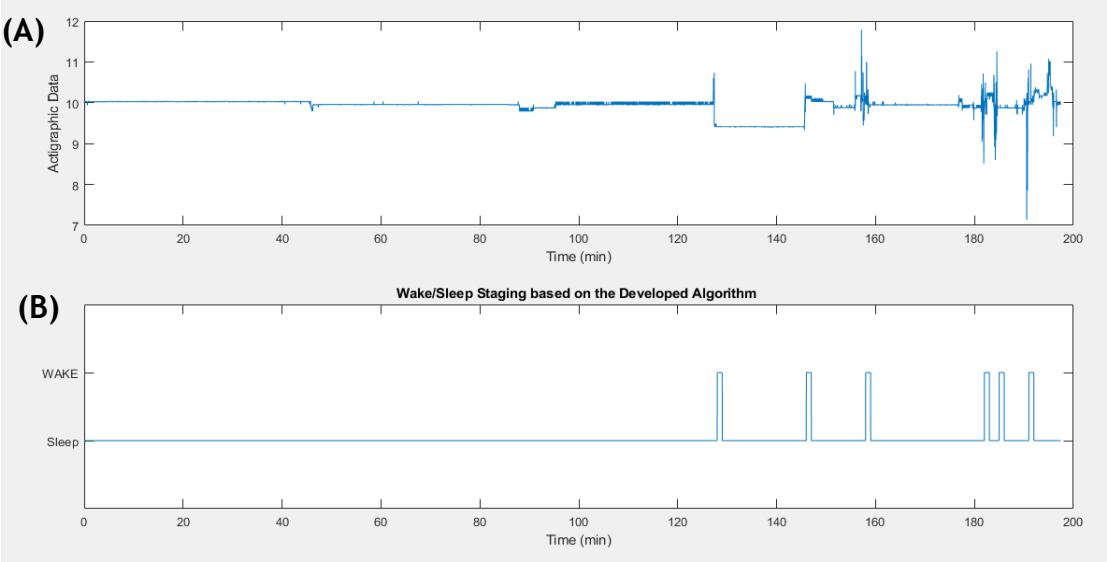


Figure 4.4.17 - (A) Variation of the magnitude of body movements and (B) wake/sleep staging based on that variation.

Analyzing the Figure 4.4.17 it is possible to verify that wake time corresponds to a higher movement. However, it is not possible to know if wake/sleep staging is correct, since PhysioNet Database does not provide this type of signal. An alternative to this evaluation would be to compare the accelerometer data while sleeping, in a resting position, during a walking and during a running. In this way, it would be possible to compare variations of body movements.

In the following section will be shown the result of sleep staging using the VitalSleep prototype for the sleep recording based on the combination on the 4 variables – ECG, EOG, temperature and actigraphy.

4.5. VitalSleep Prototype: Sleep Recording

For sleep staging using the VitalSleep prototype - it is first necessary to place the electrodes for EOG and ECG monitoring - Figure 4.5.1

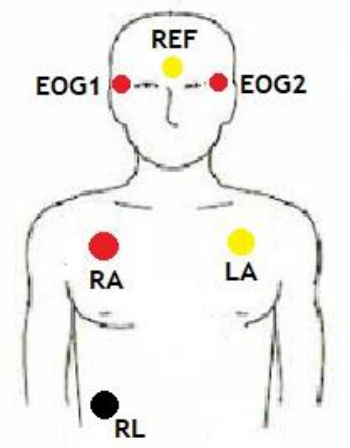


Figure 4.5.1 - Placement of EOG electrodes and ECG electrodes. REF – Reference EOG electrode, EOG1 and EOG2 – EOG electrodes, RA – Right Arm, LA – Left Arm, RL – Right Leg.

The acquisition of the sleep recording was made for 200 minutes, under normal conditions of temperature. The monitored subject does not have sleep disorders and was awaked when the alarm clocked, at the minute 195.

The prototype has the possibility of incorporating an SD card. The monitoring can be viewed in real time by sending data via Bluetooth to the ECG tool, a software from Biodevices S. A. Data can be recorded and viewed later through VJ Holter 2, a software also from Biodevices S. A. This data is finally extracted and analyzed in MATLAB. In Figure 4.5.2 it is possible to observe the signals recorded during this monitorization.

