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FINAL DEGREE PROJECT

Degree in Biomedical Engineering

AUTONOMIC NERVOUS SYSTEM RESPONSE ANALYSIS IN SUBJECTS SUFFERING FROM SLEEP APNEA SYNDROME

Report and Annexes

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Note:

This project has been developed in the context of a 5-month signal processing (MATLAB) internship at *Laboratoire de Traitement du Signal et Image* (LTSI) in Rennes, France. The developed work is part of a research which it is still being conducted and is also part of a PhD thesis which has not been published yet. The followed methodology and procedures can be divulged, nevertheless, the implemented codes are confidential and, they are now, of LTSI's property. This is the reason why no algorithms can be found nor along the project nor in the Annex chapter.

Resum

El síndrome d'apnea-hipopnea durant el son (SAS) és una malaltia subdiagnosticada que afecta el 5% de la població general. Es caracteritza per ser una malaltia multifactorial caracteritzada per provocar episodis recurrents de pausa de l'acció respiratòria (apnea) o una disminució significativa de l'amplitut respiratòria (hypopnea) durant el son, amb la possibilitat de causar la seva fragmentació, provocant alteracions càrdio-respiratòries agudes associades amb el desenvolupament de la hipertensió i malaltíes cardiovasculars a llarg termini. En estudis anteriors, es va proposar un nou sistema de monitorització i teràpia del SAS, basat en l'estimulació kinestética adaptativa i no invasiva. En el present estudi, es presenten els resultats preliminars focalitzats en la resposta fisiològica dels pacients en termes de l'amplitud de la fotopletismografia de pols (PPG) i temps de trànsit del pols (PTT).

S'ha proposat una cadena de processat de senyals que ha permès caracteritzar la fotopletismografia de pols per tal d'estimar la resposta autonòmica dels esdeveniments respiratoris quan la teràpia està activa o no.

Tot i haver obtingut resultats benèfics pel 20% dels pacients tractats, aquests no ens permeten determinar de manera global l'efecte potencial de la teràpia en termes de control de la vasoconstricció perifèrica. Nous estudis estan actualment en curs per analitzar altres indicadors autonòmics en aquesta població.

Resumen

El síndrome de apnea-hipopnea durante el sueño (SAS) es una enfermedad subdiagnosticada que afecta el 5% de la población general. Se caracteriza por ser una enfermedad multifactorial que causa episodios recurrentes de pausa de la acción respiratoria (apnea) o una reducción significativa de la amplitud respiratoria durante el sueño, causando así su fragmentación y provocando alteraciones cardio-respiratorias agudas asociadas con el desarrollo de hipertensión y enfermedades cardiovasculares a largo plazo. En estudios anteriores, se propuso un nuevo sistema de monitorización y terapia para el SAS basado en la estimulación kinestésica adaptativa y no invasiva. En este estudio se presentan resultados preliminares complementarios focalizados en la respuesta fisiológica de los pacientes a la terapia en términos de amplitud de la fotopletismografía de pulso (PPG) y del tiempo de tránsito del pulso (PTT).

Se ha propuesto una cadena de procesamiento de señales que ha permitido caracterizar la fotopletismografía de pulso afín de estimar una respuesta autonómica a los eventos respiratorios cuando la terapia esta activa o no.

Aunque se hayan obtenido resultados benéficos para el 20% de los pacientes tratados, estos resultados preliminares no nos permiten determinar de forma global el efecto potencial de la terapia en términos de control de la vasoconstricción periférica. Nuevos estudios están actualmente en curso para analizar otros indicadores autonómicos en esta población.

Abstract

Sleep apnea syndrome (SAS) is an underdiagnosed disease affecting up to 5% of the general population. It is a multifactorial disease characterized by repeated episodes of breathing pauses (apnea) or significant reduction in respiratory amplitude (hypopnea) during the patient sleep. that may cause sleep fragmentation along with acute cardio-respiratory alterations associated with the development of hypertension and cardiovascular diseases in the long-term. In previous works, it has been proposed a novel monitoring and therapeutic system for SAS, based on non-invasive adaptive kinaesthetic. This study presents preliminary results of the patient's physiological response in terms of pulse photoplethysmography (PPG) amplitude and pulse transit time (PTT).

It has been proposed a chain of signal processing that has allowed to characterize the pulse photoplethysmography in order to estimate an autonomic response to respiratory events when the therapy is active or not.

Although beneficial results have been observed on 20% of treated patients, these preliminary results do not allow us to determine in a global way the potential effect of the therapy in terms of peripheral vasoconstriction control. New studies are currently under way to analyse other autonomic indicators in this population.

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1. Introduction

The sleep apnea syndrome (SAS) has a prevalence in middle age of 2% in women and 4% in men [1]. This condition is a multifactorial disease characterized by repeated episodes of breathing pauses (apnea) or significant reduction in respiratory amplitude (hypopnea) during the patient sleep. Sleep apnea is caused by airway occlusion or lack of diaphragmatic activation by autonomic nervous system causing transient asphyxia, which is reversed when the patient wakes. These events are repetitive with severely affected patients having hundreds of respiratory events and arousals every night [2]. In-between its main clinical features we can find disordered respiration during sleep, daytime sleepiness, impaired daytime cognitive performance, reduced quality of life, increased risk of road traffic accident due to excessive sleepiness and dysphoric mood. It has been observed that patients have increased mortality and morbidity from cardiovascular events [3] due to the raise of blood pressure.

The considered gold standard treatment is the continuous positive airway pressure (CPAP) given in attempt to improve daytime sleepiness, cognitive function, daytime mood and reduce blood pressure, but its levels of compliance are poor associated with side effects and high rate of abandonment. Yet, its minimal therapeutic usage is still unknown and improvements are needed [3]. Moreover, its effect on blood pressure is a subject of controversy in the scientific community [2] being claimed to reduce daytime sleepiness and the risk of cardiovascular morbidity and mortality in the most severely affected patients but not for moderately affected ones for whom CPAP therapy may not be suitable [4].

Alternative methods have been proposed like the practice of some instruments like didgeridoo which is claimed to be an effective alternative treatment, well accepted by patients with moderate obstructive sleep apnea syndrome due to the training of the muscles of the upper airways, which control airway dilation and wall stiffening [4]. Other treatment approaches are available, such as the oral appliance therapy and the mandibular advancement devices (MAD), that are considered less cumbersome than CPAP. Nevertheless, these devices also show side effects and their efficacy strongly depends on the morphology of the patient.

Finally, SAS is also associated with an increased risk of cardiovascular diseases, especially hypertension. However, the evidence that SAS is an independent risk factor for cardiovascular disease or death has been disputed and although the overall mortality rate of patients suffering from SAS was similar to that of the normal population, patients with SAS who had been prescribed CPAP therapy died mainly form cardiovascular diseases [5]. Consequently, if we consider sleep apnea syndrome as an independent

cardiovascular risk factor, effective therapy would considerably decrease the development of these kind of diseases.

The above paragraphs underline the fact that there is still a large portion of the SAS population that remains inadequately treated or even untreated. The development of non-invasive SAS treatment methods, with improved acceptability is thus of major importance[6]. Moreover, an exhaustive study of the effects of these therapies on cardiovascular response is of high importance.

In this project, we are going to study the effect on cardiorespiratory response modulated by autonomic nervous system to the implementation of PASITHEA's device developed by *Laboratoire de Traitement du Signal et Image* (LTSI), which has already shown to cause a beneficial effect of reducing the duration of apnea and hypopneas in obstructive sleep apnea syndrome patients.

1.1. Aims of the project

The SEPIA team from the *Laboratoire de Traitement du Signal et Image* (LTSI) has been collaborating with the Sorin Group society and with the *Centre Hospitalier Universitaire* (CHU) from Grenoble to develop a pilot clinical study, which allows to evaluate a monitoring and therapeutic system for sleep apnea syndrome patients. The acquired database is rich in information about nervous system's response in this population and several encouraging results have been obtained. The main goal of the project is to develop a new analysis focused on the interaction between respiratory and cardiovascular systems [7].

1.1.1. Main aim

Regarding our background, the main goal of the project is to develop a new analysis focused on the interaction between respiratory and cardiovascular systems to be able to determine the effect on vasoconstriction of the therapy proposed by PASITHEA.

1.1.2. Specific aims

More precisely, the specific goals of the project are the following ones:

- Study and analyse the clinical problem and its physiological cause as well as the database structure acquired.
- Study of signal processing methods developed previously in the team to propose techniques to extract information and characteristics of the acquired database.
- Development of statistical analysis from extracted parameters from the database in order to study the autonomous response associated with the level of disease.

- Detailed development documentation.

1.2. Scope of the project

PASITHEA project has a life of five years, during this time the research team has been working on several studies such as the detection accuracy of the respiratory events, the effect on the sleep stage and autonomous response regarding Oxygen Saturation (SO_2). The main objective of this project is to extract response features regarding Pulse Transit Time (PTT) and Pulse Photoplethysmography Amplitude (PPG).

Obtaining these parameters, we try to understand which are the effects of stimulation on autonomic response and the changes of parasympathetic response to sleep apnea and hypopnea.

These studies will be carried on with the data from the database, more precisely, with the electrocardiographic (ECG) and pulse photoplethysmography (PPG) signals from 20 patients. After obtaining the desired characteristics we will carry on a statistical analysis to determine whether the obtained results are significant. Once we have all our processed data, we will be capable of determining our therapy effect on cardiovascular system.

2. Project Background

2.1. Laboratory of Signal and Image Processing (LTSI)

The Laboratory of Signal and Image Processing (LTSI - INSERM U 1099) is a research laboratory in science, technology and health information created in 1969. It is under the supervision of the National Institute of Health and Medical Research (INSERM) and the University of Rennes 1.

More than one hundred people work in the laboratory, whose studies are conducted by 5 teams:

- SESAME: It works on the neural systems responsible for epileptic seizures.
- SEPIA: Focus on monitoring, explanation and prevention of heart failure and apnea bradycardia.
- MetriQ: Its main aim is to develop methodology and instrumentation methods in the field of nuclear magnetic resonance. This area includes the magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS).
- IMPACT: It works on the therapeutic and surgical assistance by the image. This work concerns in particular the cardiovascular and the oncology field.
- MEDICI: focused on the development of models and informatic systems to improve decision making in surgery.

The SEPIA team, in which this project has been performed, is a global leader in its field. Among its members, we can find clinical investigators, researchers in engineering, cardiologists and paediatricians of the University Hospital Centre (CHU) Pontchaillou. It also has academic partnerships such as the University of Sherbrooke, Canada and the Clinical Research Institute of Montreal which provides experimental animal models (sheep and pigs) [7].

This team responds to clinical problems by:

- The development of new cardiac “smart” devices.
- The observation of the autonomic nervous system.
- Monitoring of apnea-bradycardia, severe discomfort and sudden death syndrome in infants.

2.2. PASITHEA

The PASITHEA project, led by Alfredo HERNANDEZ, INSERM research director of SEPIA team, integrates an industrial partner (SORIN GROUP), and two French hospitals (CHU Rennes, CIC-IT Rennes and Grenoble University Hospital) [8].

The main goal of PASITHEA project is to find a new system of detection, monitoring and treatments of SAS by means of adaptive kinaesthetic stimulation, improving apnoeic patient care and simplifying the diagnosis. The hypothesis underlying this therapy is that a controlled kinaesthetic stimulation can activate subcortical centres that control the upper airway muscles without generating cortical arousal, so the breathing resumes without respiratory events associated with SAS.

This project has been entitled "Personalized and Adaptive kinaesthetic StImulation Therapy, based on cardio-respiratory Holter monitoring for slEp Apnea syndromes" (PASITHEA). The system is composed of three main components [9]:

a. A cardiorespiratory ambulatory recorder (Holter), providing data acquisition and wireless transmission of the acquired data in real time.
b. A kinaesthetic stimulation system, comprising a stimulation signal generator and a kinaesthetic actuator, typically positioned behind the ear.
c. A control device for adaptive kinaesthetic stimulation which will be embedded, in a first phase, into a computer.

These three components interact using a specific wireless communication protocol, based on Bluetooth (BT) technology. We can find a schema of the device in Figure 2.1 for an easier comprehension. In Figure 2.2 the first prototype of PASITHEA's device is showed.

2.2.1. PASITHEA's device

The device provides a new system for detection, monitoring and treatment of SAS, directed to improve patient management by integrating both a real-time diagnostic approach and a better treatment tolerance that may improve long-term observance.

2.2.1.1. Cardiorespiratory Holter

A commercially available Sorin Holter system was modified by partner SORIN CRM in order to meet the requirements of the project. The new cardiorespiratory Holter prototype is capable of acquiring and locally recording two ECG channels (sampling frequency: 256 Hz, resolution 10µV, frequency response:0.05-80Hz), nasal pressure (sampling frequency: 256 Hz) and blood oxygen saturation (SaO_2)

(sampling frequency: 1Hz) during a whole night. This system can also transfer these data in real-time (every 100ms) through a Bluetooth Low Energy (BTLE) link towards the real-time signal processing application for further processing [9].

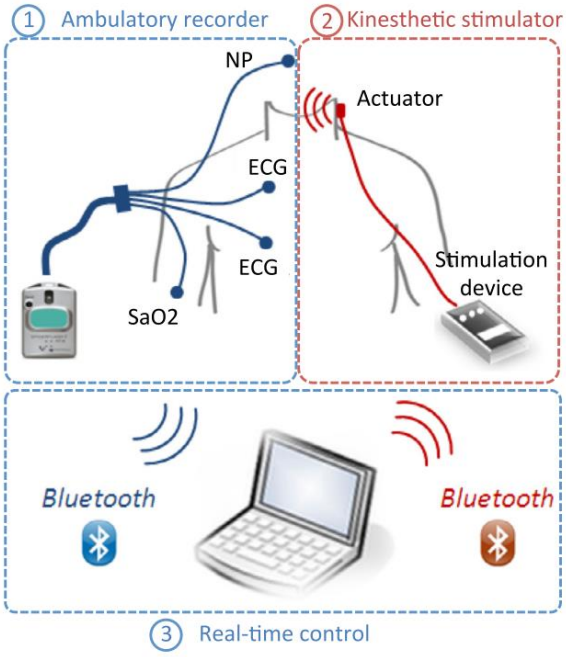

Figure 2.2 General diagram of PASITHEA system showing its main components: 1) Cardio-respiratory Holter, 2) Kinaesthetic stimulator, 3) Real-Time application for data processing and control.

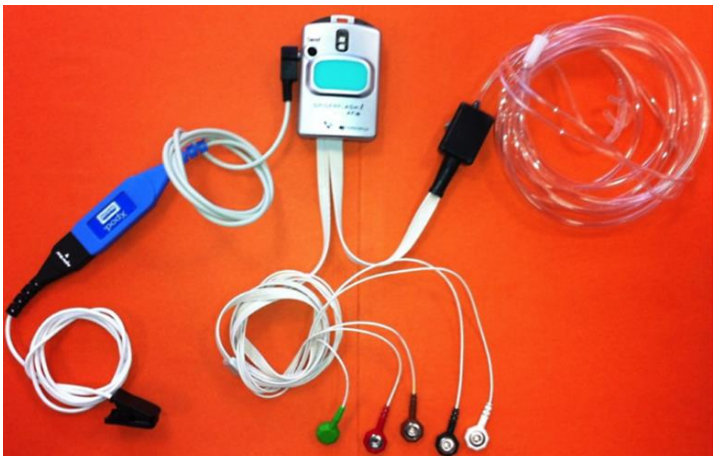

Figure 2.1 Prototype of the cardiorespiratory Holter device with associated sensors: ECG electrodes, SaO_2 ear sensor and nasal pressure cannula.

2.2.1.2. Kinaesthetic stimulation system

The kinaesthetic stimulation system has been developed by LTSI, based on previous prototypes already used for kinaesthetic simulation therapy for apnea-bradycardia on preterm new-borns. The system consists in a command module and a kinaesthetic actuator.

The command module is a battery-operated device that can generate dynamic stimulation signals in an adaptive fashion. This module is based on an ATmega168 micro-controller, embedding a custom, multi-agent software that handles all the functionalities of the device. In particular, the micro-controller can synthesize sinus signals with varying amplitudes and frequencies, to be presented as input to a driver circuit that will handle the kinaesthetic effector. The command module can function either in an "autonomous" or a "slave" mode. The slave mode requires establishing a BT connection with a master system (in this case, the real-time control application) that will command the operation of the stimulator.

The stimulating device is a resonant linear actuator with optimal resonance frequency of 175 Hz (model C10-100, Precision Microdrive Ltd, London, UK). At 100% of the acceptable input signal amplitude ($2V_{RMS}$), this actuator generates a typical normalized acceleration of 13.7 m/s^2 [9].

