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Respiration Extraction using Principal Component Analysis

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Master Thesis by

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Declaration

I declare that this thesis is entirely my own work.

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Abstract

Breathing Rate (BR), measured in cycles per minute (cpm) is an important physiological parameter which provides valuable diagnostic and prognostic information which is benefited in predicting lower respiratory tract infections, indication of severity of pneumonia and associated with mortality in intensive care unit (ICU) patients and is also useful in treatment of many common disease such as cardiac disorder, asthma, pulmonary diseases and sleep apnea. Current routine practices for obtaining BR measurement outside critical care involves manual counting chest movement using spirometers and respiratory effort belt these practices is time consuming, inaccurate with motion artefacts. For this reason it is necessary to use accurate automated method to measure BR in ambulatory patients. Many algorithms have been made in estimating BR from ECG signals but have not yet widely adopted into clinical practices. ECG Derived Respiration (EDR) is an indirect method and attractive procedure to extract the respiration from ECG using principal component analysis (PCA), which is the aim of this thesis. In this thesis, 33 subjects clinical data were used with the mean length of the signal were 118.18±4.15 mins, 1-minute windowing procedure was used for all the signals. The correlation coefficient (ρ) between the extracted EDR and the direct respiration signals is computed. In relation to the correlation coefficient, the window is classified as incorrectly estimated (|ρ|<0.5) and correctly estimated (|ρ|>0.5).

The number of incorrectly estimated windows is 29±14 [24±12%] for each subject, associated with a distribution of correlation coefficients equal to 0.37±0.03. On the contrary, the number of correctly estimated windows is 89±15 [76±12%] for each subject associated with a distribution of correlation coefficients equal to 0.74±0.02.

In the conclusion, Our PCA-based procedure is a promising method for EDR extraction.

INDEX

Introduction

Respiration is an important physiological parameter, which can be modulated by bioelectric and biomechanical signals like electrocardiography (ECG), impedance plethysmography and thorax acceleration [1-2]. Respiration signals are usually recorded with spirometry, pneumography or plethysmography techniques. These techniques require use of unwieldy devices, which may interfere with the natural breathing and which are unmanageable in certain applications like ambulatory monitoring, stress testing, and sleep studies. Nevertheless, respiratory and cardiac system joint study is a great interest in these applications and the use of different methods for extraction of respiratory information. Respiratory activity influences electrocardiographic measurements in different ways. During respiratory cycle, chest movements and changes in thorax impedance distribution due to filling and emptying of lungs cause a rotation of the electrical axis of the heart which affects to beat morphology. Effect of the respiration induced heart displacement on ECG was first studied by Einthoven et al [2] and quantified further detail in [3]. Respiration modulates the heart rate (HR), it increases during inspiration and decreases during expiration [4].

It is possible to extract a surrogate respiratory signal from ECG (Indirect measurement, being in a cost effective and easy to measure). Respiratory induced amplitude and frequency modulations of ECG are caused by the combination of three different phenomena's [5], such as:

- Respiratory induced modulation of HR leading to the frequency modulation of the ECG.
- Filling and emptying of air in the lungs (leads to changes in the transthoracic impedance), which lead to an amplitude modulation of the ECG.
- Mean electrical axis of the cardiac vector changes its direction during respiration, leading to both an amplitude modulation and frequency modulation of the ECG.

Many algorithms have been published for ECG derived respiration (EDR). Generally these algorithms can be divided [6] based on beat morphology (single lead methods based on R-wave amplitude or area of the QRS complex [7, 8], multiple lead methods based on variations in angle of mean electrical axis [9]), based on heart rate variability [10] and finally based on a combination of both (beat morphology and heart rate variability) [11]. All of these methods have their advantages and disadvantages. But among all these methods have not yet widely adopted into clinical practices [6, 7, 8, 12]. Among these methods, one of the simplest approaches is single lead of ECG method (typically from lead II or V4, because these leads are the most affected by the presence of the air in the lungs). Different methods vary in the pre-processing of the ECG signal and in the choice of ECG lead or electrode placement.