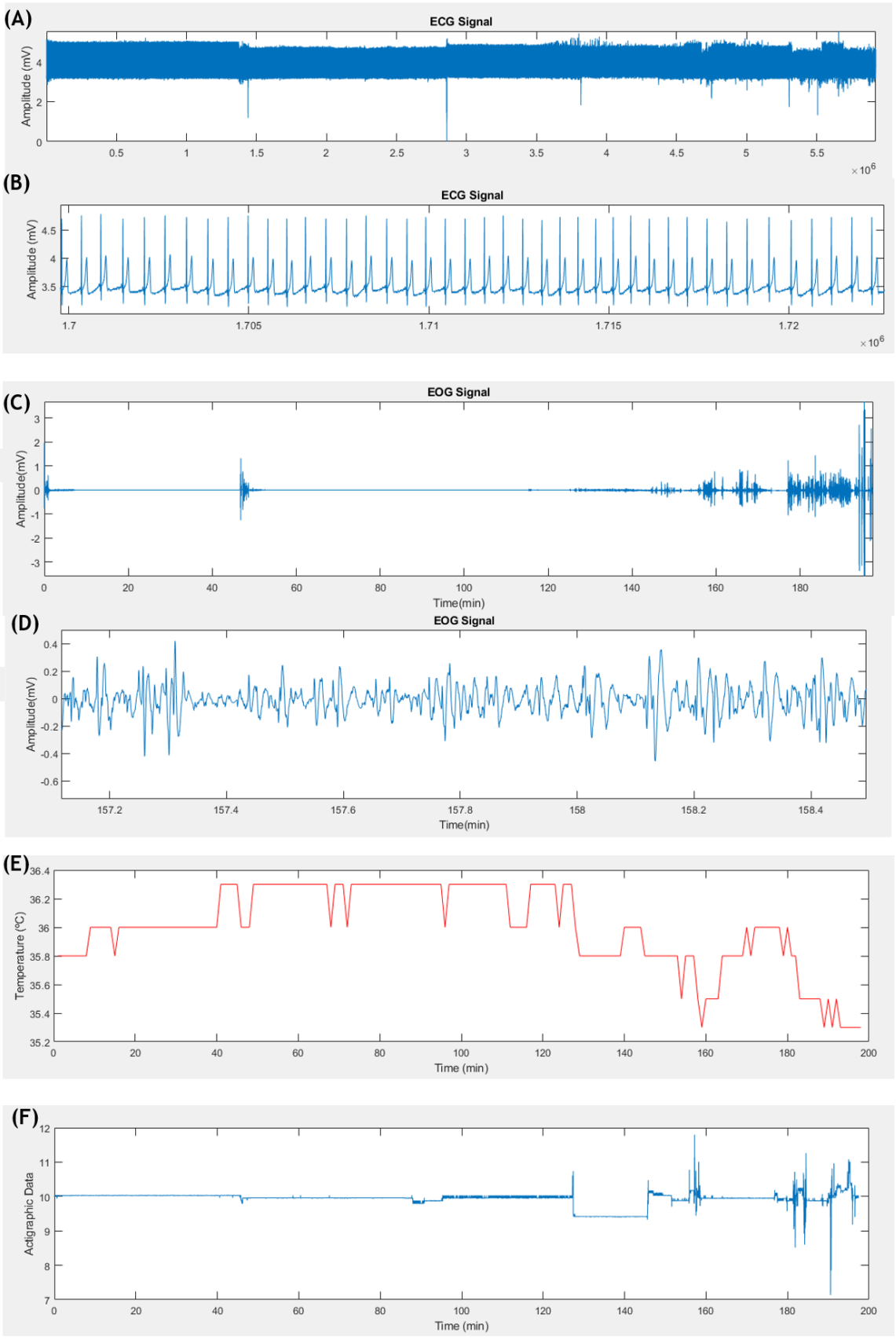


Figure 4.5.2 – Signals recorded during sleep using VitalSleep prototype. (A) ECG signal, (B) segment of ECG signal, (C) EOG signal, (D) segment of EOG signal, (E) temperature signal and (F) actigraphy signal.

For the sleeping stage it was developed an algorithm based on the algorithms already developed – the algorithm that combines the ECG and the EOG variables, the algorithm based on the actigraphy signal and the algorithm based on the temperature variations. In Figure 4.5.3 it is possible to observe the workflow used to design the algorithm.

So, first it was used the algorithm based on the combination of ECG and EOG variables to stage the sleep in Wake, REM sleep, light sleep and deep sleep. Since both algorithms based on the temperature variations and actigraphy data only can differentiate sleep and wake time, if the segments that were classified in light sleep (using the combination algorithm between ECG and EOG variables) corresponds to a wake time in the algorithm based on the temperature or based on the actigraphy, then the segment was reclassified as wake.

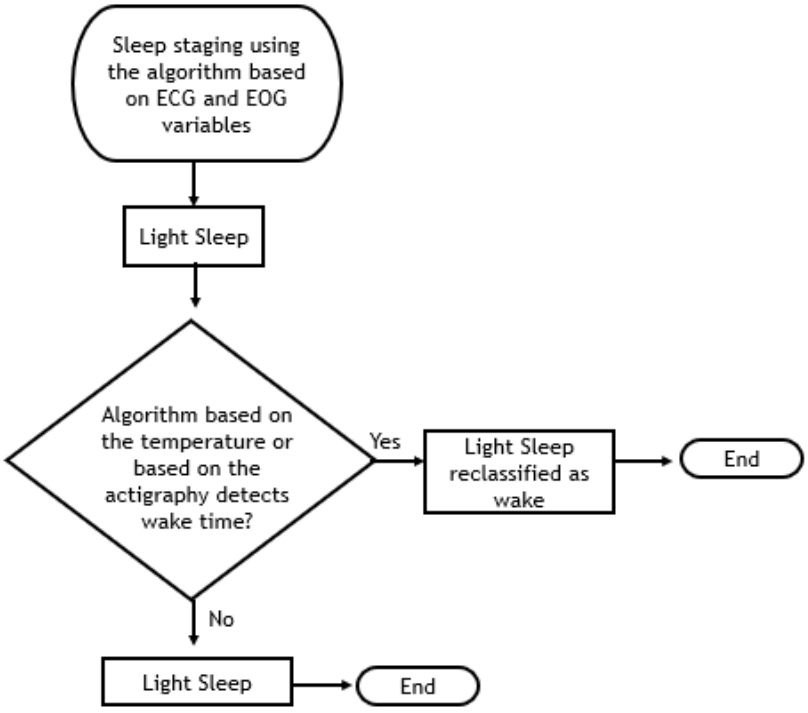


Figure 4.5.3 – Developed sleep staging algorithm based on the 4 signals: ECG, EOG, temperature and actigraphy.

In Figure 4.5.4 it is possible to observe the sleep staging based on the developed algorithm.