2.2.1.3.Real-time processing and control application

This application, is in charge of establishing wireless communication links with the Holter and the stimulator, receiving data from the cardio-respiratory Holter, performing real-time signal processing on the received signals for the detection of apnea or hypopnea episodes and according the detector's output, apply the proposed "on-off" controller and send the appropriate command to the kinaesthetic stimulator through a Bluetooth (BT) link [9].

2.2.1.4. Wireless communications and data acquisition

The control application establishes wireless BT links with the Holter and the stimulator device and performs device initialization and management using specifically developed application-level communication protocols. Methods of error correction and verification of the integrity of the BT links have been integrated in the protocol and are also handled by the control application. Data acquisition is initiated and terminated by the application and all available signals are received in real-time from the device at their original sampling rates [9].

2.2.1.5. Real-time respiratory event detector

The respiratory event detector is based on the segmentation of respiratory cycles from the acquired nasal pressure signal. A full respiratory cycle is defined as inhalation followed by exhalation. Inhalation is detected when the nasal pressure signal exceeds a positive threshold value ($\lambda_I(t)$). Exhalation is detected when nasal pressure signal falls below a negative threshold value ($\lambda_E(t)$). Both thresholds are updated independently, through time, according to the patient's breathing patterns. An apnea is detected as the absence of inhalation for more than 3 to 10 seconds ($\Delta_a \epsilon$ [3, … ,10] s). A hypopnea event is detected when inhalation amplitude falls below 50% below inhalation baseline for more than 5 to 10 seconds ($\Delta_h \epsilon$ [5, … ,10] s). However, some additional criterions were added [9]:

- For apnea detection: an apnea was detected not only as the absence of inhalation for a certain time but also as a "flat" breathing line, i.e. nasal pressure amplitude had to stay within the inhalation and exhalation thresholds.
- The time to detect apnea (Δ_a) was not a fixed parameter but would be set, within limits, as the average of the patient's latest respiratory cycle periods.
- The time to detect hypopnea (Δ_h) was not a fixed parameter but linked to the amplitude of inhalation drop: a quicker detection for severe hypopnea (with large drop) and a slower detection for less severe hypopnea.

2.2.1.6. Control of the kinaesthetic stimulation

In this first version of PASITHEA system a real-time "on-off" control method was implemented into the application, using as control variable detector's output. When respiratory event detection is confirmed, around 8 s after the beginning of the respiratory event, a command is sent to the kinaesthetic stimulator to activate it. Although the system is able to apply different stimulation strategies for different types of respiratory events, during the acquisition of our database we used the following characteristics: A constant amplitude is applied to the patient at a frequency of 175 Hz. Kinaesthetic stimulation is organized into bursts of a maximum duration of 3 s each, followed by a silent period of 2 s. A maximum of 3 bursts were applied in a given detected respiratory event. This burst-based stimulation is applied in order to minimize patient habituation to the stimulation as well as the fragmentation of the patient's sleep. When the detector confirms the end of the respiratory event (first detected deflection on the nasal pressure signal above a given threshold during a respiratory event) a command is sent to stop kinaesthetic stimulation [9].

2.2.2. Data acquisition and patient population

The followed protocol has been approved by the ethics committee of the Grenoble University Hospital (HYPNOS study), and involving five centres: The University Hospitals of Angers, Grenoble, Montpellier, Rennes and Tours. The first objective of this study is to validate the autonomous response to device's stimulation.

After signing an informed consent, all patients underwent a full polysomnography (PSG) in a sleep laboratory. Nasal pressure (NP), electrocardiography (ECG) and oxygen saturation (SaO_2) were simultaneously acquired and processed by the PASITHEA system. Using a t-deviation tube, the same nasal pressure was presented as input to the sensors of both the cardiorespiratory Holter and the PSG systems. Central reading of PSG was performed by an expert, blinded core-lab (CHU Grenoble France) who provided the overall Apnea Hypopnea Index (AHI) together with an accurate scoring of individual events (start, duration and type of event) for each patient.

A total of 46 severe obstructive apnea (OSA) patients (mean age: 58.5, BMI: 30.1 kg/m^2, AHI: 47.7/h – with 92% of obstructive events, 75% male) were included in this study. 12 patients were included in a titration phase, dedicated to optimize the parameters of the respiratory event detector and to establish the amplitude of the kinaesthetic bursts that were used for the rest of the study. The 34 remining patients were included on the study phase, with a fixed stimulation amplitude of 80% of the maximum power of the stimulator (normalized acceleration of approx. $11m/s^2$). This stimulation amplitude value was determined during the titration phase. 4 patients were totally excluded from the analysis due to problems with de PSG recording, or to a bad nasal cannula signal, preventing correct detection of respiratory events. Additionally, 4 other patients were excluded from the therapy analysis because the stimulation therapy was not delivered (failure of the stimulator cable or connector), 6 other patients were excluded due to the absence of ECG recording. Finally, 20 patients are available for the analysis of the therapy [9].

2.2.3. The Database

LTSI provided HYPNOS database with all the signal acquired during the polysomnographic studies of the patients. They were 8 hour-length signals. The ones used along this study are the ones described in Table 2.1. In the first place, we have electrocardiographic signal (ECG) from standard polysomnographic study, which was recorded in µV. The next signal we can find is the respiratory signal (DEB), extracted with a t-deviation cannula and measured in µV. In third the place, we have the

stimulation signal (SKIN) which gives us information about the kinaesthetic stimulations received by the patients and its amplitude. The fourth signal we have is the pulse photoplethysmography obtained from the polysomnographic study in µV. And, to end, we have the information about stimulated and non-stimulated cycles in CyclesOnOff. Each recording started with an initialization segment of 60 minutes during which no stimulation was delivered, in order to let the patient to fall asleep. After this period, the therapy evaluation is started, by defining consecutive periods in which the stimulator was active for 30 minutes, followed by inactive periods of 30 minutes, so that each patient represents its own reference.

Signal	**Description**
ECG	Electrocardiographic recording in µV.
DEB	Respiratory signal recorded in µV.
SKIN	Stimulatory signal recorded in µV.
PULSE	Pulse photoplethysmographic signal recorded in µV.
CyclesOnOff	Information about the beginning and the end of each stimulated and non-stimulated cycle

Table 2.1 Database signal description.

2.3. Related Physiology

In this part of the project the physiology related to our analysis is described. First, starting with a brief description of what is the Autonomic Nervous System (ANS) to be able to understand the related mechanisms. Followed by the definition of sleep apnea and hypopnea, which is the base of our study. And, finally, the physiological response to respiratory events.

2.3.1. Autonomic Nervous System

The autonomic nervous system plays a major homeostatic role in the regulation of the "milieu intérieur". Control of the ANS is complex, but fundamentally it functions on reflex arcs which may be modulated

by a variety of inputs. Despite its name, it is not "autonomic", being regulated by centres in the central nervous system, particularly the hypothalamus. It essentially acts as a motor system undertaking a large number of specialized tasks, both stimulatory and inhibitory, in a wide range of target organs, tissues, blood vessels, glands and even single units such as mast cells. Closely associated with the efferent nerves is a complex network of afferent fibres like sensory chemoreceptor, mechanoreceptor, nocioceptor, thermoreceptor, baroreceptor and osmoreceptor signals back to central nervous system (CNS) centres where the complex homeostatic reflex arcs are regulated. The ANS can be divided into three divisions based on anatomical and physiological considerations. The *sympathetic division* forms the major part of the ANS innervating more structures than the parasympathetic system. The *parasympathetic division* arises in the brain stem and supplies the seventh, ninth and tenth cranial nerves. The heart, lungs and the abdominal viscera are served by preganglionic fibres distributed by the vague nerve. There are also large numbers of afferent parasympathetic fibres which outnumber the motor fibres and feed-back the multitude of sensory signals necessary for homeostasis. The *enteric division* is made up of the nerves and ganglionic plexuses that are found in the walls of the gastrointestinal tract, gall bladder, and within the pancreas. It forms a complicated meshwork of sensory, motor and interneuronal components that uses a diverse array of neurotransmitters.

The enteric nervous system is largely pre-programmed to produce the classical peristaltic movements associated with each section of the gastrointestinal tract, but its effects are modified by local reflex arcs, extrinsic autonomic input, hormones and immune mediators [10].

In Figure 2.3 we have a description of the sympathetic and parasympathetic divisions of ANS as well as the organs and mussels they act on.

Along this project, we are going to focus on the *sympathetic* and *parasympathetic* divisions. To be able to determine and successfully understand which is the effect of our therapy we have to know the functions that each division of ANS develop. In first place, *sympathetic* division is the one that prepares our body for the called "fight or flight", which means that prepares our body for stressful or emergency situations by means of increasing heart rate and forcing heart contractions, releasing energy stored in the liver, increasing the speed at which energy is used to perform body functions, increasing muscle strength, widening the airways to make breathing easier, increasing transpiration, decreasing digestion and urination and controlling the release of semen ejaculation. On the other hand, *parasympathetic* division controls body process during ordinary situations, conserves and restores. Its main functions are to stimulate the digestive tract to process food and eliminate wastes, slow heart rate, reduce blood pressure and control erections [11].

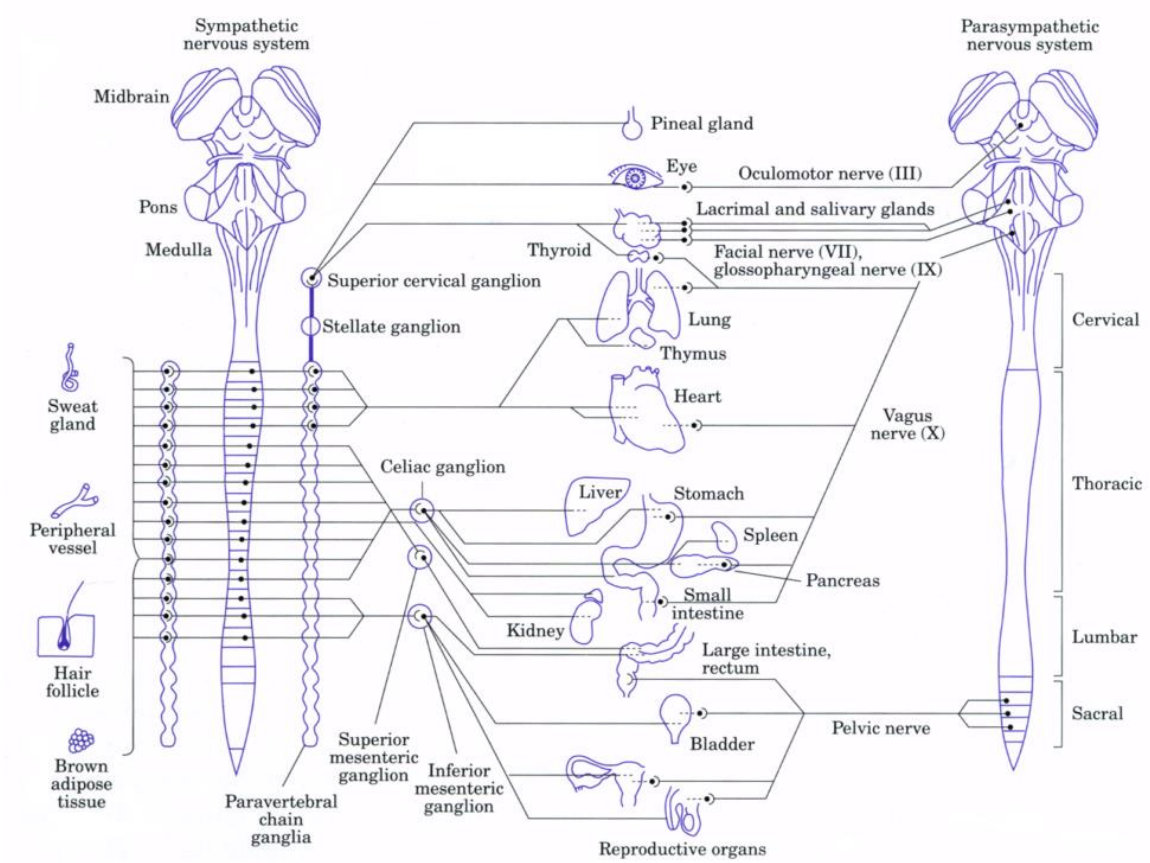

Figure 2.3 The sympathetic and parasympathetic divisions of ANS [10].

2.3.2. Sleep Apnea Syndrome

Sleeping is a physiologic process which enables the body to reset and obtain energy to start a new day. However, 30 years ago, approximately, it was found that the disordered and even disrupted breathing during sleep is a substantial medical problem. Inside the so-called Sleep Apnea Syndrome (SAS) there are several types of disorders.

The most common one is *Obstructive Sleep Apnea Syndrome* (OSAS), affecting more than 10% of the population over the age of 65 [12]. In this condition, the tone of the upper-airway musculature is inadequate to maintain airway patency. When the upper airway is floppy, the anatomical structures of the upper airway are drawn into the airstream as the diaphragm descends and obstruct inspiratory airflow.

The second most common disorder during sleep is *Central Sleep Apnea* (CSA), which is also a loss of inspiratory airflow, but it occurs because of a loss of phasic diaphragmatic activity.

And, in third place, we have *Hypopneas*, which are breathing events which are lower than normal ones. In Figure 2.4 the different abdominal motion for each type of apnea can be observed.

These events may recur hundreds of times in a single night with serious health implications. The resulting sleep fragmentation and blood gas modifications cause malfunctions of sleep-related restorative processes, and induce chemical and structural injuries in the cells of the central nervous system. Not only it cause daytime sleepiness, it can lead to systemic hypertension and increase in the likelihood of cardiovascular diseases [13]. Nonetheless, treatment to restore breathing during sleep can prevent these consequences.

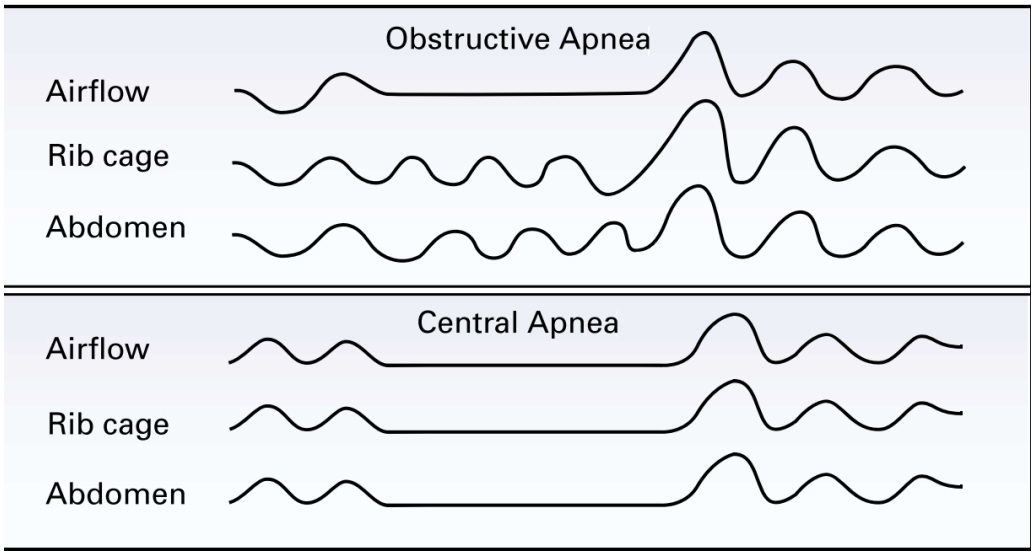

Figure 2.4 Respiratory motion of chest wall with no nasal air flow for obstructive Apnea and Central Apnea.[12]

2.3.3. PPT and PPG response to respiratory events during sleep

As seen in previous parts, physiological responses are dependent on autonomic nervous system. So, to be able to relate all the concepts we have to start defining the following ones:

PPG (Pulse Photoplethysmography): Simple optical technique used to detect volumetric changes of blood in peripheral circulation. It is a low cost and non-invasive method used to take measurements at the surface of skin. The technique provides valuable information related to cardiovascular system.

Recent advances in technology has revived the interest in this technique, which is widely used in clinical and physiological measurement and monitoring.

PPG Amplitude: Difference between the value of PPG on the maximal fraction of the peak and the lower part of the wave. Used to estimate the skin blood flow using infrared light. Researchers from different domains of science have become increasingly interested in PPG because of its advantages as non-invasive, inexpensive, and convenient diagnostic tool. Traditionally, it measures the oxygen saturation, blood pressure, cardiac output, and for assessing autonomic functions [14].

PPT (Pulse Transit Time): Quantitative measure of the time that pulse wave needs for passing from one arteria, typically the aorta, to another, typically in the periphery. Evaluated as the time interval between the ECG R peak and the corresponding PPG wave [13].