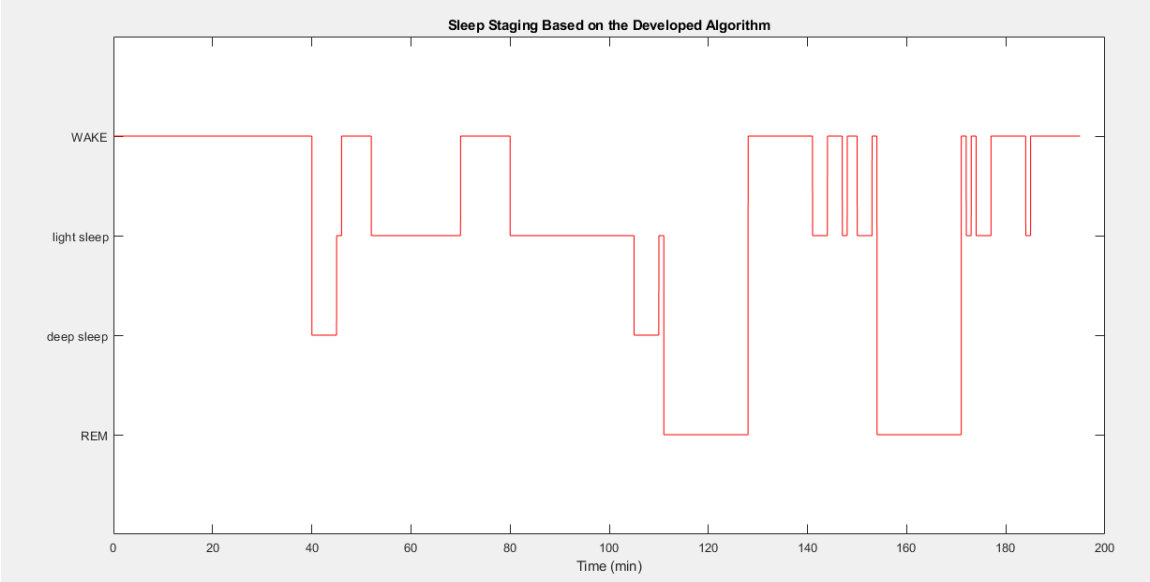


Figure 4.5.4 - Sleep staging based on the developed algorithm.

Although it is not possible to rigorously compare these results with the results of a known correct sleep staging, it is possible to analyze the results in a more general way, comparing them with an Exam provide by PhisioNet Database - Figure 4.5.5.

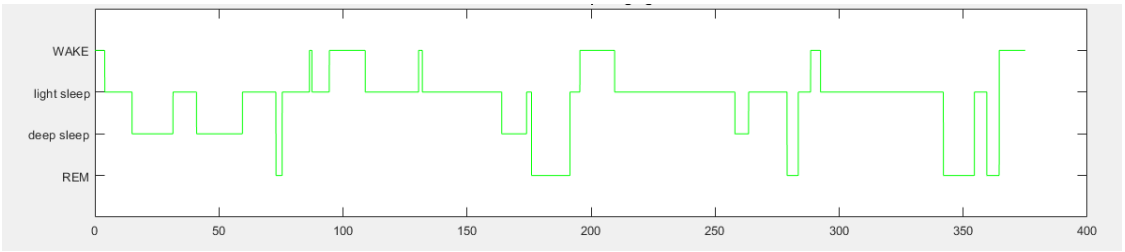


Figure 4.5.5 – Exam of a subject without sleep disorders provided by PhysioNet Database.

This comparation is possible due to the fact that both exams were recorded from subjects without sleep disorders and despite variations in the sequences of a hypnogram, it is possible to describe a normal night's sleep: N1 phase occurs (light sleep) in the first moment of sleep, then the sleep becomes deeper and deeper, passing through phase N2 (light sleep) to phase N3 (deep sleep). The first episode of deep sleep is long, between 20 to 60 minutes. Then, sleep progresses to a lighter sleep state (phases N2 and N1) and may occurs a transient wakefulness period before the first REM stage, which appears about 90 minutes after the onset, and lasts between 1 and 5 minutes. Thus, ends the first cycle of sleep. It should be noted that the REM phase increase throughout the night, contrary to deep sleep. In addition, the periods of vigilance of short duration are very frequent at the end of the night [9].

Taking into account the variation of sleep during a normal night's sleep, and comparing the sleeping recording using VitalSleep prototype and the Exam provide by PhysioNet Database, it is possible to verify that, despite the first phase after the wake time, is the deep sleep when it should be light sleep, the first REM phase occurs about 90 minutes after sleep onset and lasts

about 10 minutes, and the second REM phase has a longer duration. In addition, before REM phases it is possible to see a progression from deep sleep to lighter sleep. The short-term waking periods at the end of sleep are also characteristic in a normal hypnogram.

Although it is not possible to rigorously evaluate the accuracy of results, similarities to a standard night sleep hypnogram are observed. However, it is necessary to use more data to evaluate the results, since only one exam is not enough, it is necessary to monitoring the sleep using VitalSleep prototype for different persons and with a medical label. The lack of time to do more exams was due to the time dispending in the development of the hardware and signal processing.

Chapter 5

Conclusions and Future Work

Sleep has a major importance in the mental and physical recovery of the body. However, sleep disorders are often underestimated.

Wearable devices appear as an alternative to the standard exam to monitor sleep – polysomnography. These devices can perform a continuously monitoring of physiological parameters, at user's home, without the need of a specialist and are less expensive.

This Master Thesis showed that although there are some commercial devices that allow ambulatory sleep monitoring, is an area that still must grow. The objective of this dissertation was to contribute on this field of studies, by developing a prototype of a wearable system for sleep monitoring – VitalSleep - that could measure electrooculogram, oxygen saturation, electrocardiogram, temperature and body movements. These last three already acquired by VitalJacket®. The prototype hardware was developed with all variables mentioned above, except with the oxygen saturation due to hardware problems and lack of time. Efforts were posteriorly made to make possible the incorporation of the oxygen saturation sensor, namely, to have the values of the TX root and RX root of the AFE4400 power supply inside the range of expected values of the power management circuit. The implementation of the oxygen saturation sensor in the forehead and in the ear should further be tested considering that the use of this sensor in the forehead may be more comfortable to the user due to the presence of less cable apparatus. Furthermore, as mentioned in the subsection "4.2.6 Wearable Prototype Assembly" some problems in the acquisition of the EOG signal are probably due to the unstable incorporation of the cables to the PCB therefore it is important to improve the incorporation of EOG electrode cables. Considering these alterations, the next steps for the improvement of the hardware are the production, assembly, test and validation of the new developed board prototype.

The development of the VitalSleep prototype was not only focused on the hardware but also in the analysis of the signals acquired and the development and evaluation of the sleeping stage algorithms. Regarding this latter, it was used simple methods to monitor the sleep, although it would be interesting to analyse other characteristics of the EOG signal, such as the time curvature of the REM and SEM waves, and the differences of the LF and HF component

during the last cycles of one night of sleep. Additionally, for the algorithm based on the ECG and EOG variables it is necessary to evaluate them using more data, since the PhysioNet Database only provide two exams without any sleep disorders. For the algorithms based on the temperature and on the actigraphy data, it is necessary to evaluate them with a specialist.

Finally, it is also necessary to acquire more sleep recordings of different people using the VitalSleep prototype and evaluate the sleeping stage algorithm with a sleeping stage made by a specialist.

References

[1] S. Oh, H. Kwon, and V. K. Varadan, “Wireless Remote Monitoring System for Sleep Apnea,” *Nanosensors, Biosensors, Info-Tech Sensors Syst. 2011*, vol. 7980, pp. 1–10, 2011.

[2] A. Roebuck, V. Monasterio, E. Gedei, M. Osipov, J. Behar, A. Malhotra, T. Penzel, and G. Clifford, “A review of signals used in sleep analysis,” *Physiol Meas.*, vol. 35, no. 1, pp. 1–73, 2015.

[3] X. F. Teng, C. C. Y. Poon, Y. T. Zhang, and P. Bonato, “Wearable Medical Systems for p-Health,” *IEEE Rev. Biomed. Eng.*, vol. 1, pp. 62–74, 2008.

[4] M. Engin, A. Demirel, E. Z. Engin, and M. Fedakar, “Recent developments and trends in biomedical sensors,” *Meas. J. Int. Meas. Confed.*, vol. 37, no. 2, pp. 173–188, 2005.

[5] J. P. S. Cunha, B. Cunha, A. S. Pereira, W. Xavier, N. Ferreira, and L. Meireles, “Vital-Jacket: A wearable wireless vital signs monitor for patients’ mobility in cardiology and sports,” *Pervasive Comput. Technol. Healthc. (PervasiveHealth), 2010 4th Int. Conf. on-NO Permis.*, pp. 1–2, 2010.

[6] L. Dotto, “Sleep stages, memory and learning.,” *CMAJ*, vol. 154, no. 8, pp. 1193–6, 1996.

[7] L. B. Minor, “Harnessing the Power of Data in Health,” *Stanford Med. Heal. Trends Rep.*, no. June, 2017.

[8] M. Richard B. Berry, MD; Rita Brooks, MEd, RST, RPSGT; Charlene E. Gamaldo and M. C. L. M. Susan M. Harding, MD; Robin M. Lloyd, “American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events : Rules, Terminology, and Technical Specifications, Version 2.2,” *Am. Acad. Sleep*, vol. 28, no. 3, pp. 391–397, 2016.

[9] T. Paiva and T. Penzel, “Características básicas do sono,” in *Centro de Medicina do Sono: Manual Prático*, Lidel., 2011, p. 263.

[10] S. C. Oh, V. K. Varadan, and R. E. Harbaugh, “Wireless Point-Of-Care Health Monitoring Systems for Sleep Disorders,” *Int. J. Nanotecnhology Nanomedicine Res.*, 2017.

[11] T. Paiva and T. Penzel, “Estadiamento do sono - Classificação visual no adulto e na criança,” in *Centro de Medicina do Sono: Manual Prático*, Lidel., 2011, p. 263.

[12] R. W. McCarley, “Neurobiology of REM and NREM sleep,” *Sleep Med.*, vol. 8, no. 4, pp. 302–330, 2007.

[13] C. R. Soldatos, F. A. Allaert, T. Ohta, and D. G. Dikeos, “How do individuals sleep around the world? Results from a single-day survey in ten countries,” *Sleep Med.*, vol. 6, no. 1, pp. 5–13, 2005.

[14] M. J. Sateia, “International classification of sleep disorders-third edition highlights and modifications,” *Chest*, vol. 146, no. 5, pp. 1387–1394, 2014.

[15] R. B. Daroff, *The International Classification of Sleep Disorders: Diagnostic and Coding Manual*. 1991.

[16] C. Kushida, M. Littner, T. Morgenthaler, C. Alessi, D. Bailey, J. Coleman, L. Friedman, M. Hirshokowitz, S. Kapen, M. Kramer, T. Lee-Chiong, D. Louve, J. Owens, J. Pancer, and M. Wise, “Practice parameters for the indications for polysomnography and related procedures: an update for 2005.,” *Sleep*, vol. 28, pp. 499–521, 2005.

[17] S. Walker, S. Holloway, K. Patrick, N. Goatman, S. Jones, B. Niu, B. Turnbough, R. Roashan, and H. Ingram, “IHS Medical Devices & Healthcare IT: A Complete Source of Market Intelligence,” 2014.

[18] R. Ferber, R. Millman, M. Coppola, J. Fleetham, C. F. Murray, C. Iber, V. McCall, G. Nino-Murcia, M. Pressman, and M. Sanders, “Portable recording in the assessment of obstructive sleep apnea,” *Sleep*, vol. 17, no. 4, pp. 378–92, 1994.