When a respiratory event is produced, it causes an increase in the respiratory effort which produces an increase in the amplitude oscillations of PTT, which decreases after an apnoeic event due to a sympathetic activation related to arousal, which also produces heart rate increment, higher stroke volume, vasoconstriction, which in turn generate pulse wave acceleration giving a decrease in PPG amplitude [13]. In figures Figure 2.5 and Figure 2.6 we have a diagram of the followed sequence for an easier understanding.

By the stimulation that PASITHEA's device, the expected response would be an activation of subcortical centres which control the upper airway muscles, without generating cortical arousal, which would result in a parasympathetic activation, producing vasodilation, decrease of blood pressure and heart rate decrement. Which is traduced in minor changes of PTT and PPG amplitude after respiratory events regarding its initial situation before the event occurs

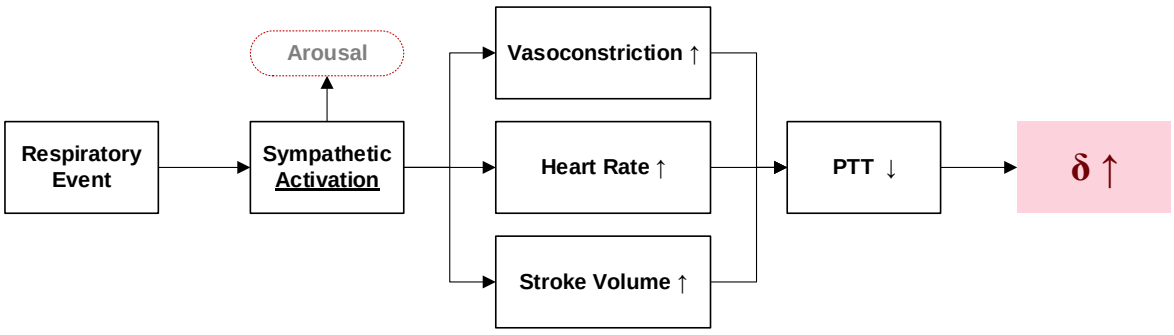

Figure 2.5 Sequence of physiological responses regarding PTT taking place after a respiratory event.

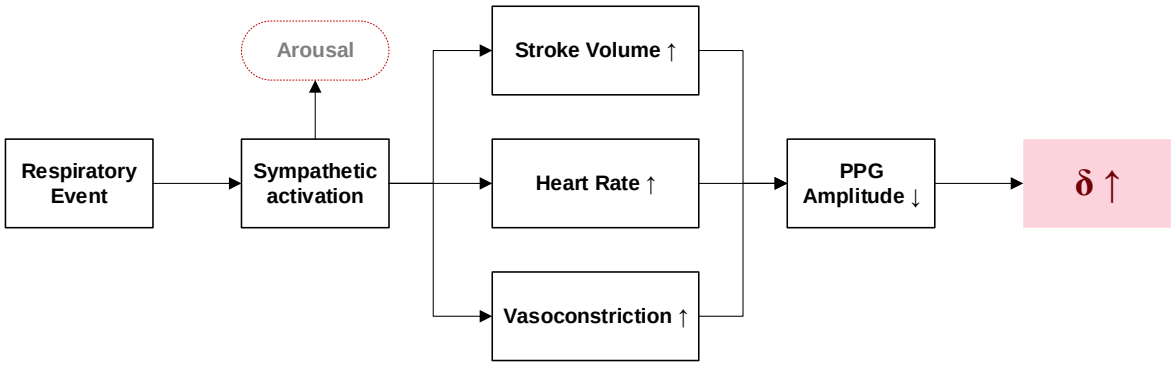

Figure 2.6 Sequence of physiological responses regarding PPG Amplitude taking place after a respiratory event.

3. Methodology

Along chapter 3 the proposed signal processing chain used to develop the project is explained. The followed methodology can be divided in three big blogs:

- The first one is ECG signal processing, in which a R-wave detector is implemented and a revision of all detections is realised to make sure not to advance with mistaken data to further steps.
- Along the second block we extract PPG characteristics. In first place, we filter the signal by means of autonomous learning parameters. Once PPG signal is filtered, its local extrema (minima and maxima) are found and corrected to make sure there exist a correlation between filtered PPG extrema and R-wave detections as well as a coupling between maxima and minima, which means that for each peak there exist a corresponding valley. From the previous output, we obtain PPG Amplitude and PTT signals.
- The signal's analysis is realised in the third block. The followed method is based on the collection of a delta (δ) value based on the detection of the four respiratory cycles after a respiratory event occurs, however, it will be explained further in this section. With the obtained data, a statistic analysis and a Wilcoxon test is produced to validate the significance of the obtained results.

In Figure 3.1 we can find a diagram of the implemented procedures, input and output signals for each section.

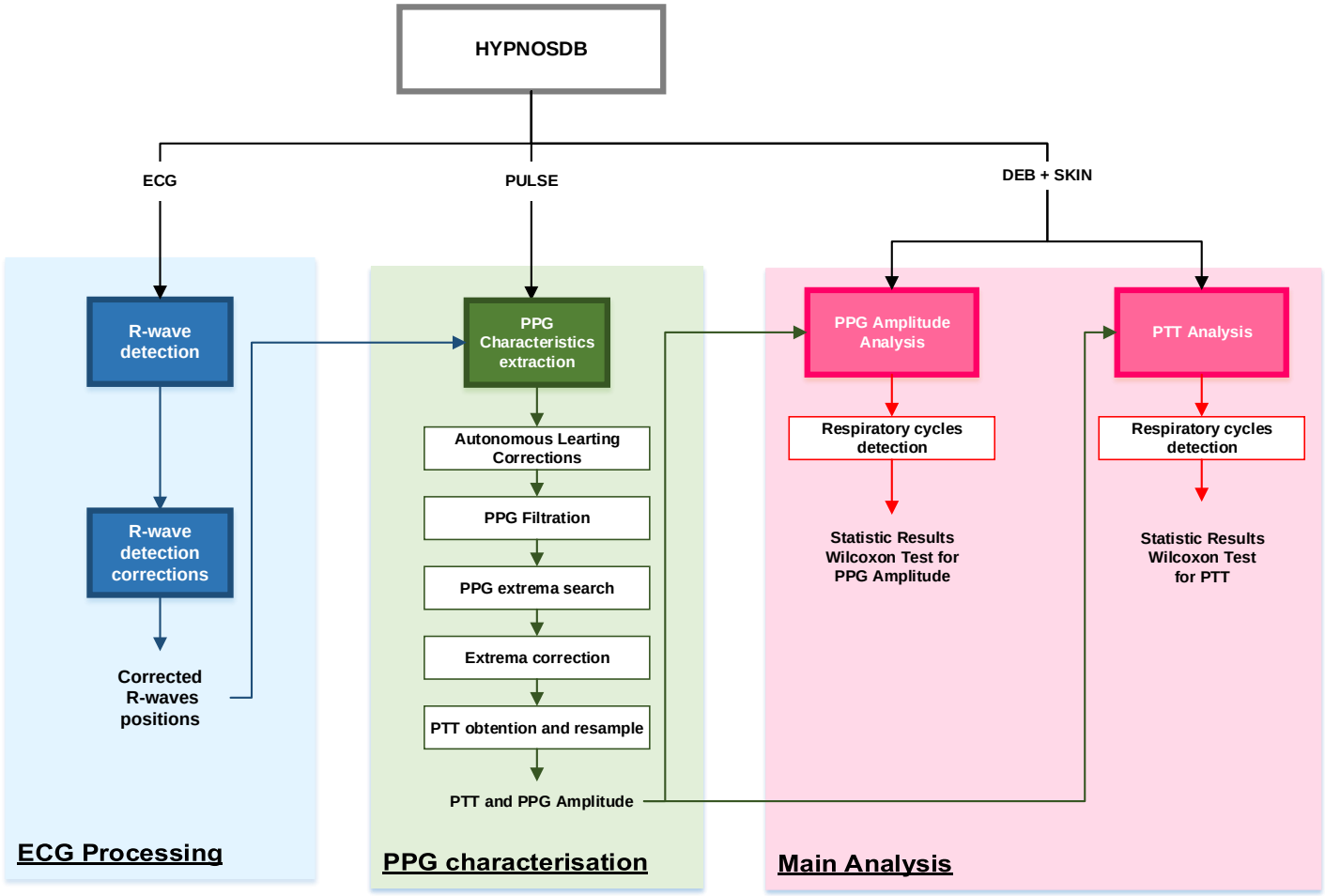

Figure 3.1 Diagram of the followed procedures.

3.1. ECG characterisation

To start with our analysis, we need to localize the positions of QRS complexes along the 8 hours of the recordings. This information is of high importance because it is the raw data we are going to use along the project.

The main aim was to localise QRS complexes, so the easier and more precise method to do it is to localise R-waves along the electrocardiographic signal (ECG). The used detector is taken from LTSI's library. It is an updated version of the one used by *J.Dumont et al* [15] for ECG beats delineation. It is based on successive filtering which filters are designed using Remez method. Multiple parameters (threshold adjustments, closed-eyes period duration, cut-off frequencies, order of filters, window sizes, etc) were optimized for noisy signals using evolutionary algorithms.

A problem that appeared by the usage of the detector was that it is an external library in C language which works at 1000 Hz and our signals had a sampling rate of 1024 Hz. As a result, some detections were moved some samples from peak's position. The implemented solution was to find local maxima in a window of 25 samples around the output detection. However, to make sure that all detections were correct they were revised one by one, for all patients, with a function which was also from LTSI's library. The aforementioned, provided a graphic interface which let us move wrong detections and position them in the correct place as well as navigate along the signal by means of windows of a previously selected size. During the correction process, we chose a window of 10000 samples to have a good quality of the image and be able to advance faster. When a modification was made, the function saved them automatically and returned the input detection vector with the same name and length but with the previously modified data.

The process of correcting all subjects' R-wave detections was very tedious, it involved 8-hours signals for 20 patients. However, it was a crucial part of the project because, due to interpersonal differences and different used calibration while acquiring the data caused some misdetections. Being sure of having correct R-wave detections was very important for PTT analysis because it is one of the basic parameters needed to obtain it.

Once we had extracted the positions for R-waves from ECG signals we could move on to the next block of analysis, PPG characteristics extraction.

In Figure 3.2 we can find an example of the window size used to correct R-wave position detections. It can be observed that it is of a sufficient size which allow us to see properly signal characteristics, but at the same time allow as to advance along the signal with a proper rhythm.

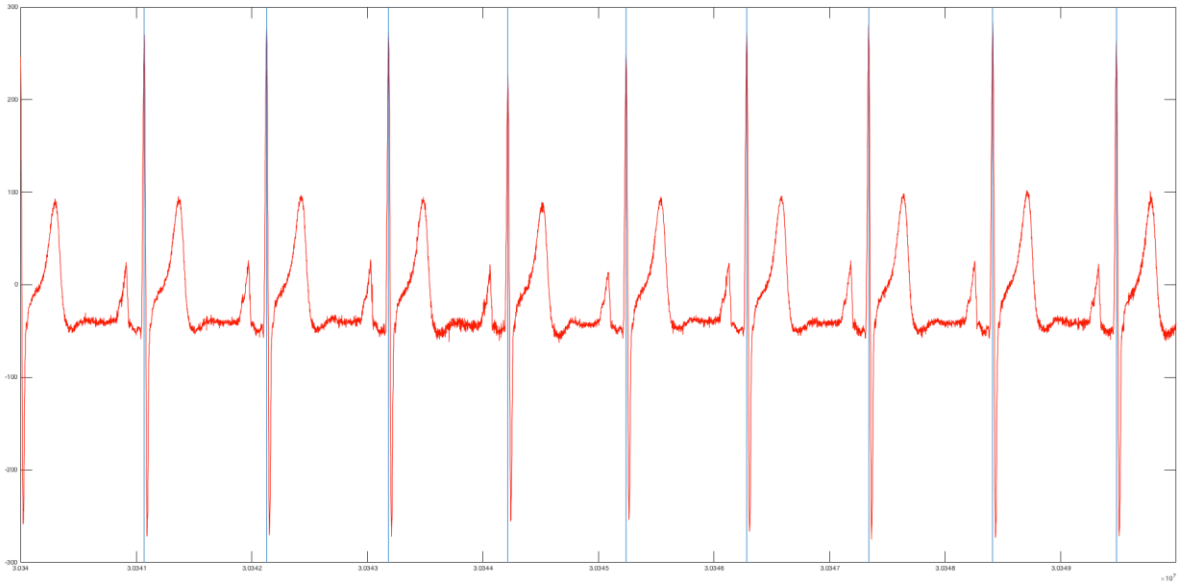

Figure 3.2 Used window for the correction of R-wave position detection.

3.2. PPG characterisation

In this subchapter of the methodology we are going to explain which PPG's characteristics were obtained and which procedures were implemented.

First of all, in order to be able to obtain the desired variables from our PPG signals, we have to condition them. That means developing a filtering process to extract noise and interferences which can lead to wrong detections and false our final results.

The first step in the signal characterisation was to filter PPG signal. When processing a signal what we look for is to delete the noise and interferences contained. Nevertheless, is of high importance to maintain a compromise of signal/noise because it is really easy to ruin other parts of our signal containing valuable information.

For that reason, we have used an autonomous learning code in which we inserted a signal window of a user-chosen length that contained an example of good signal morphology and an example of noise

morphology. In Figure 3.3 we can find an example of good PPG signal and an example of noise morphology inserted in the autonomous learning code. By means of a graphic interface, we could classify manually which parts of the signal where the model for good signal morphology and which were the example of noise ones. Finally, the code returned us B parameters.

The main aim of this procedure was to choose a piece of signal which could be used as a standard for all patients, however, due to the different calibrations during data acquisition and interpersonal differences there were some signals for which individual parameters had to be obtained.

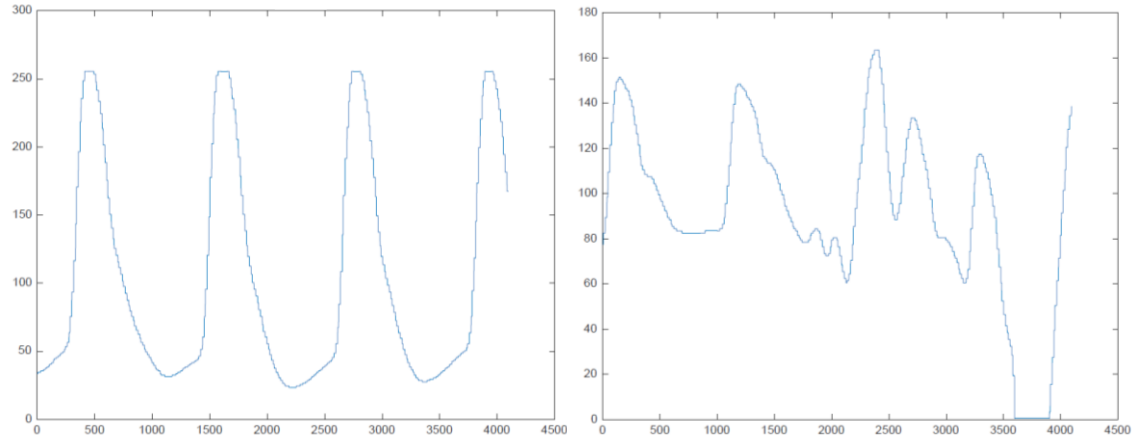

Figure 3.3 Example of good PPG signal and noise for the autonomous learning codes.

B parameters were used as polynomial values to develop a polynomial interpolation that resembled PPG wave signal. The polynomial interpolation was compared to the original signal. There also was a minimum percentage of similarity which we fixed to 90% after several performance observations. If the similarity percentage was lower, the piece of the signal which diverged was deleted. In Figure 3.4 we have an example of filtered signal due to its saturation.

Then, we needed to localize pulse waves. The easiest and more robust method was to detect its local maxima. As PPG signal is really constant and it was already filtered we did not have major problems due to wrong detections, however, random checks were done to ensure the reliability of the analysis.