[19] P. Tiihonen, M. Sc, T. Hukkanen, and H. Tuomilehto, “Evaluation of a Novel Ambulatory Device for Screening of Sleep Apnea,” *Telemed. e-Health*, vol. 15, no. 3, pp. 283–289, 2009.

[20] E. Estrada, H. Nazeran, J. Barragan, J. R. Burk, E. A. Lucas, and K. Behbehani, “EOG and EMG: Two important switches in automatic sleep stage classification,” *Annu. Int. Conf. IEEE Eng. Med. Biol. - Proc.*, pp. 2458–2461, 2006.

[21] M. H. Bonnet, D. Carley, M. C. Consultant, P. E. Consultant, C. G. Chairman, R. Harper, B. Hayes, M. Hirshkowitz, S. Keenan, M. P. Consultant, T. Roehrs, J. Smith, S. Weber, and P. Westbrook, “EEG Arousals: Scoring Rules and Examples,” *Sleep*, vol. 15, no. 2, pp. 173–184, 1992.

[22] T. Paiva and T. Penzel, “Aspectos técnicos e variáveis de registo,” in *Centro de Medicina do Sono: Manual Prático*, 2011, p. 263.

[23] G. Garcia-Molina, F. Abtahi, and M. Lagares-Lemos, “Automated NREM sleep staging using the Electro-oculogram: A pilot study,” *Proc. Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. EMBS*, pp. 2255–2258, 2012.

[24] A. Banerjee, S. Datta, M. Pal, A. Konar, D. N. Tibarewala, and R. Janarthanan, “Classifying Electrooculogram to Detect Directional Eye Movements,” *Procedia Technol.*, vol. 10, pp. 67–75, 2013.

[25] A. Prasannaraj and R. Dharmalingam, “Integrated EOG based interface to control wireless robot,” *IJAICT*, vol. 1, no. 2, pp. 241–244, 2014.

[26] E. Trull, J. Mize, A. Sadeghian, and M. Sadeghian, “Implementation and use of the electrooculogram in sleep monitoring,” 2015.

[27] T. Penzel, J. W. Kantelhardt, L. Grote, J. Peter, and A. Bunde, “Comparison of Detrended Fluctuation Analysis and Spectral Analysis for Heart Rate Variability in Sleep and Sleep Apnea,” *IEEE Trans. Biomed. Eng.*, vol. 50, no. 10, pp. 1143–1151, 2003.

[28] J. Camm, “Guidelines Heart rate variability,” *Eur. Heart J.*, vol. 17, pp. 354–381, 1996.

[29] H. Jiang, J. Li, H. Feng, and T. Wang, “‘R-R intervals’ Analysis and Sleep Stages,” *J. Biomed. Eng. Res.*, pp. 1672–6278, 2003.

[30] D. E. Vigo, J. Dominguez, S. M. Guinjoan, M. Scaramal, E. Ruffa, J. Solernó, L. N. Siri, and D. P. Cardinali, “Nonlinear analysis of heart rate variability within independent frequency components during the sleep-wake cycle,” *Auton. Neurosci. Basic Clin.*, vol. 154, no. 1–2, pp. 84–88, 2010.

[31] M. Kesek, K. A. Franklin, C. Sahlin, and E. Lindberg, “Heart rate variability during sleep and sleep apnoea in a population based study of 387 women,” *Clin. Physiol. Funct. Imaging*, vol. 29, no. 4, pp. 309–315, 2009.

[32] J. Trinder, J. Kleiman, M. Carrington, S. Smith, S. Breen, N. Tan, and Y. Kim, “Autonomic activity during human sleep as a function of time and sleep stage,” *J Sleep Res*, vol. 10, no. 4, pp. 253–264, 2001.

[33] M. Ako, T. Kawara, S. Uchida, S. Miyazaki, K. Nishihara, J. Mukai, K. Hirao, J. Ako, and Y. Okubo, “Correlation between electroencephalography and heart rate variability during sleep,” *Psychiatry Clin. Neurosci.*, vol. 57, no. 1, pp. 59–65, 2003.

[34] F. Versace, M. Mozzato, G. De Min Tona, C. Cavallero, and L. Stegagno, “Heart rate variability during sleep as a function of the sleep cycle,” *Biol. Psychol.*, vol. 63, no. 2, pp. 149–162, 2003.

[35] P. Busek, J. Vankova, J. Opavsky, J. Salinger, and S. Nevsimalova, “Spectral analysis of heart rate variability in sleep,” *Physiol. Res.*, vol. 54, pp. 369–376, 2005.

[36] R. B. Berry, R. Budhiraja, D. J. Gottlieb, D. Gozal, C. Iber, V. K. Kapur, C. L. Marcus, R. Mehra, S. Parthasarathy, S. F. Quan, S. Redline, K. P. Strohl, S. L. D. Ward, and M. M. Tangredi, “Rules for scoring respiratory events in sleep: Update of the 2007 AASM manual for the scoring of sleep and associated events,” *J. Clin. Sleep Med.*, vol. 8, no. 5, pp. 597–619, 2012.