To find PPG amplitude we found wave peaks and valleys to have maximum and minimum values. Despite the fact that having the aforementioned data, we could not obtain PPG amplitude values yet. To

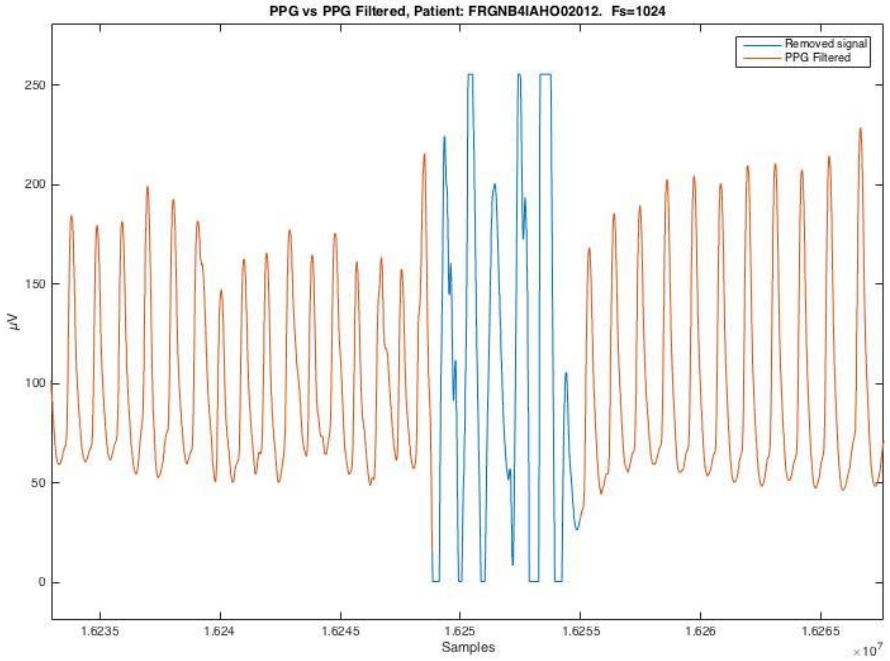

Figure 3.4 PPG filtration example.

do so we needed to coordinate peak values with valley ones in order to obtain the amplitude for each wave. For that, we considered the detection of a wave when a local maximum was found and it was coordinated with its corresponding following local minima. This coordination was made with a very easy procedure, for every peak detection a window was opened from the present numerator to de following one and local minimum was searched within these values. The resultant vectors had each peak and the corresponding valley in the same vector index, they were paired.

In addition, PPG peaks were coordinated with R-wave detections. That means that for each removed segment of PPG signal, R detections corresponding to that segment of the signal were deleted as well. As previously done for local extrema, pulse peaks and R-waves were coordinated. That means that for every R-wave detection a window was created from that detection to the following one and PPG peaks were searched and stored in the same vector number as the corresponding ECG wave. The result was that for every detected R-wave we must have a PPG peak behind it, and for each PPG peak there must be a R-wave detection in front. This procedure eased considerably our analysis. In Figure 3.5 we have an example of R detections, PPG peaks and valleys coordination.

Once we had all basic characteristics, we pursued to extract the values of times when R-waves and PPG peaks took place. From them and as all data was linked, we were able to extract pulse transit time (PTT), as showed in Eq. 1Figure 3.5, with the following simple operation:

Eq. 1

$$PTT = \frac{PPG\ peak}{fs} - \frac{PPG\ peak}{fs}$$

R-R interval was also calculated as showed in Eq. 2:

Eq. 2

$$RR = R(i) - R(i-1)$$

PPG amplitude was calculated in the following way:

Eq. 3

$$PPGAmp = Max - Min$$

For PTT, RR and PPG amplitude a correction was necessary due to their length. As they were extracted from specific points of the signals they needed to be resampled so that their total length was the same as the original signal one.

Once we extracted all desired parameters we saved them and kept them to realise the following analysis for PPG amplitude and PTT.

Nevertheless, we were given a PTT calculation by the polysomnography from a patient. We compared it with the one we extracted to make sure our method's performance was acceptable.

After the comparison shown in Figure 3.6, we can be confident that our PTT extraction was completely satisfactory and it had even less noise that the given one.

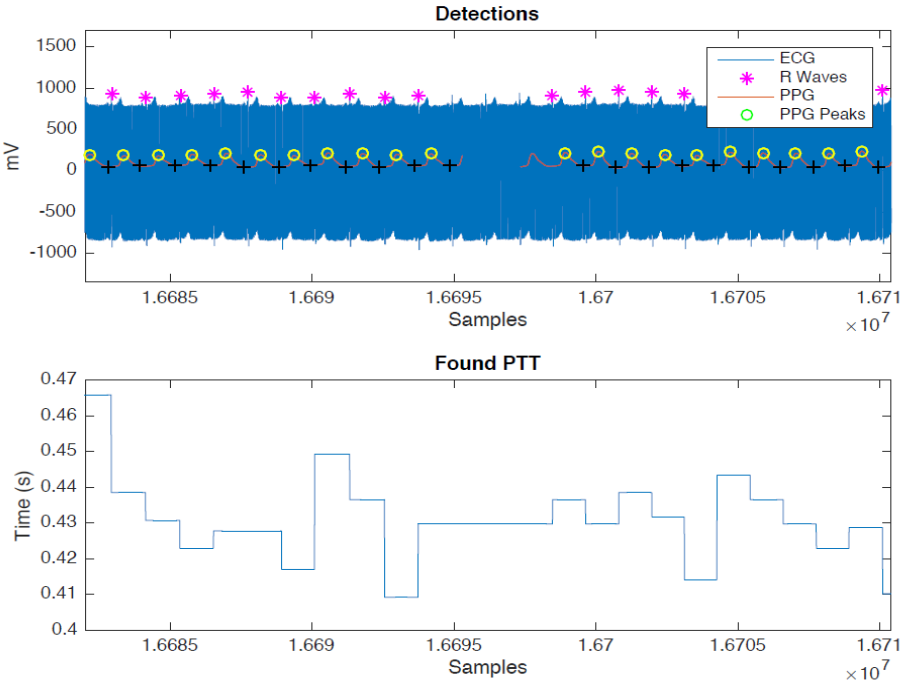

Figure 3.5 R-wave, PPG peaks and valleys coordinaion with an example of the extracted PTT for that window.

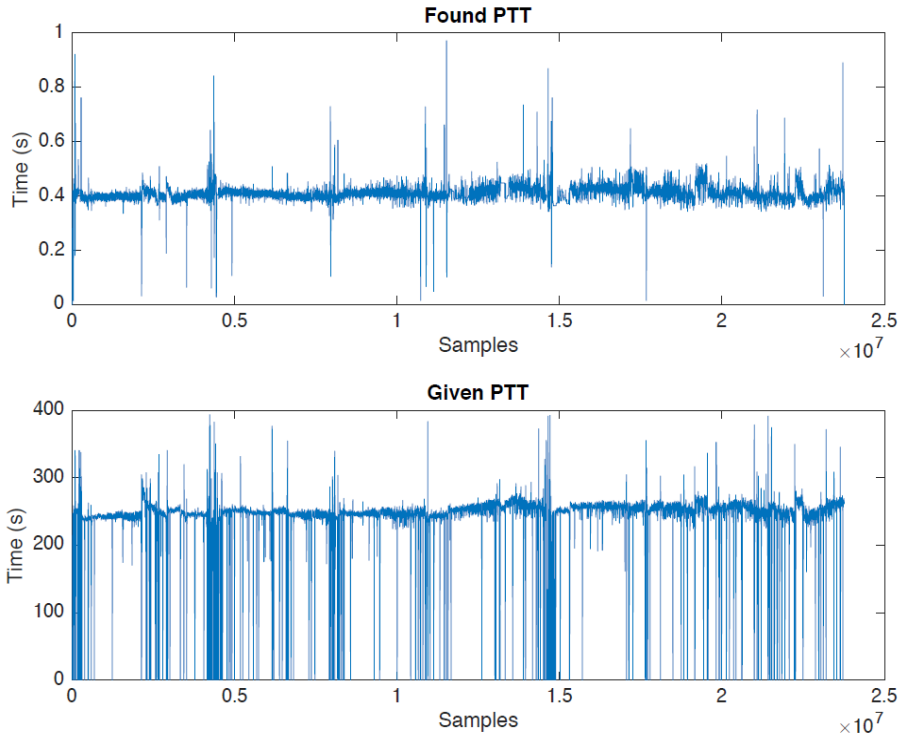

Figure 3.6 Comparison between found PTT and given PTT which proves our improvement.

3.3. PTT and PPG Analysis

Once all necessary characteristics were extracted, we proceed to its analysis. Our main aim was to find the parasympathetic response on cardiovascular system due to a kinaesthetic stimulus after a respiratory event detection. For this reason, we are going to analyse changes in Pulse Photoplethysmography Amplitude (PPG) as well as in Pulse Transit Time (PTT). The same method was used for both parameters, for this reason it will only be explained once in the project.

These analyses were divided in three main parts:

- Sleep information
- PPG/PTT Analysis
- Disclosure

3.3.1. Sleep Information

The goal of this step is to extract useful information about all respiratory events that took place during the recording of the signals helped by the annotations developed by the doctors who analysed them previously.

At the beginning of it, as in all procedures, we got real data from original signals. Then, stimulation signal (SKIN) was filtered with a butterwort bandpass filter between 160-190 Hz. From the annotations, we could classify the respiratory events between apnea or hypopneas as well as determining its start, end time and position along the respiratory signal.

Right after, excluding rules were imposed so as to have a better classification of each event. These rules were extracted from the clinical annotations made by doctors and provided to the lab.

Finally, all apnea and hypopneas are checked simultaneously with SKIN signal to determine whether they were stimulated. For that reason, we took a window of SKIN signal from the start of the event to the end of it plus three seconds, which is the time it can take to detect that an event is taking place.

To end, we save all data to go on with our analysis.

3.3.2. PPG Amplitude and PTT Analysis

Is in this section where we are going to use all data extracted previously in the project and we are going to conduce PPG amplitude and PTT main analysis to see the vasoconstrictive response to kinaesthetic stimulation.

In a primary state of our analysis, we tried several methods based on the mean values of PPG Amplitude and PTT after apnoeic and hypopneic events. After obtaining the results for the corresponding statistic analysis and Wilcoxon test comparing stimulated event to not stimulated, no significative values were obtained so we decided to carry on a more exhaustive method based on the analysis event per event.

The chosen analysis method is based on delta calculation between the signal before and after each respiratory event. In first place, we calculate the mean value of the signal from 10s before the start of the event to the start of the event. This way we obtained a reference value.

Eq. 4

$$Ref = S(s(i) - (10 * fs) : s(i))$$

Being S the analysed signal (PPG or PTT), s the vector which contains the sample number at which the event start, i the number of event we are analysing, fs our sampling rate and Ref the reference value we are looking for.

Following *J.Pagani et al.* [16], we are going to use the length of four respiratory cycles after the end of the event to analyse the effect on the signals. Defining a respiratory cycle as the piece of signal detected from the detected intersection point in the ascending wave (inhalation) to the same point in the following wave. We have chosen four of them because it was the average respiratory cycles we could find in our signals. Moreover, we have just used signals which actually had this number of cycles for a more accurate analysis. These cycles were detected by means of a function which returned the positions of the beginning of the first and the end of the fourth respiratory cycle for apnea and hypopnea separately. This function will be commented in the following section. During the period of time between detections the minimum value of the analysed signal was searched and saved under the name of *inc*.

Eq. 5

$$inc = \min(S(r_1 : r_4))$$

Being r_1 the beginning of the first respiratory cycle and r_4 the end of the fourth respiratory cycle.

Finally, to have our delta value we subtract inc value to Ref as showed in Eq. 6.

Eq. 6

$$\delta = Ref - inc$$

Where δ is the delta value we were looking for. In figure Figure 3.8 and Figure 3.7 we have a graphic representation of delta method for a stimulated and non-stimulated event, for PPG amplitude and PTT.

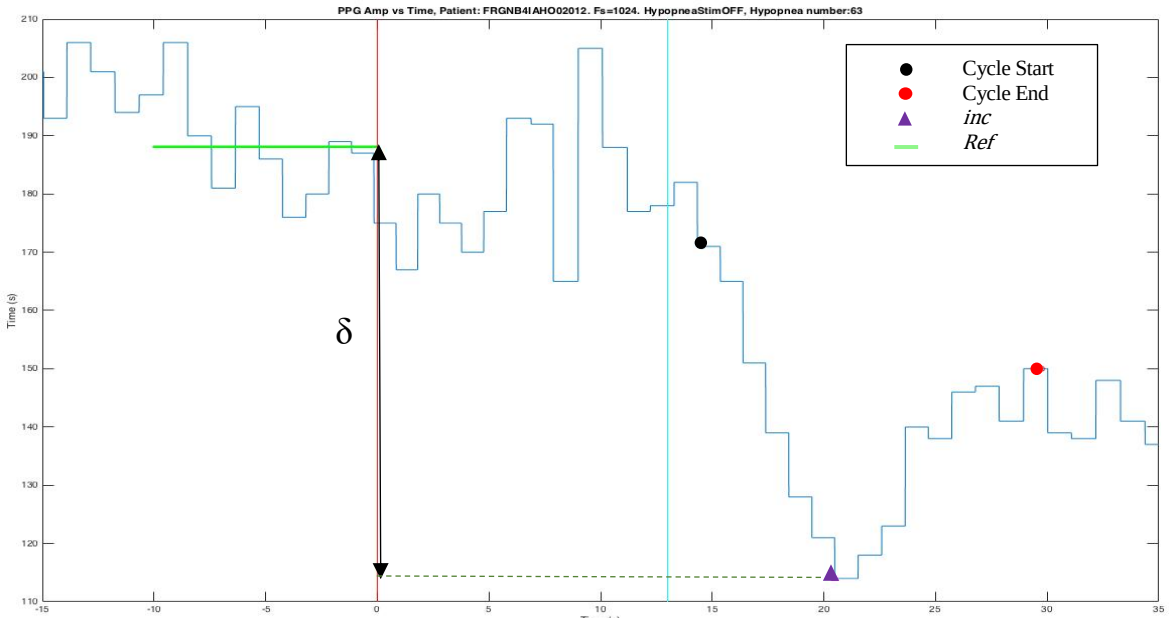

Figure 3.7Delta method for non-stimulated hypopnea on PPG Amplitude signal.

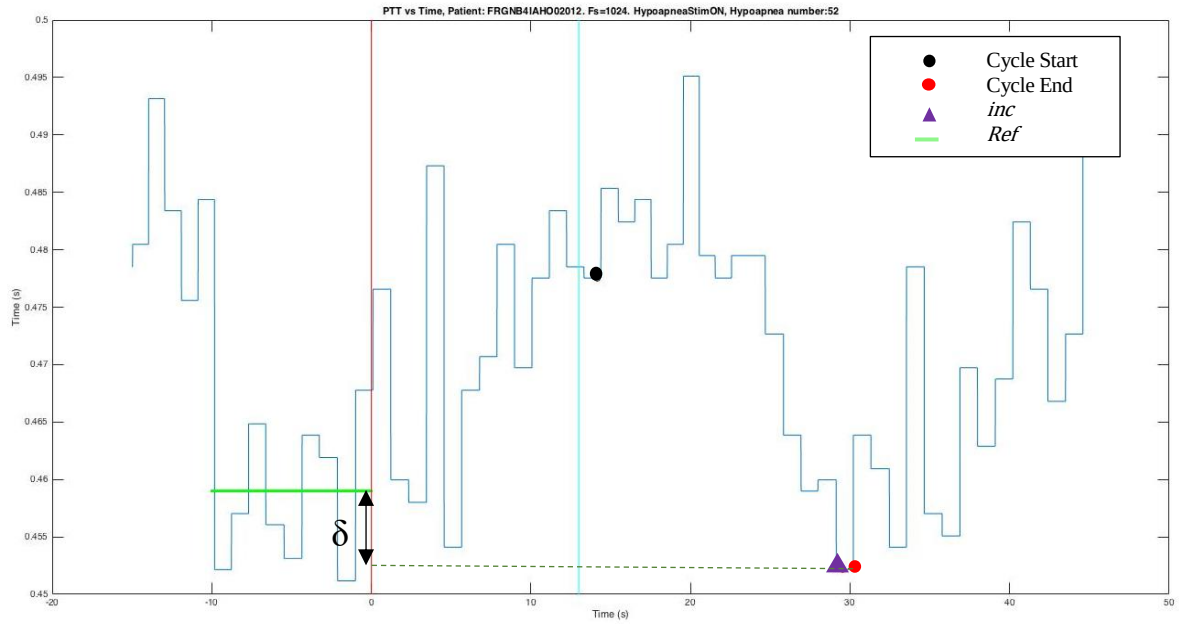

Figure 3.8 Delta method for a stimulated hypopnea for PTT.

Running this procedure for all patients and all events we obtained the necessary input data to develop the statistical analysis. For each patient, we extracted the mean delta value for apnea and hypopnea, standard deviation, median value, Q1 and Q3. To determine whether the obtained results were significant, we carried on a Wilcoxon test the output of which must be $p<0,05$ to be considered as significant.

Regarding the theoretical background, when an hypoxia (diminished availability of oxygen to the body tissues.) takes place, there is an increase in sympathetic activity causing vasoconstriction, which is reflected in pulse photoplethysmography (PPG) signal by decreases in the signal amplitude fluctuation[17], as we could observe in the previous figures. Moreover, pulse transit time (PTT) decreases after an apnoeic event due to a sympathetic activation which produces heart rate increment, higher stroke volume, and vasoconstriction, which in turn, generate pulse wave acceleration[13]. Regarding this information, our hypothesis is that our therapy must avoid the effect of respiratory events, which means that the obtained increment value is not significantly higher or lower in relation to the reference one for stimulated events. For this reason, we developed the Wilcoxon test in both right and left senses to find in which patients the stimulation had no effect (signal decrease) or had a too meaningful effect (signal increase).

The results of the Wilcoxon test can be found in the corresponding section of Results chapter, the result to the statistical analysis can be found in Tables A1-A4 in the Annexes.

3.3.3. Disclosure

The main aim of this part of the was to produce plots of each respiratory event of each patient to be able to produce a random check of the performance of the implemented method. In these plots, we represented the respiratory signal with indications of start and end detections of the respiratory events, stimulation signal and PTT/PPG amplitude signal. Both respiratory and PTT/PPG Amplitude signals have represented the limits of the windows used along the method.

With this graphical representation, we can determine if the detections were accurate and whether the obtained results were right. To this extent, we could consider these plots as check ones.

In the following figures (Figure 3.10 and Figure 3.9), we can find an example of these plots which were used to follow the development of our analysis.

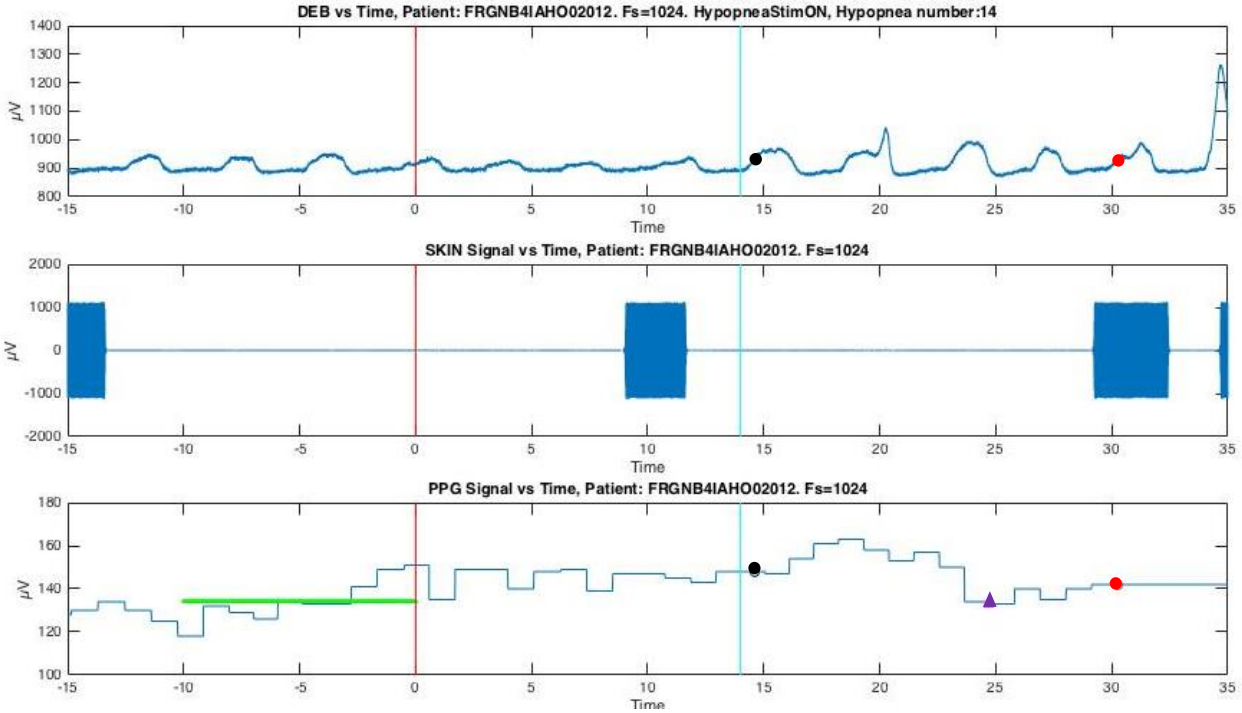

Figure 3.9 Check plot for subject FRGNB4IAHO02012 hypopnea 14, PPG amplitude analysis.

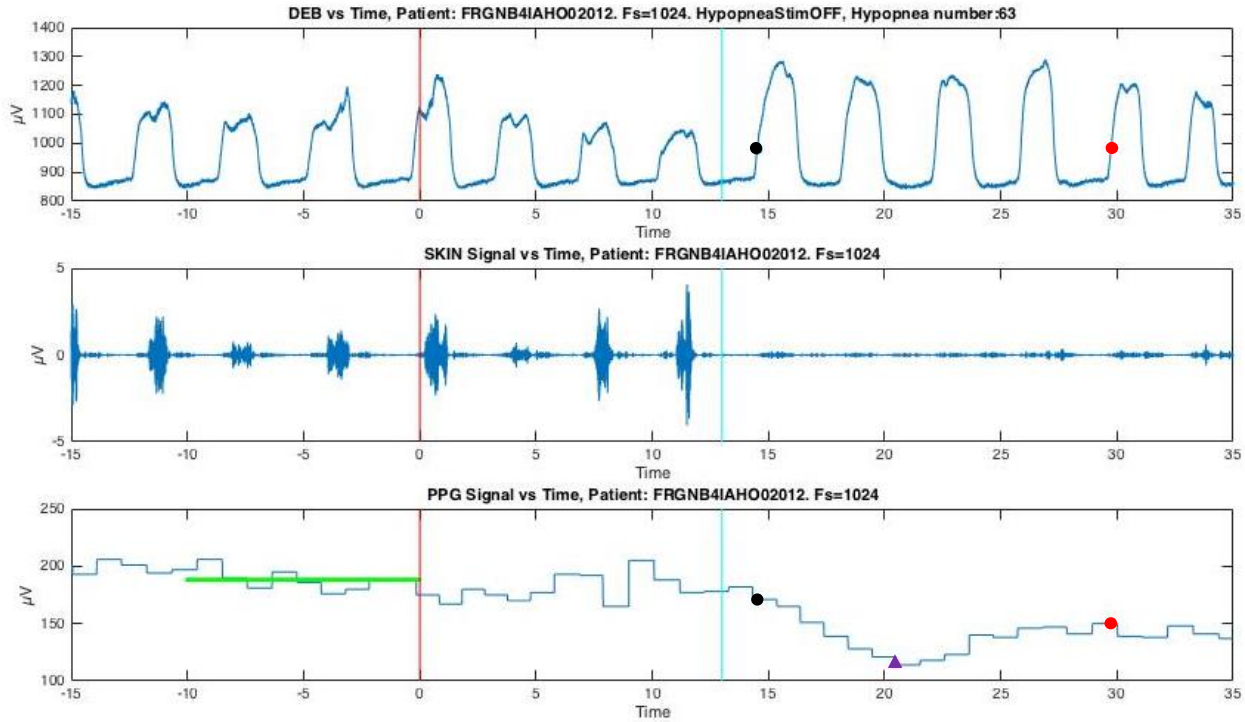

Figure 3.10 Check plot for subject FRGNB4IAHO02012 hypopnea 63, PPG amplitude analysis.

Finally, the most significant extracted parameters are saved in order to upload them in LTSI's database. From each ECG signal we extracted the RR series, R-wave detection and PTT with coordination of PPG signal, from which PPG amplitude was extracted.

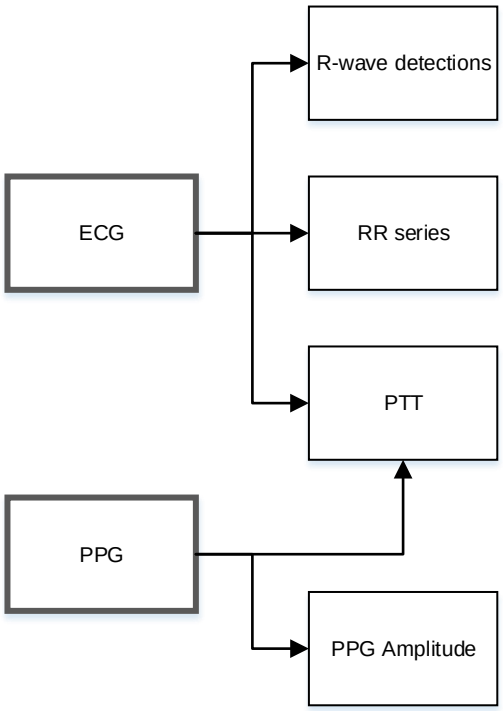

Figure 3.11 Precedence of the stored data in LTSI's database.

3.4. Respiratory Cycles detection

Normally, functions are not explained because they are not of high importance in the analysis development, however, the implementation of this one plays a key role in our project because it provides not only the detections of the beginning and the end of the respiratory cycles, but also selects the respiratory events after which we can find the number of desired cycles. Before creating the function to detect respiratory cycles, the periods were detected by means of *findpeaks* MATLAB command. However, as the signal was not uniform, had a really high sample frequency and had different characteristics depending on the patient and on the data acquisition calibration, the resultant output data contained lots of mistakes.

In order to develop a robust function, we have to make sure it gets the correct detections. To achieve it, our program analyses a window of the input signal which goes from the sample where the respiratory event ends to 25s after as it can be observed in Eq. 7. This value was taken knowing that the average duration of a cycle is 2s and during sleep it is longer, anticipating the fact that in-between cycles we can find a respiratory event which will create a longer duration.

Eq. 7

$$W = S(e(i) : e(i) + (25 * fs))$$

Where W is the window, S is the signal we were processing, e is the end of the respiratory event, i is the counter of events and fs is the sampling rate.

Afterwards, we calculate the mean value of the samples contained within the window. This value will be very useful because we used it as a threshold value in the following step. Having obtained the mean value, we looked for the points in which the respiratory signal crossed the threshold, in other words, for which samples the actual value was lower than the threshold and the next one was higher or vice versa.

To get rid of fake detections caused by signal noise, we imposed the condition that consecutive detections must be separated by a distance of the 30% of the sampling rate. That means that at least a respiratory cycle must last 0,3 s. We took such a low value because it has been observed that many times after an apnea takes place the patient realises a very quick inspiration which we have also counted as respiratory cycle. These quick cycles are a result of the attempt to restore normal breath after an apnea or hypopnea.

Once all intersections are detected, we made sure that at least 9 points were detected, 4 respiratory cycles. Afterwards, all found intersections were classified as ascendant, assigning them a 1, or descendant,

assigning them a 0 in a check vector. Perfect detections would have a special pattern in their check vector: [1 0 1 0 1 0 1 0 1]. Given that, we looked for this motif in the check vector and saved the position of the first detection and the position of the last one. In Figure 3.12 we can find an example of the output window taken as a result of the detection of the beginning of the first cycle and the end of the fourth.

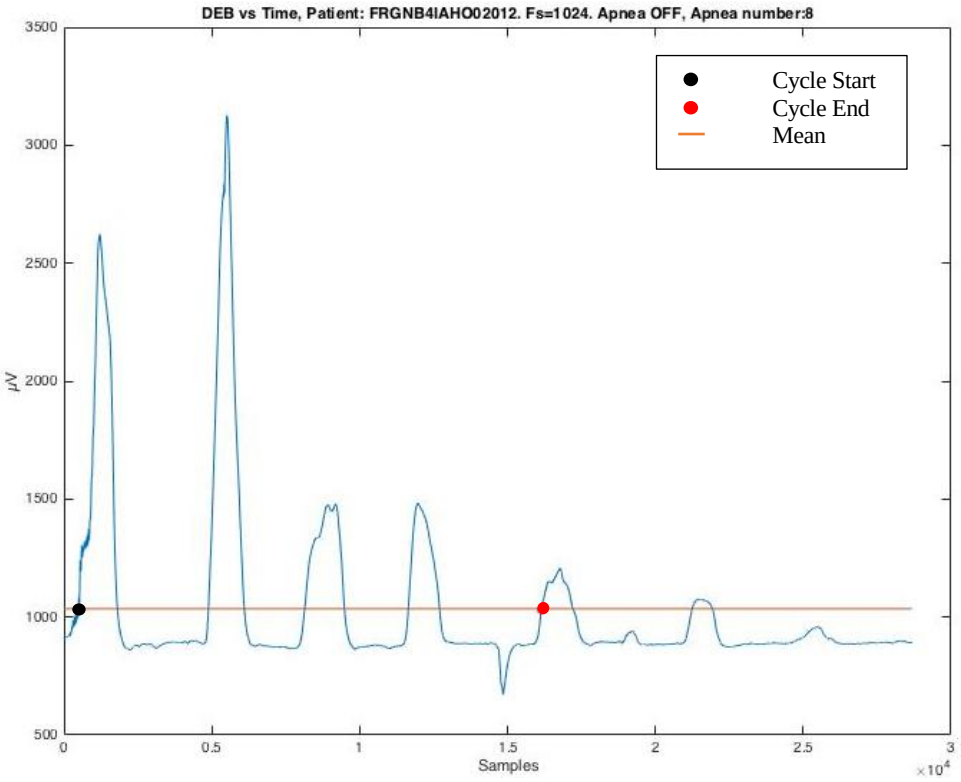

Figure 3.12 Example of output detection of the begining of the first respiratory cycle and the end of the fourth.

Although this is the main detection method, due to interpersonal difference and non-identical data acquisition calibration, some special-case-mean modifications had to be included in the code. This way we increased the number of correct detections and decrease missed ones.

The first special case introduced was focused on the events when the mean window value is found in a zone with lots of noise. In these cases, the best solution was to lower the threshold value 15 μV so that the threshold found a cleaner signal zone. This value was determined empirically from disclosure observation. By doing it, we got rid of the problematic areas and it was easier for our program to establish correct detections. In Figure 3.13, Figure 3.14 and Figure 3.15 the benefits of the implementation of the particular-case methods can be observed.

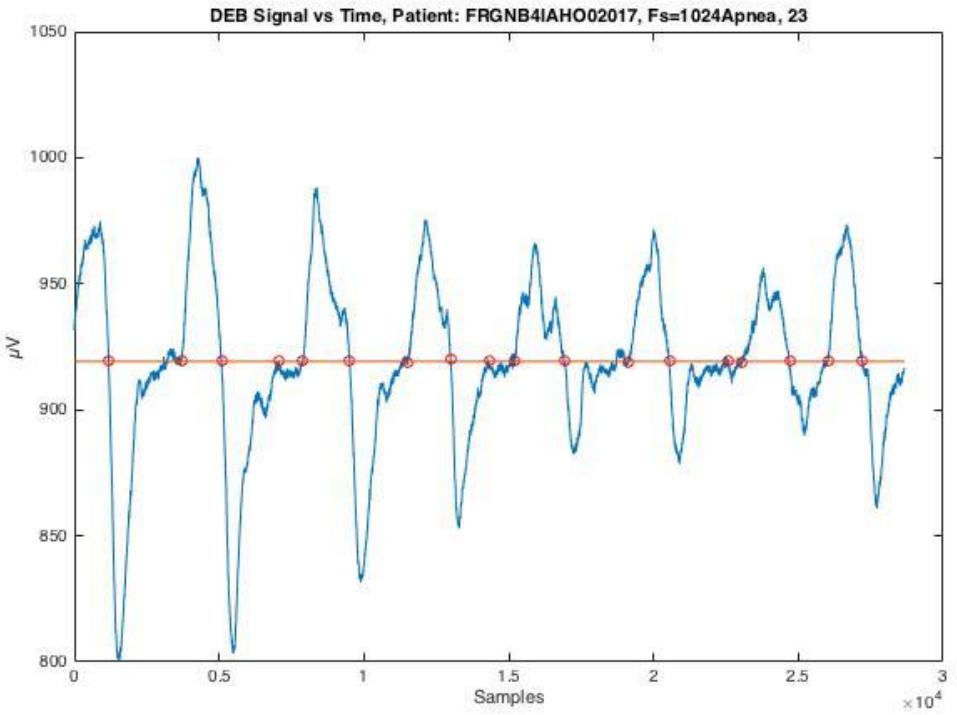

Figure 3.13 Intersection detections with basic respiratory cycles method.