[37] I. Korhonen and A. Yli-Hankala, “Photoplethysmography and nociception,” *Acta*

Anaesthesiol. Scand., vol. 53, no. 8, pp. 975–985, 2009.
[38] A. Louise, E. Judee, and N. G. . Prasad, "Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults," *Hear. Lung*, vol. 27, no. 6, pp. 387–408, 1994.
[39] N. Saquib, M. T. I. Papon, I. Ahmad, and A. Rahman, "Measurement of heart rate using photoplethysmography," *Proc. 2015 Int. Conf. Netw. Syst. Secur. NSysS 2015*, 2015.
[40] P. Fung, G. Dumont, C. Ries, C. Mott, and M. Ansermino, "Continuous noninvasive blood pressure measurement by pulse transit time," in *Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, 2004, vol. 1, no. 4, pp. 738–741.
[41] W. Murray and P. A. Foster, "The peripheral pulse wave: Information overlooked," *J. Clin. Monit.*, vol. 12, no. 5, pp. 365–377, 1996.
[42] O. Ozeke, O. Erturk, M. Gungor, S. B. Hizel, D. Aydin, M. K. Celenk, H. Dincer, G. Ilicin, F. Ozgen, and C. Ozer, "Influence of the right-versus left-sided sleeping position on the apnea-hypopnea index in patients with sleep apnea," *Sleep Breath.*, vol. 16, no. 3, pp. 617–620, 2012.
[43] E. R. van Kesteren, J. P. van Maanen, A. A. J. Hilgevoord, D. M. Laman, and N. de Vries, "Quantitative Effects of Trunk and Head Position on the Apnea Hypopnea Index in Obstructive Sleep Apnea," *Sleep*, vol. 34, no. 8, pp. 1075–1081, 2011.
[44] L. C. Lack, M. Gradisar, E. J. W. Van Someren, H. R. Wright, and K. Lushington, "The relationship between insomnia and body temperatures," *Sleep Med. Rev.*, vol. 12, no. 4, pp. 307–317, 2008.
[45] R. J. E. M. Raymann, D. F. Swaab, and E. J. W. Van Someren, "Skin temperature and sleep-onset latency: Changes with age and insomnia," *Physiol. Behav.*, vol. 90, no. 2–3, pp. 257–266, 2007.
[46] H. J. Burgess, a L. Holmes, and D. Dawson, "The relationship between slow-wave activity, body temperature, and cardiac activity during nighttime sleep.," *Sleep*, vol. 24, no. 3, pp. 343–9, 2001.
[47] W. C. Liao, "Effects of passive body heating on body temperature and sleep regulation in the elderly: A systematic review," *Int. J. Nurs. Stud.*, vol. 39, no. 8, pp. 803–810, 2002.
[48] C. J. Van Den Heuvel, J. T. Noone, K. Lushington, and D. Dawson, "Changes in sleepiness and body temperature precede nocturnal sleep onset: Evidence from a polysomnographic study in young men," *J. Sleep Res.*, vol. 7, no. 3, pp. 159–166, 1998.
[49] L. Lack and M. Gradisar, "Acute finger temperature changes preceding sleep onsets over a 45-h period," *J. Sleep Res.*, vol. 11, no. 4, pp. 275–282, 2002.
[50] R. J. E. M. Raymann, D. F. Swaab, and E. J. W. Van Someren, "Skin deep: Enhanced sleep depth by cutaneous temperature manipulation," *Brain*, vol. 131, no. 2, pp. 500–513, 2008.
[51] P. Kumari, L. Mathew, and P. Syal, "Increasing trend of wearables and multimodal interface for human activity monitoring: A review," *Biosens. Bioelectron.*, vol. 90, no. September 2016, pp. 298–307, 2017.
[52] Z. A. Khan, S. Sivakumar, W. Phillips, and B. Robertson, "ZEQoS: A new energy and QoS-aware routing protocol for communication of sensor devices in healthcare system," *Int. J. Distrib. Sens. Networks*, vol. 2014, 2014.
[53] M. Toorani, "On vulnerabilities of the security association in the IEEE 802.15.6 standard," *Lect. Notes Comput. Sci. (including Subser. Lect. Notes Artif. Intell. Lect. Notes Bioinformatics)*, vol. 8976, pp. 245–260, 2015.
[54] C. Otto, A. Milenković, C. Sanders, and E. Jovanov, "System architecture of a wireless body area sensor network for ubiquitous health monitoring," *J. Mob. Multimed.*, vol. 1, no. 4, pp. 307–326, 2006.
[55] A. Pantelopoulos and N. G. Bourbakis, "A survey on wearable sensor-based systems for health monitoring and prognosis," *IEEE Trans. Syst. Man Cybern. Part C Appl. Rev.*, vol. 40, no. 1, pp. 1–12, 2010.
[56] R. Paradiso, G. Loriga, and N. Taccini, "A wearable health care system based on knitted integrated sensors," *IEEE Trans. Inf. Technol. Biomed.*, vol. 9, no. 3, pp. 337–344, 2005.
[57] S. Hesselbacher, A. Mattewal, M. Hirshkowitz, and A. Sharafkhaneh, "Classification, technical specifications, and types of home sleep testing devices for sleep-disordered breathing," *Sleep Med. Clin.*, vol. 6, no. 3, pp. 261–282, 2011.