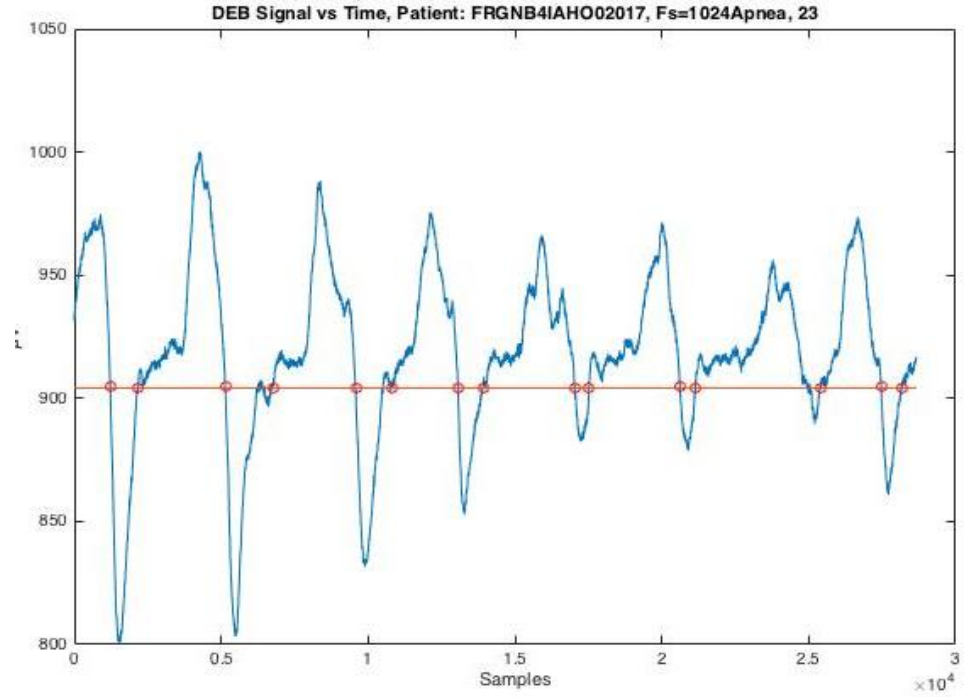

Figure 3.14 Intersections detections with respiratory cycles particular-case method 1.

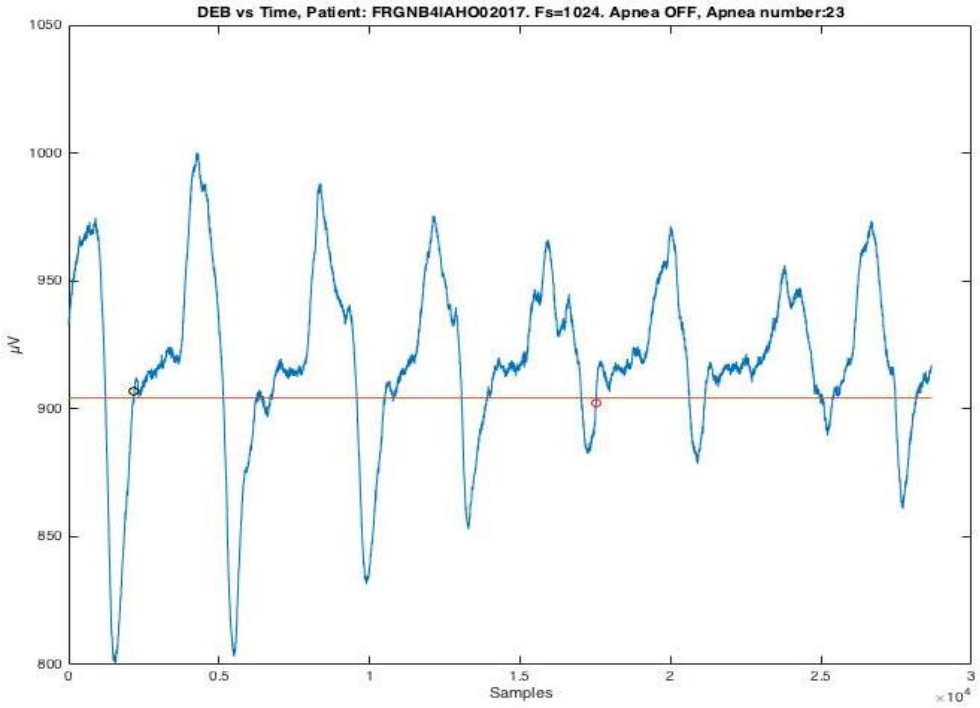

Figure 3.15 Output window after detecting correctly the four respiratory cycles.

The second particular-case method introduced was for those windows which contained relatively high maxima and low minima and as a result their mean value was located in a zone of signal instability. For that reason, the proposed solution was to multiply the mean value for 2.5 and move it to a cleaner zone. This value was also stablished after check plots observation.

Moreover, the distance between intersections was also increased to the 40% of the sampling rate. Its reason why was because the points would be localized in the ascending or descending part of the wave so, theoretically, they would be positioned further apart one from each other. In the following figures (3.16-3.18), we can find an example:

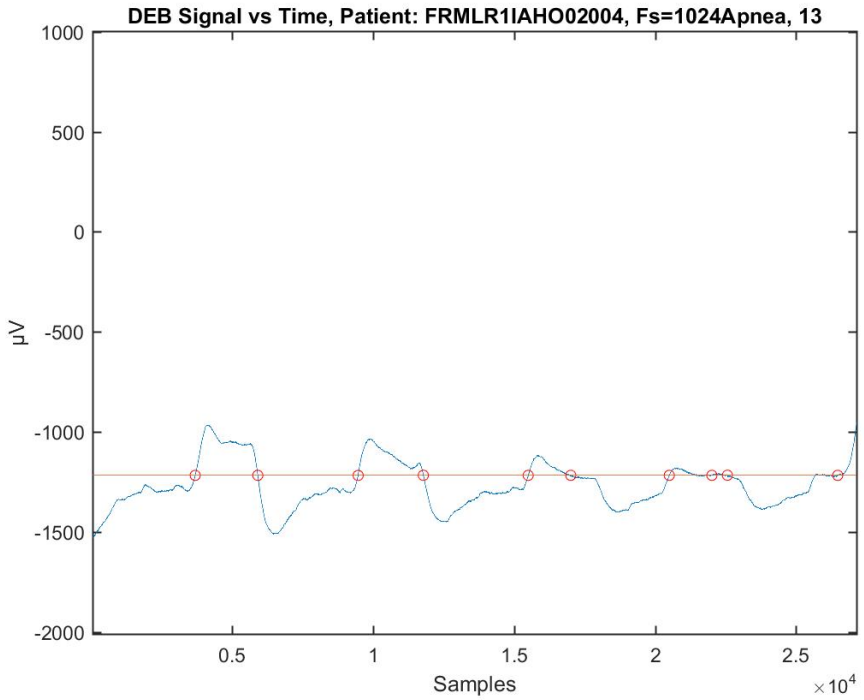

Figure 3.16 Intersection detections using basic respiratory cycles detector method.

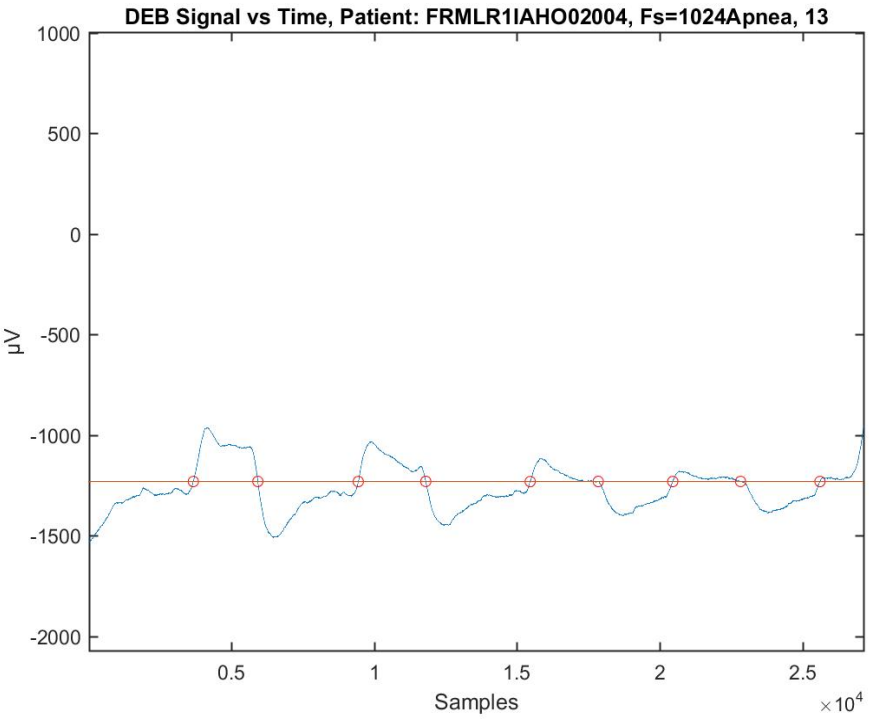

Figure 3.17 Detections of respiratory cycles for particular-case method 2.

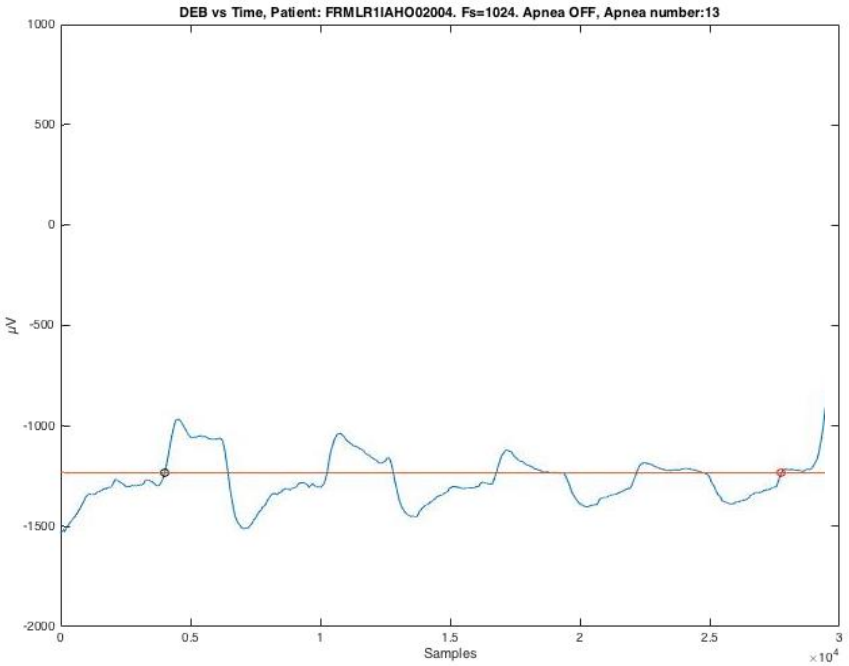

Figure 3.18 Output window from the respiratory cycles detection function using particular-case method 2.

4. Environmental impact analysis

This chapter will talk about the environmental impact of the project, which means the consequences from a wrong usage, a bad function of the presented device in PASITHEA's objectives or a wrong analysis carried on.

As previously said in the introduction, PASITHEA's device is presented as a new therapy to Sleep Apnea Syndrome (SAS), which is a multifactorial disease characterized by repeated episodes of breathing pauses (apnea) or significant reductions in respiratory amplitude (hypopnea) during the patient's sleep The sleep apnea syndrome (SAS) has a prevalence in middle age of 2% in women and 4% in men [1] and has a high impact in populations suffering from cardiovascular diseases and type 2 diabetes (long term metabolic disorder characterized by high blood sugar, insulin resistance, and relative lack of insulin), where the presence of SAS increases the risk of complications.

Patients suffering from SAS show apnea or hypopnea episodes that can be repeated from 5 to 100 times per hour of sleep, with durations ranging from 10 seconds to several minutes, strongly affecting the sleep structure of the patient. Regarding therapy, the gold-standard treatment is by continuous positive airway pressure (CPAP). The CPAP machine delivers a continuous stream of compressed air via a nose or full-face mask. This positive pressure keeps the airway open and prevents it from collapsing, so that unobstructed breathing becomes possible Yet, its minimal therapeutic usage is still unknown and improvements are needed [3]. Moreover, its effect on blood pressure is a subject of controversy in the scientific community [2] being claimed to reduce daytime sleepiness and the risk of cardiovascular morbidity and mortality in the most severely affected patients but not for moderately affected ones for whom CPAP therapy may not be suitable [4].

Treating SAS is very important as it has a wide variety of side effects which can cause significant sleep fragmentation and acute cardiorespiratory responses, that may be deleterious in the long term, being associated with higher cardiovascular and metabolic morbidities. Moreover, SAS represent a major healthcare issue, affecting more than 5% of the middle-aged population [6].

Therefore, new therapeutic solutions are also needed. As a consequence, LTSI has developed this method for detecting, monitoring and treatment of SAS to improve the quality of life of people suffering from this disease. Different analysis has been carried on and this project is one of them, to discover which is the real consequence to stimulation regarding blood pressure changes. A bad performance of the device could lead to systemic hypertension and an increase in the likelihood of cardiovascular diseases [13].

A bad analysis would provoke a false idea of its effect resulting to be health damaging for the subjects who uses it thinking it will improve their quality of life.

5. Results

In this chapter, we are going to present the obtained results of our analysis. Firstly, we show the results concerning PPG Amplitude for apnea and hypopnea in different sections not to confuse them. In second place, PTT analysis results can be found, and as said previously, apnea results are separated from hypopnea ones. Statistic analysis results are not placed in this section, they can be found in the annex.

5.1. PPG Amplitude results

In the first place, PPG amplitude results are presented. This are divided in two sections: results for Apnea and for Hypopnea. In each section, we will find a table which shows the results of the Wilcoxon rank sum test.

5.1.1. Apnea

Patients	P-Value Apnea	h2 Right	P-Value Apnea	h2 Left
FRGNB4IAHO02009	0,0206	1	0,9798	0
FRGNB4IAHO02010	0,3372	0	0,6653	0
FRGNB4IAHO02012	0,0844	0	0,9308	0
FRGNB4IAHO02013	0,9588	0	0,0424	1
FRGNB4IAHO02014	0,4765	0	0,5706	0
FRGNB4IAHO02015	0,9864	0	0,0154	1
FRGNB4IAHO02016	0,9167	0	0,1310	0
FRGNB4IAHO02017	0,3874	0	0,6187	0
FRGNB4IAHO02018	0,9785	0	0,0221	1
FRGNB4IAHO02020	0,9643	0	0,0714	0
FRGNB4IAHO02022	0,6190	0	0,3832	0
FRGNB4IAHO02023	0,4043	0	0,5993	0
FRGNB4IAHO02024	0,7568	0	0,2626	0
FRTRS5IAHO02007	0,7771	0	0,2327	0
FRTRS5IAHO02010	0,0983	0	0,9122	0
FRMLR1IAHO02001	0,4465	0	0,5552	0
FRREN4IAHO02003	0,9170	0	0,0835	0
FRREN4IAHO02004	0,1307	0	0,8954	0
FRMLR1IAHO02004	0,9896	0	0,0107	1

Table 5.1. Wilcoxon rank sum test for PPG amplitude.

Table 5.1. shows results from Wilcoxon test in which the results from delta left and right analysis are shown. We are going to consider only 19 of the 20 patients because one of the studied subjects did not have any stimulated apnea.

Right analysis means that delta value for stimulated events (ON) is significantly higher than for non-stimulated events (OFF), in other words, vasoconstriction is more significant in ON events. For this analysis, we have just one patient with a p-value lower than 0.05 that represents the 5,26% of our patient population.

Left analysis means that delta value for non-stimulated events (OFF) is significantly higher than for stimulated events (ON), meaning vasoconstriction is more significant in OFF events. For PPG apnea analysis, we have 4 patients with a p-value lower than 0.05 which represents the 21,05% of our patient population.

For the other patients, we did not obtain significative results ($p<0,05$).

5.1.2. Hypopnea

Patients	P-Value Hypopnea Right	h2 Right	P-Value Hypopnea Left	h2 Left
FRGNB4IAHO02009	0,0000	1	1,0000	0
FRGNB4IAHO02010	0,0444	1	0,9559	0
FRGNB4IAHO02012	0,5411	0	0,4625	0
FRGNB4IAHO02013	0,0381	1	0,9623	0
FRGNB4IAHO02014	0,7500	0	0,5000	0
FRGNB4IAHO02015	0,1552	0	0,8488	0
FRGNB4IAHO02016	0,6587	0	0,3464	0
FRGNB4IAHO02017	0,3426	0	0,6841	0
FRGNB4IAHO02018	0,7385	0	0,2631	0
FRGNB4IAHO02019	0,0919	0	0,9106	0
FRGNB4IAHO02020	0,9274	0	0,0736	0
FRGNB4IAHO02022	0,3896	0	0,6116	0
FRGNB4IAHO02023	0,5062	0	0,4979	0
FRGNB4IAHO02024	0,0674	0	0,9340	0
FRTRS5IAHO02007	0,0663	0	0,9344	0
FRTRS5IAHO02010	0,5242	0	0,4879	0
FRMLR1IAHO02001	0,6552	0	0,3520	0
FRREN4IAHO02003	0,9722	0	0,0476	1
FRREN4IAHO02004	0,3774	0	0,6251	0
FRMLR1IAHO02004	0,8097	0	0,1934	0

Table 5.2 Wilcoxon test results for PPG amplitude Hypopnea.

Table 5.2. shows results from Wilcoxon test in which results from hypopnea delta left and right analysis are shown.

Right analysis means that delta value for stimulated events (ON) is significantly higher than for non-stimulated events (OFF), vasoconstriction is more significant in ON events. For this analysis, we have 3 patients with a p-value lower than 0.05 which represents the 15% of our patient population.

Left analysis means that delta value for non-stimulated events (OFF) is significantly higher than for stimulated events (ON), in other words, vasoconstriction is more significant in OFF events. For PPG

hypopnea analysis, we have 1 patient with a p-value lower than 0.05 which represents the 5% of our patient population.

5.2. PTT Results

For PTT results the same presentation structure is followed. The analysis is divided in Apnea and Hypopnea, in each part we can find attached a table containing the Wilcoxon rank sum test, the tables containing the statistic parameters can be found in the annex.

5.2.1. Apnea

Patients	P-Value Apnea Right	h2 Right	P-Value Apnea Left	h2 Left
FRGNB4IAHO02009	0,8622	0	0,1398	0
FRGNB4IAHO02010	0,3225	0	0,6800	0
FRGNB4IAHO02012	0,8779	0	0,1449	0
FRGNB4IAHO02013	0,8885	0	0,1140	0
FRGNB4IAHO02014	0,8191	0	0,2162	0
FRGNB4IAHO02015	0,9167	0	0,0910	0
FRGNB4IAHO02016	0,9881	0	0,0238	1
FRGNB4IAHO02017	0,7376	0	0,2677	0
FRGNB4IAHO02018	0,9631	0	0,0379	1
FRGNB4IAHO02020	0,6786	0	0,4286	0
FRGNB4IAHO02022	0,9543	0	0,0463	1
FRGNB4IAHO02023	0,2566	0	0,7464	0
FRGNB4IAHO02024	0,9864	0	0,0158	1
FRTRS5IAHO02007	0,1692	0	0,8388	0
FRTRS5IAHO02010	0,1351	0	0,8781	0
FRMLR1IAHO02001	0,7334	0	0,2679	0
FRREN4IAHO02003	0,2784	0	0,7227	0
FRREN4IAHO02004	0,6797	0	0,3660	0
FRMLR1IAHO02004	0,1471	0	0,8559	0

Table 5.3 Wilcoxon test results for PTT Apnea.

Table 5.3. shows results from PPG Wilcoxon test in which results from apnea delta left and right analysis are shown. We are going to consider only 19 of the 20 patients because one of the subjects did not have any stimulated apnea.

Right analysis means that delta value for stimulated events (ON) is significantly higher than for non-stimulated events (OFF), which means that vasoconstriction is more significant in ON events. For this analysis, we have no patient with a p-value lower than 0.05 which represents the 0% of our patient population.

Left analysis means that delta value for non-stimulated events (OFF) is significantly higher than for stimulated events (ON), meaning vasoconstriction is more significant in OFF events. For PTT apnea analysis, we have 4 patients with a p-value lower than 0.05 which represents the 21,05% of our patient population.

5.2.2. Hypopnea

Patients	P-Value Hypopnea Right	h2 Right	P-Value Hypopnea Left	h2 Left
FRGNB4IAHO02009	0,0008	1	0,9992	0
FRGNB4IAHO02010	0,0012	1	0,9988	0
FRGNB4IAHO02012	0,1439	0	0,8581	0
FRGNB4IAHO02013	0,0040	1	0,9961	0
FRGNB4IAHO02014	1,0000	0	0,2500	0
FRGNB4IAHO02015	0,8006	0	0,2042	0
FRGNB4IAHO02016	0,7581	0	0,2463	0
FRGNB4IAHO02017	0,7581	0	0,2655	0
FRGNB4IAHO02018	0,4021	0	0,5997	0
FRGNB4IAHO02019	0,0168	1	0,9838	0
FRGNB4IAHO02020	0,5150	0	0,4877	0
FRGNB4IAHO02022	0,3837	0	0,6174	0
FRGNB4IAHO02023	0,3490	0	0,6548	0
FRGNB4IAHO02024	0,1403	0	0,8622	0
FRTRS5IAHO02007	0,0249	1	0,9754	0
FRTRS5IAHO02010	0,3810	0	0,6305	0
FRMLR1IAHO02001	0,0818	0	0,9211	0
FRREN4IAHO02003	0,2738	0	0,7897	0
FRREN4IAHO02004	0,2884	0	0,7139	0
FRMLR1IAHO02004	0,0601	0	0,9412	0

Table 5.4 Wilcoxon text results for PTT Hypopnea.

Table 5.4. shows results from Wilcoxon test in which results from PTT hypopnea delta left and right analysis are shown.

Right analysis means that delta value for stimulated events (ON) is significantly higher than for non-stimulated events (OFF), which means that vasoconstriction is more significant in ON events. For this analysis, we have 5 patients with a p-value lower than 0.05 which represents the 25% of our patient population.

Left analysis means that delta value for non-stimulated events (OFF) is significantly higher than for stimulated events (ON), which means vasoconstriction is more significant in OFF events. For PPG

hypopnea analysis, we have 0 patients with a p-value lower than 0.05 which represents the 0% of our patient population.

6. Discussion

Along this project apnea and hypopnea have been analysed to study the activation of parasympathetic system to influence blood vessels by means of kinaesthetic stimulation. After observing the obtained results, we can conclude that hypopneas have been treated in a too general way given that their morphologies can vary from one to another. In addition, oxygen saturation levels during respiratory events play a key role in autonomic nervous system activation as many other physiological aspects that were not taken into account. Finally, further analyses are needed and are being conducted to be able to reach a plausible conclusion for hypopneas.

On the other hand, for apnea analysis we are able to observe important characteristics. To begin, we are going to discuss apnea results for PPG amplitude analysis. For the previous one, we had a population of 19 subjects due to the fact that we had to delete one because it had no stimulated apnea and it could compromise our study. From the 19 remaining, we obtained a statistically significant decrease ($p<0.05$) in delta value for stimulated events respect to non-stimulated for 4 patients, who also had statistically significant decrease in their oxygen saturation analysis, which can be found in the annex. That means that their pulse wave amplitude increased after simulation as a result of blood vessels vasodilatation produced by a parasympathetic response to stimulation. These subjects had an average decrease of 43,57% of their delta mean value, meaning that their pulse amplitude was a 43,57% more similar on stimulated events. On the other hand, we obtained one subject which showed non-stimulated PPG amplitude values with a lower delta value than stimulated ones, consequence of an increase of vasoconstriction due to sympathetic activation, which is the opposite effect we wanted to produce. This is a possibility that we had to have in mind, the possibility of producing the opposite effect than the desired one. That may be a consequence of bad patient population selection or due to other physiological activation aspects we did not take into account. In Figure 6.1 we can find a schema of the hypothetical physiological response to kinaesthetic stimulation. For the rest of the studied patient population we did not obtain significant results.

After obtaining these results, we can affirm that the research is being conducted on the right direction, however, further analyses are needed to precise other physiological aspects that were not considered in this project.

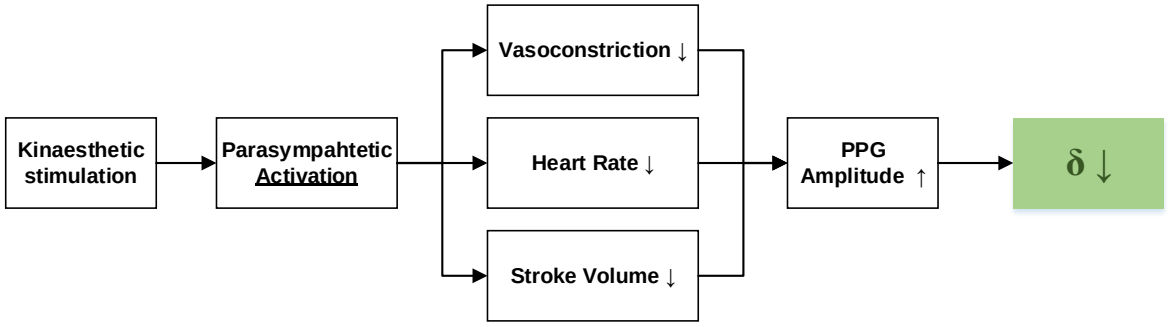

Figure 6.1 Hypothetic physiologic response to kinaesthetic stimulation.

For PTT apnea analysis, we counted on a 20-subject population. Out of which for 4 subjects we obtained statistically significant results ($p<0.05$). The previous showed a significant delta value which was lower for stimulated apnea than for non-stimulated ones, a mean of 65,48% lower for ON with respect from OFF events. Three out of these four subjects showed to be responders in oxygen saturation analysis. This effect is a consequence of stimulation which provoked a parasympathetic activation, decreasing heart rate and stroke volume, causing vasodilatation and finishing in an increase of pulse transit time which decreased delta value. In Figure 6.2 we can find a schema of the hypothetic physiological response to kinaesthetic stimulation. No statistically significant values were found for right sided analysis, so no opposite effect was produced in any subject. For the rest of subjects, we didn't obtain significant results and further analyses should be carried on because, at the moment, it is not possible to determine the produced effect on them.

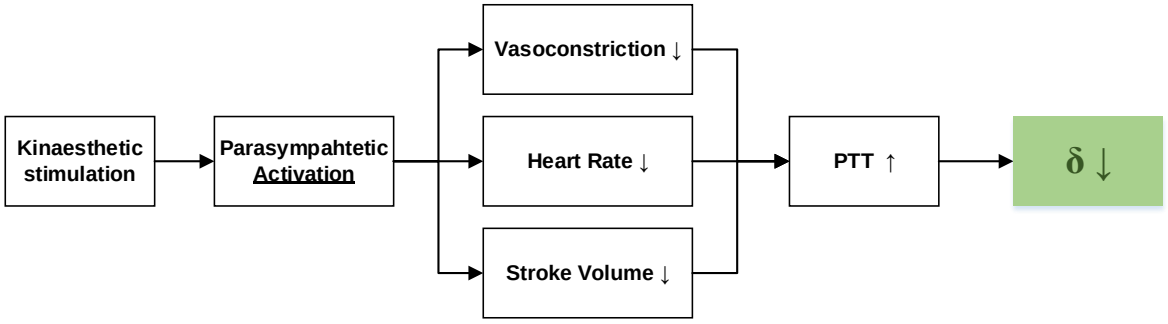

Figure 6.2 Hypothetic physiological response to kinaesthetic stimulation.

Sleep Apnea Syndrome (SAS) is a complex clinical problem which depends on several physiological aspects. Along this project, we have focused on the effect on parasympathetic activation regarding nothing but the response on PPG amplitude and PTT, but it should be studied taking into account many other aspects like oxygen saturation, personal illnesses, autonomic response or sleep stage, that's why further research is being conducted.

7. Conclusions

Regarding the analysis of autonomic nervous system response analysis in subjects suffering from sleep apnea/ hypopnea syndrome we can firmly affirm that further research must be conducted. For apnea, in PPG amplitude and in PTT analysis we have obtained a 21,05% and 20% respectively of patient population who had a reduction effect on vasoconstriction. This percentage is too low to affirm that the proposed therapy developed a beneficial effect on vasoconstriction. On the other hand, it is not a low enough percentage to quit the research. Moreover, we just obtained one patient for PPG amplitude and none in PTT analysis which showed the contrary effect to the desired one. That means that the proposed therapy does not provoke cardiorespiratory system illnesses.

For hypopnea, we obtained a 15% and a 20% of patient population for PPG amplitude an PTT analysis respectively who showed an increase of delta value, meaning that vasoconstriction was increased. Though, we concluded that for hypopnea the conducted analysis was too general given that these types of events can have a wide variety of morphologies with different physiological effects which should be deeply studied.

In addition, for both apnea and hypopnea analysis, patients were eligible for the study if they had a history of severe obstructive sleep apnea within the past 6 months, with evidence of periodic breathing with apnea. Consequently, another cause for the lack of response may be due to inappropriate patient selection, for example patients presenting an autonomic dysfunction. Another cause may be that during data acquisition, stimulation properties (amplitude, burst duration, frequency) were the same for all patients and kept constant during the whole night, which should be improved to adapt it to patient characteristics to improve its performance.

Regarding the experience of working in LTSI, there was a complete integration and adaptation in the team, as well as being familiar with the laboratory's facilities and being used to its working environment.

On the other hand, this internship has tough me how it is like to work in the research field, teaching me many things like how to look for inspiration in the literature when the analysis arrived to a dead end, how to ask for help whenever is needed and not feeling embarrassed about it, how to recognize different morphologies of QRS complexes even if they are upside down, how to detect respiratory cycles of all morphologies, and to improve my MATLAB skills among many others. But one of the most important things I have learned during these 5 months is how, through a computer, we can be able to observe

people's health problems and, even though we can just see graphics or signals, never forget they come from a human being, always keeping in mind that our goal is to improve people's quality of life.

To end, this experience has also given me the opportunity to be in a foreign country and to improve my level of French and English language as well as the chance to meet people from all around the world, letting me discover their cultures and their opinions, broadening my horizons for starting new adventures in the future.

8. Economic Analysis

In this section of the project all economic expenses are explained. The economic analysis will have the same scope as the project itself, which means, it will not have into account the cost of data acquisition and previous analysis carried on. More precisely, it will be divided into the following parts: Engineering costs and office IT costs.

The engineering costs are estimated as 25 €/h as the average salary for a junior engineer.

1.1. Engineering costs

In this part of the economic analysis we are going to show the costs of engineering work for the different functions that needed to be done.

Phase	**Hours**	**€/h**	**Phase cost (€)**
Literature Reading	31	25	775
Codes development	413	25	10325
Report writing	61	25	1525
Meetings	6	25	150
Total cost			**12775**

Table 8.1 Engineering costs.

1.2. Office IT costs

As this project has been developed entirely in a computer soported base some licences are needed. The principal used programmes are MATLAB and pack Office 2017.

Program	**Cost (€)**
MATLAB	500
MATLAB Report Generator	200
Signal Processing Toolbox	200
Microsoft office professional 2016	253,90
Total	**1153,9**

Table 8.2 Office IT costs.

1.3. Total costs

Finally, a table with all the expenses is presented. In this recap table, we can find the total of all previously presented tables and the expenses due to meetings with the research team and project coordinators.

Concept	**Cost (€)**
Engineering Costs	12775
Office IT	1153,9
Total	13928,9
Total (with IVA 21%)	**16853,9**

Table 8.3 Total project costs.

Finally, we can affirm that the total cost of hiring an intern to develop this project has been **16853,9**€.