[58] N. C. Van Wouwe, P. J. L. Valk, and B. J. Veenstra, “Sleep Monitoring : A Comparison Between Three Wearable Instruments,” *Mil. Med.*, vol. 176, pp. 811–816, 2017.
[59] J. M. Kelly, R. E. Strecker, and M. T. Bianchi, “Recent Developments in Home Sleep-Monitoring Devices,” *ISRN Neurol.*, vol. 2012, 2012.
[60] A. Klein, O. R. Velicu, and R. Seepold, “Sleep stages classification using vital signals recordings.”
[61] “Jawbone UP3.” [Online]. Available: https://jawbone.com/fitness-tracker/up3. [Accessed: 04-Nov-2017].
[62] “Intel Support.” [Online]. Available: https://www.intel.com/content/www/us/en/support/articles/000025310/emerging-technologies/wearable-devices.html. [Accessed: 04-Nov-2017].
[63] D. Andre, R. Pelletier, J. Farringdon, S. Safi, W. Talbott, R. Stone, N. Vyas, D. Wolf, S. Vishnubhatla, S. Boehmke, J. Stivoric, and A. Teller, “The Development of the SenseWear armband , a Revolutionary Energy Assessment Device to Assess Physical Activity and Lifestyle,” *BodyMedia, Inc.*, pp. 1–19, 2006.
[64] M. Hiroyasu, S. Sasahara, and T. Matsui, “Roll-over Detection and Sleep Quality Measurement using a Wearable Sensor,” in *29th Annual International Conference of the IEEE EMBS*, 2007, pp. 1507–1510.
[65] M. M. Sharif and A. S. Bahammam, “Sleep estimation using BodyMedia ’ s SenseWear ™ armband in patients with obstructive sleep apnea,” *Ann. Thorac. Med.*, vol. 8, no. 1, pp. 53–58, 2013.
[66] “Equivital.” [Online]. Available: http://www.equivital.co.uk/. [Accessed: 07-Nov-2017].
[67] “Hexoskin Smart T-Shirt.” [Online]. Available: http://www.hexoskin.com/. [Accessed: 07-Nov-2017].
[68] O. R. Velicu, N. M. Madrid, and R. Seepold, “Experimental Sleep Phases Monitoring,” 2016.
[69] “Nyx Devices.” [Online]. Available: http://nyxdevices.com/product/. [Accessed: 07-Nov-2017].
[70] P. J. Bello, C. J. Darling, and T. S. Lipoma, “Somnus: A Sleep Diagnostics Shirt Employing Respiratory Patterns Through Chest Expansion,” in *2011 Design of Medical Devices Conference*, 2011, pp. 1–5.
[71] “Vital Connect.” [Online]. Available: https://vitalconnect.com/solutions/vitalpatch/. [Accessed: 07-Nov-2017].
[72] N. Selvaraj, “Screening of Sleep Architecture using a Disposable Patch Sensor,” pp. 145–148, 2017.
[73] A. M. Chan, N. Selvaraj, N. Ferdosi, and R. Narasimhan, “Wireless Patch Sensor for Remote Monitoring of Heart Rate , Respiration , Activity , and Falls,” in *35th Annual Internation Conference on the IEEE EMBS*, 2013, pp. 6115–6118.
[74] “Neuroon Open.” [Online]. Available: https://neuroonopen.com/. [Accessed: 11-Nov-2017].
[75] Philips, “SmartSleep : quantifying slow wave activity enhancement.”
[76] “ApneaLink.” [Online]. Available: https://www.resmed.com/us/en/healthcare-professional/products/diagnostics/apnealink-air.html. [Accessed: 07-Nov-2017].
[77] D. J. Lesser, G. G. Haddad, R. A. Bush, and M. S. Pian, “The utility of a portable recording device for screening of obstructive sleep apnea in obese adolescents,” *J. Clin. Sleep Med.*, vol. 8, no. 3, pp. 271–277, 2012.
[78] CleveMed, “Sleep Scout.” [Online]. Available: https://clevemed.com/sleepscout-portable-sleep-monitor/. [Accessed: 07-Nov-2017].
[79] S. S. Grover, I. Bajwa, A. R. Butchko, J. Jasko, and R. Vasko, “Home Monitoring of Sleep Disorders,” *Philips Respironics*, 2009.
[80] D. Y. Park, H. J. Kim, C. H. Kim, Y. S. Kim, J. H. Choi, S. Y. Hong, J. J. Jung, K. I. Lee, and H. S. Lee, “Reliability and validity testing of automated scoring in obstructive sleep apnea diagnosis with the embletta X100,” *Laryngoscope*, vol. 125, no. 2, pp. 493–497, 2015.
[81] “Compumedics.” [Online]. Available: https://www.compumedics.com.au/products/somte-psg/. [Accessed: 01-Nov-2017].
[82] T. Suzuki, K. Ouchi, K. Kameyama, and M. Takahashi, “Development of a sleep