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Annex

PPG Amplitud statistic analysis for Apnea events

Patients	**Mean Delta Apnea OFF**	**Mean Delta Apnea ON**	**Std Apnea OFF**	**Std Apnea ON**	**Median Apnea OFF**	**Median Apnea ON**	**Q3 Apnea OFF**	**Q3 Apnea ON**	**Q1 Apnea OFF**	**Q1 Apnea ON**
FRGNB4IAHO02009	63,8492	80,5103	35,2124	25,9662	60,6168	81,0223	87,7170	100,5690	40,3370	63,9980
FRGNB4IAHO02010	4,0999	6,6497	21,4017	24,0415	2,1107	8,3010	17,5844	17,6910	-9,7856	-9,3050
FRGNB4IAHO02012	23,6265	49,5143	31,0208	20,9310	24,1216	50,2324	43,0057	65,1158	1,8886	33,7332
FRGNB4IAHO02013	40,6091	24,5033	35,4374	29,3273	34,7619	22,3387	61,6863	48,3376	19,7044	4,2883
FRGNB4IAHO02014	17,0736	19,2272	10,7634	18,0208	13,5523	15,2449	25,2555	34,5973	9,7719	8,0748
FRGNB4IAHO02015	57,6123	34,6423	28,3078	42,2207	51,9593	29,6230	64,0733	51,1341	39,1629	4,9855
FRGNB4IAHO02016	23,0308	-3,5158	21,9277	34,7651	24,0753	-17,0630	41,1917	22,7218	15,5781	-26,3666
FRGNB4IAHO02017	39,6105	46,1894	36,2903	48,9245	30,4938	41,2613	56,9798	81,2310	11,1864	2,9110
FRGNB4IAHO02018	48,0747	31,5635	32,0257	25,1883	49,1320	29,5807	72,6884	57,9496	23,2134	12,2936
FRGNB4IAHO02019	54,0688	NaN	36,9535	NaN	59,1676	NaN	74,2168	NaN	26,5417	NaN
FRGNB4IAHO02020	54,5491	30,1405	22,1296	11,0041	54,5491	27,3542	70,1971	37,7235	38,9011	25,0120
FRGNB4IAHO02022	29,9276	29,1275	17,9902	18,2297	25,1094	24,2956	38,1969	40,7654	18,6146	14,2819
FRGNB4IAHO02023	34,5499	32,3815	24,7379	19,9259	30,9593	35,3852	49,1223	45,7181	16,7893	20,4852
FRGNB4IAHO02024	49,1386	42,8116	25,3070	21,5841	47,0152	40,5031	59,9711	54,0869	28,5728	29,8012
FRTRS5IAHO02007	0,0552	0,0522	0,0402	0,0373	0,0467	0,0349	0,0686	0,0750	0,0325	0,0271
FRTRS5IAHO02010	0,0232	0,0455	0,0395	0,0402	0,0265	0,0488	0,0478	0,0801	0,0189	0,0193
FRMLR1IAHO02001	0,7625	0,8984	0,9165	1,0811	0,6013	0,5620	1,1964	1,4311	0,2933	0,2354
FRREN4IAHO02003	31,2444	26,2182	25,5979	24,9054	30,4965	19,2752	48,5337	42,2017	13,2606	11,5079
FRREN4IAHO02004	10,0339	20,7389	12,6565	10,7343	7,8525	20,7389	19,4695	28,3292	1,1269	13,1486
FRMLR1IAHO02004	0,0554	0,0460	0,0187	0,0222	0,0533	0,0389	0,0709	0,0530	0,0432	0,0338

Table A.1 Statistic Analysis of PPG amplitude delta results for apnea

PPG Amplitud statistic analysis for Hypopnea events

Patients	Mean Delta Hypo OFF	Mean Delta Hypo ON	Std Hypo OFF	Std Hypo ON	Median Hypo OFF	Median Hypo ON	Q3 Hypo OFF	Q3 Hypo ON	Q1 Hypo OFF	Q1 Hypo ON
FRGNB4IAHO02009	33,2246	85,9816	37,7901	36,2884	36,6877	96,3220	61,2718	103,8530	7,4386	63,6629
FRGNB4IAHO02010	21,5525	26,9783	20,5513	18,6614	20,3095	23,3697	34,7128	35,1496	8,3019	15,5839
FRGNB4IAHO02012	21,0243	17,6183	27,3473	31,6012	16,9785	18,7861	42,1384	41,1915	-0,1191	-0,2109
FRGNB4IAHO02013	16,3215	25,1171	32,1349	23,3243	13,4219	24,0510	35,5338	44,6394	0,0000	9,6924
FRGNB4IAHO02014	18,0219	13,1536	0,0000	28,0544	18,0219	-0,6709	18,0219	33,9102	18,0219	-4,1470
FRGNB4IAHO02015	44,7805	57,4718	38,7077	34,2579	35,1109	57,0698	64,9326	84,9707	23,6211	26,2670
FRGNB4IAHO02016	37,5899	35,8521	32,2400	20,7324	39,4161	33,0472	62,4816	50,3567	18,2951	21,7371
FRGNB4IAHO02017	22,4270	32,6036	35,2937	34,8770	22,9263	28,8091	40,7382	64,1404	1,1897	4,7133
FRGNB4IAHO02018	39,8195	35,0571	35,8871	29,7854	35,7244	30,6922	66,0549	47,7806	15,3616	14,3634
FRGNB4IAHO02019	42,9461	53,7599	33,5538	23,0677	42,4973	48,5513	68,8124	72,9893	16,4030	38,8494
FRGNB4IAHO02020	28,1491	21,8358	23,8037	17,5676	27,2182	23,7205	42,7899	34,2109	13,3948	8,9431
FRGNB4IAHO02022	23,3962	23,1031	20,4971	16,8086	17,9917	20,4810	37,7233	31,7352	8,4767	10,1223
FRGNB4IAHO02023	32,8430	30,9473	28,9696	23,9750	27,5181	24,7787	49,4633	50,0529	11,6102	11,6126
FRGNB4IAHO02024	38,1002	46,4409	20,8308	26,3042	37,7333	52,7888	50,9481	64,6775	23,1967	27,0037
FRTRS5IAHO02007	0,0422	0,0474	0,0373	0,0328	0,0324	0,0372	0,0524	0,0556	0,0198	0,0265
FRTRS5IAHO02010	0,0375	0,0487	0,0265	0,0517	0,0314	0,0395	0,0565	0,0502	0,0197	0,0170
FRMLR1IAHO02001	0,9031	0,8242	0,6604	0,5690	0,8355	0,6967	1,2524	1,3231	0,4541	0,3332
FRREN4IAHO02003	40,9476	20,5579	12,7257	17,6454	43,9103	15,0511	48,1189	37,9014	30,8998	9,5105
FRREN4IAHO02004	15,7191	18,1673	20,2397	19,8374	17,9463	21,8147	29,7920	26,3447	2,7948	7,3023
FRMLR1IAHO02004	0,0646	0,0578	0,0209	0,0186	0,0636	0,0638	0,0737	0,0686	0,0524	0,0507

Table A.2 Statistic results for PPG amplitude for Hypopnea.

PTT statistic analysis for Apnea events

Patients	**Mean Delta Apnea OFF**	**Mean Delta Apnea ON**	**Std Apnea OFF**	**Std Apnea ON**	**Median Apnea OFF**	**Median Apnea ON**	**Q3 Apnea OFF**	**Q3 Apnea ON**	**Q1 Apnea OFF**	**Q1 Apnea ON**
FRGNB4IAHO02009	0,0445	0,0459	0,0578	0,0775	0,0373	0,0313	0,0532	0,0406	0,0170	0,0182
FRGNB4IAHO02010	0,0004	0,0107	0,0488	0,0239	0,0074	0,0090	0,0241	0,0294	-0,0080	-0,0075
FRGNB4IAHO02012	0,0339	0,0102	0,0376	0,0289	0,0305	0,0264	0,0388	0,0271	0,0162	-0,0108
FRGNB4IAHO02013	0,0439	0,0190	0,0741	0,0172	0,0214	0,0144	0,0584	0,0272	0,0064	0,0075
FRGNB4IAHO02014	0,0856	0,0155	0,1224	0,0045	0,0176	0,0154	0,1746	0,0175	0,0136	0,0126
FRGNB4IAHO02015	0,0227	0,0171	0,0117	0,0160	0,0240	0,0126	0,0293	0,0156	0,0127	0,0089
FRGNB4IAHO02016	0,0195	-0,0033	0,0090	0,0199	0,0186	0,0031	0,0202	0,0102	0,0126	-0,0184
FRGNB4IAHO02017	0,0523	0,0457	0,0932	0,0949	0,0246	0,0144	0,0594	0,0594	0,0095	0,0046
FRGNB4IAHO02018	0,0503	0,0379	0,0630	0,0636	0,0388	0,0296	0,0614	0,0397	0,0177	0,0115
FRGNB4IAHO02019	0,0280	NaN	0,0206	NaN	0,0262	NaN	0,0421	NaN	0,0141	NaN
FRGNB4IAHO02020	0,0516	0,0298	0,0454	0,0121	0,0516	0,0286	0,0837	0,0318	0,0195	0,0234
FRGNB4IAHO02022	0,0543	0,0448	0,0733	0,0712	0,0324	0,0255	0,0519	0,0426	0,0205	0,0155
FRGNB4IAHO02023	0,0347	0,0278	0,0563	0,0173	0,0236	0,0273	0,0333	0,0350	0,0153	0,0156
FRGNB4IAHO02024	0,0345	0,0216	0,0214	0,0073	0,0313	0,0229	0,0366	0,0257	0,0255	0,0159
FRTRS5IAHO02007	0,0703	0,1378	0,0772	0,1567	0,0480	0,0459	0,1088	0,3332	0,0190	0,0232
FRTRS5IAHO02010	0,0324	0,0422	0,0492	0,0396	0,0297	0,0505	0,0438	0,0688	0,0105	0,0179
FRMLR1IAHO02001	0,0219	0,0218	0,0547	0,0487	0,0134	0,0126	0,0267	0,0219	0,0070	0,0052
FRREN4IAHO02003	0,0373	0,0256	0,0766	0,0267	0,0199	0,0229	0,0335	0,0438	0,0094	0,0069
FRREN4IAHO02004	0,0118	0,0104	0,0053	0,0056	0,0126	0,0104	0,0164	0,0144	0,0094	0,0065
FRMLR1IAHO02004	0,0269	0,0163	0,0713	0,0098	0,0120	0,0160	0,0203	0,0219	0,0069	0,0116

Table A.3 Statistic analysis results for PTT analysis for Apnea.

PTT statistic analysis for Hypopnea events

Patients	Mean Delta Hypo OFF	Mean Delta Hypo ON	Std Hypo OFF	Std Hypo ON	Median Hypo OFF	Median Hypo ON	Q3 Hypo OFF	Q3 Hypo ON	Q1 Hypo OFF	Q1 Hypo ON
FRGNB4IAHO02009	0,0190	0,0371	0,0142	0,0190	0,0164	0,0384	0,0238	0,0537	0,0109	0,0192
FRGNB4IAHO02010	0,0270	0,0533	0,0291	0,0793	0,0242	0,0342	0,0374	0,0579	0,0097	0,0184
FRGNB4IAHO02012	0,0182	0,0232	0,0137	0,0159	0,0165	0,0198	0,0254	0,0243	0,0096	0,0127
FRGNB4IAHO02013	0,0126	0,0204	0,0188	0,0291	0,0113	0,0161	0,0191	0,0237	0,0000	0,0116
FRGNB4IAHO02014	0,0381	0,0155	0,0000	0,0144	0,0381	0,0199	0,0381	0,0254	0,0381	0,0045
FRGNB4IAHO02015	0,0242	0,0211	0,0215	0,0234	0,0193	0,0149	0,0305	0,0240	0,0108	0,0062
FRGNB4IAHO02016	0,0310	0,0261	0,0232	0,0154	0,0267	0,0249	0,0479	0,0324	0,0180	0,0168
FRGNB4IAHO02017	0,0458	0,0265	0,0654	0,0418	0,0410	0,0099	0,0642	0,0545	0,0065	0,0057
FRGNB4IAHO02018	0,0406	0,0467	0,0604	0,0699	0,0289	0,0291	0,0451	0,0420	0,0170	0,0185
FRGNB4IAHO02019	0,0234	0,0285	0,0198	0,0115	0,0186	0,0276	0,0323	0,0380	0,0103	0,0220
FRGNB4IAHO02020	0,0263	0,0249	0,0188	0,0146	0,0224	0,0242	0,0369	0,0322	0,0131	0,0173
FRGNB4IAHO02022	0,0418	0,0466	0,0675	0,0742	0,0238	0,0233	0,0349	0,0355	0,0124	0,0148
FRGNB4IAHO02023	0,0316	0,0429	0,0336	0,0649	0,0253	0,0265	0,0360	0,0422	0,0127	0,0174
FRGNB4IAHO02024	0,0213	0,0261	0,0158	0,0158	0,0187	0,0215	0,0287	0,0301	0,0120	0,0141
FRTRS5IAHO02007	0,0623	0,0774	0,0925	0,0883	0,0269	0,0462	0,0491	0,0882	0,0144	0,0232
FRTRS5IAHO02010	0,0240	0,0238	0,0225	0,0138	0,0176	0,0227	0,0285	0,0292	0,0106	0,0135
FRMLR1IAHO02001	0,0200	0,0150	0,0440	0,0074	0,0113	0,0132	0,0162	0,0200	0,0081	0,0105
FRREN4IAHO02003	-0,0691	0,0468	0,2186	0,0470	0,0251	0,0282	0,0365	0,0648	-0,1045	0,0191
FRREN4IAHO02004	0,0188	0,0288	0,0299	0,0596	0,0165	0,0162	0,0201	0,0222	0,0111	0,0117
FRMLR1IAHO02004	0,0228	0,0297	0,0449	0,0384	0,0145	0,0196	0,0207	0,0262	0,0089	0,0137

Table A.4 Statistic results of PTT for Hypopnea.

Saturation Analysis delta method for Apnea

	Num, ASOFF	Num, ASON	AON deltamean	AON deltastd	AOFF deltamean	AOFF deltastd	Adelta p value
FRGNB4IAHO02009	89	26	139.848	157.056	484.585	102.147	1,0693
FRGNB4IAHO02010	43	75	148.364	311.031	0,80062	324.728	0,9416
FRGNB4IAHO02012	20	3	120.232	0,977865	615.966	347.469	0,0200
FRGNB4IAHO02013	55	34	237.722	30.223	3.393	708.072	0,0052
FRGNB4IAHO02014	33	33	597.825	383.992	51.729	383.696	0,9627
FRGNB4IAHO02015	16	17	295.203	291.296	521.834	308.074	0,0122
FRGNB4IAHO02016	7	3	122.468	0,686535	44.511	150.328	0,0083
FRGNB4IAHO02017	54	27	270.415	209.405	541.348	127.707	0,0241
FRGNB4IAHO02018	57	28	233.454	355.868	69.589	56.005	0,8488
FRGNB4IAHO02019	12	0	NaN	NaN	794.931	580.774	0,0000
FRGNB4IAHO02020	2	6	180.766	595.814	0,496274	0,775577	0,9286
FRGNB4IAHO02022	91	75	419.686	706.144	515.605	398.622	0,1949
FRGNB4IAHO02023	125	52	232.693	415.622	19.813	263.477	0,7024
FRGNB4IAHO02024	19	8	241.998	0,70752	535.133	421.041	0,0013
FRTRS5IAHO02007	55	35	70.406	228.197	42.579	133.305	0,0899
FRTRS5IAHO02010	52	32	191.323	246.845	229.237	13,8	0,9150
FRMLR1IAHO02001	187	113	215.826	939.555	183.157	488.988	0,1239
FRREN4IAHO02003	310	121	340.674	406.712	275.933	616.933	0,9635
FRREN4IAHO02004	18	3	382.412	33.171	151.113	288.875	0,8306
FRANG4IAHO02001	136	19	145.266	164.275	370.665	325.147	8,2467
FRANG4IAHO02002	18	12	238.162	410.512	313.314	318.151	0,4747
FRANG4IAHO02003	130	98	228.576	336.499	228.645	264.974	0,3121
FRANG4IAHO02004	13	7	255.152	159.308	389.983	361.796	0,1917
FRMLR1IAHO02004	89	32	0,859491	0,992649	298.776	119.073	0,3134

Table A.5 Saturation analysis for Apnea with delta method.

Saturation Analysis delta method for Hypopnea

	Reference ON Mean	Reference ON Std	Reference OFF Mean	Reference OFF Std	p value	Overlapped Windows	Same Delta From Overlapped Windows
FRGNB4IAHO02009	962.981	0,7394	957.096	0,8682	0,0033	15	0
FRGNB4IAHO02010	941.613	13.761	938.037	142.364	0,0517	38	0
FRGNB4IAHO02012	918.528	136.831	914.678	168.738	0,2500	5	0
FRGNB4IAHO02013	95.255	163.133	949.021	155.472	0,0406	44	0
FRGNB4IAHO02014	955.505	173.236	965.667	0	0,7500	1	0
FRGNB4IAHO02015	93.287	202.217	933.491	168.523	0,6450	0	0
FRGNB4IAHO02016	96.655	120.296	966.377	126.078	0,4647	7	0
FRGNB4IAHO02017	935.177	0,4607	939.806	237.688	0,8893	0	0
FRGNB4IAHO02018	963.363	194.709	962.488	173.169	0,1474	21	0
FRGNB4IAHO02019	951.345	13.685	933.665	29.704	0,0034	3	0
FRGNB4IAHO02020	956.414	162.822	956.807	130.978	0,5519	41	0
FRGNB4IAHO02022	951.431	231.611	956.623	229.476	0,9817	30	0
FRGNB4IAHO02023	934.258	176.325	940.091	135.772	0,9255	8	0
FRGNB4IAHO02024	977.767	0,8059	971.084	153.885	0,0073	20	0
FRTRS5IAHO02007	975.597	115.888	972.872	158.404	0,1577	14	0
FRTRS5IAHO02010	947.231	140.798	939.582	110.862	0,0171	16	0
FRMLR1IAHO02001	836.332	571.698	849.288	465.422	0,8088	4	0
FRREN4IAHO02003	856.277	691.789	914.332	173.669	0,9995	4	0
FRREN4IAHO02004	906.045	226.824	907.828	170.412	0,5457	8	0
FRANG4IAHO02001	897.255	243.977	925.028	188.135	0,9965	9	0
FRANG4IAHO02002	927.077	165.163	92.352	159.224	0,0826	15	0
FRANG4IAHO02003	895.053	210.245	897.652	210.351	0,7081	10	0
FRANG4IAHO02004	920.654	209.318	914.447	152.815	0,2482	1	0
FRMLR1IAHO02004	957.038	109.409	951.074	150.609	0,0366	8	0

Table A.6 .Saturation Analysis of hypopnea for delta method.