monitoring system with wearable vital sensor for home use," in *International Conference on Biomedical Electronics and Devices*, 2009, pp. 326–331.
[83] S. Lee, S. Nam, H. Shin, and A. E. Setup, "The Analysis of Sleep Stages with Motion and Heart Rate Signals from a Handheld Wearable Device," *ICTC 2016*, pp. 1135–1137, 2016.
[84] K.-M. Chang and S.-H. Liu, "Wireless Portable Electrocardiogram and a Tri-Axis Accelerometer Implementation and Application on Sleep Activity Monitoring," *Telemedicine and e-Health*, vol. 17, no. 3, pp. 177–184, 2011.
[85] M. Rofouei, M. Sinclair, R. Bittner, T. Blank, N. Saw, G. Dejean, and J. Heffron, "A Non-invasive Wearable Neck-cuff System for Real-time Sleep Monitoring," in *2011 Internation Conference on Body Sensor Networks*, 2011.
[86] W. Wongdhamma, T. Q. Le, and S. T. S. Bukkapatnam, "Wireless wearable multi-sensory system for monitoring of sleep apnea and other cardiorespiratory disorders," *IEEE Int. Conf. Autom. Sci. Eng.*, pp. 605–610, 2013.
[87] G. Troster, "The Agenda of Wearable Healthcare," *IMIA Yearb. Med. informatics*, pp. 125–138, 2005.
[88] S. Seneviratne, Y. Hu, T. Nguyen, G. Lan, S. Khalifa, K. Thilakarathna, M. Hassan, and A. Seneviratne, "A Survey of Wearable Devices and Challenges," *IEEE Commun. Surv. Tutorials*, vol. 19, no. 4, pp. 2573–2620, 2017.
[89] J. Hayward, G. Chasin, and H. Zervos, "Wearable Tecnhology 2017-2017: Markets, Players, 1090 Forecasts," 2017.
[90] C. Dalsgaard and R. Sterrett, "White paper on smart textile garments and devices : a market overview of smart textile wearable technologies," *Ohmatex APS*, pp. 1–11, 2014.
[91] D. Léger, B. Poursain, D. Neubauer, and M. Uchiyama, "An international survey of sleeping problems in the general population," *Curr. Med. Res. Opin.*, vol. 24, no. 1, pp. 307–317, 2008.
[92] K. Harding and M. Feldman, *Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem*, vol. 47, no. 4. 2008.
[93] N. Goatman, "Sleep Diagnostics , Sleep Therapy & Sleep Interfaces – World - 2013," *IHS Electron. Media*, 2013.
[94] D. Dias, N. Ferreira, and J. P. S. Cunha, "VitalLogger: An adaptable wearable physiology and body-Area ambiance data logger for mobile applications," 2017.
[95] C. Mondal, M. K. Azam, M. Ahmad, S. M. K. Hasan, and M. R. Islam, "Design and implementation of a prototype Electrooculography based data acquisition system," *2nd Int. Conf. Electr. Eng. Inf. Commun. Technol. iCEEiCT 2015*, no. May, pp. 21–23, 2015.
[96] A. M. Boukadoum and P. Y. Ktonas, "EOG-Based Recording and Automated Detection of Sleep Rapid Eye Movements: A Critical Review, and Some Recommendations," *Psychophysiology*, vol. 23, no. 5. pp. 598–611, 1986.
[97] T. I. Incorporated, "AFE4400 Integrated Analog Front-End for Heart Rate Monitors and Low-Cost Pulse Oximeters," 2014.
[98] T. I. Incorporated, "AFE4400 and AFE4490 Development Guide," 2014.
[99] "MPLAB ® Code Configurator User's Guide," 2014.
[100] "Physionet Database." [Online]. Available: https://physionet.org/. [Accessed: 04-Jun-2018].
[101] A. L. Goldberger, G. B. Moody, R. G. Mark, and A. L. Goldberger, "PhysioNet : Physiologic signals , Time Series and Related Open Source Software for Basic, Clinical, and Applied Research," in *33rd Annual International Conference of IEEE EMBS*, 2011, pp. 8327–8330.
[102] A. L. Goldberger, L. A. N. Amaral, L. Glass, J. M. Hausdorff, P. C. Ivanov, R. G. Mark, J. E. Mietus, G. B. Moody, C.-K. Peng, and H. E. Stanley, "PhysioBank, PhysioToolkit, and PhysioNet : Components of a New Research Resource for Complex Physiologic Signals," *Circulation*, vol. 101, no. 23, pp. 215–220, 2000.
[103] J. Pan and W. J. Tompkins, "A Real-Time QRS Detection Algorithm," *IEEE Trans. Biomed. Eng.*, vol. BME-32, no. 3, pp. 230–236, 1985.
[104] H. Kwon, H. Yoon, D. Jung, S. Choi, J. Choi, Y. Lee, D.-U. Jeong, and K. Park, "Heart rate variability in patients with major depressive disorder and healthy controls during non-REM sleep and REM sleep," *2017 39th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc.*, pp. 2312–2315, 2017.
[105] G. G. Berntson, D. L. Bigger, J. T. Jr., Eckberg, P. Grossman, P. G. Kaufmann, M. Malik, H. N. Nagaraja, S. W. Porges, J. P. Saul, P. H. Stone, and M. Van Der Molen, "Heart Rate

Variability: Origins, Methods and Interpretive Caveats," *Psychophysiology*, vol. 34. pp. 623–648, 1997.

[106] L. Toscani, P. F. Gangemi, a Parigi, R. Silipo, P. Ragghianti, E. Sirabella, M. Morelli, L. Bagnoli, R. Vergassola, and G. Zaccara, "Human heart rate variability and sleep stages.," *Ital. J. Neurol. Sci.*, vol. 17, no. 6, pp. 437–439, 1996.

[107] G. Moody, "Spectral analysis of heart rate without resampling," *Comput. Cardiol. 1993, Proc.*, no. 1, pp. 715–718, 1993.

[108] J. Hayano, E. Yuda, and Y. Yoshida, "Sleep stage classification by combination of actigraphic and heart rate signals," *2017 IEEE Int. Conf. Consum. Electron. - Taiwan, ICCE-TW 2017*, pp. 387–388, 2017.

[109] P. K. Stein and Y. Pu, "Heart rate variability, sleep and sleep disorders," *Sleep Med. Rev.*, vol. 16, no. 1, pp. 47–66, 2012.

[110] W. J. H. Nauta, "Hypothalamic Regulation of Sleep in Rats. An Experimental Study," *Sleep (Rochester)*, no. 11, 1946.

[111] K. Kesper, S. Canisius, T. Penzel, T. Ploch, and W. Cassel, "ECG signal analysis for the assessment of sleep-disordered breathing and sleep pattern," *Med. Biol. Eng. Comput*, pp. 135–144, 2012.

[112] Y. Zhao, M. Li, L. Huang, D. He, and H. Yang, "Sleep stage assessment based on autocorrelation and spectral analysis of heart rate variability," in *Conference of Real-time Computing and Robotics*, 2017, pp. 5–10.

[113] B. V. Vaughn, S. R. Quint, J. A. Messenheimer, and K. R. Robertson, "Heart period variability in sleep," *Electroencephalogr. Clin. Neurophysiol.*, vol. 94, no. 3, pp. 155–162, 1995.

[114] L.Moreno-Alsasua, B.Garcia-Zapirain, and A.Mendez-Zorilla, "Analysis of the sleep quality of elderly people using biomedical signals," *Biomed. Mater. Eng.*, vol. 26, pp. 1077–1085, 2015.

[115] D. Coakley, R. Williams, and J. Morris, "Minute eye movement during sleep," *Electroencephalogr. Clin. Neurophysiol.*, pp. 126–131, 1979.

[116] S. Das, S. Pal, and M. Mitra, "Real time heart rate detection from PPG signal in noisy environment," *2016 Int. Conf. Intell. Control. Power Instrumentation, ICICPI 2016*, pp. 70–73, 2017.