In this thesis, the experimental EDR technique by using single lead of ECG method has been demonstrated, which has been existed already [7, 8]. This method has traditional approach based on interaction of electrical axis on heart and mechanical thorax movement [13]. The main aim of this thesis was to investigate Principal Component Analysis (PCA) could detect the respiration and access the PCA as a tool to extract the respiration signal from a single lead ECG.

Chapter 1

Respiratory System

Respiration is an act of breathing. Respiratory system is also known as breathing system. The respiratory system is made up of the organs, which are involved in breathing. It consists of nose, pharynx, larynx, trachea, bronchi, and lungs as depicted in Fig. 1.

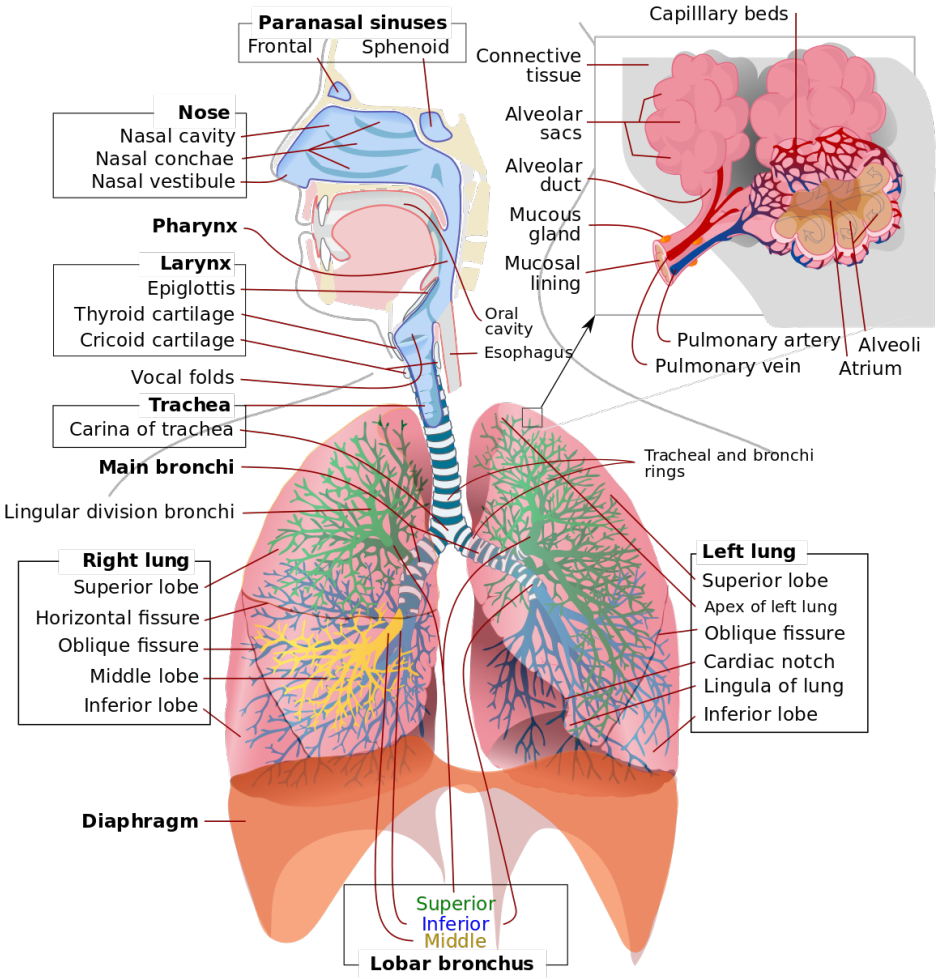

Figure 1: Respiratory System

1.1 Anatomy of Respiratory system

In Humans, Respiratory tract is the anatomy of the respiratory system that involved in the respiration process. The respiratory system can be divided based on airways tract (just for understanding purpose): the upper respiratory tract and the lower respiratory tract.

1. **Upper Respiratory Tract:** It includes the external nose, with its nasal cavity, frontal sinuses, maxillary sinus, larynx, and trachea.

Nose: It consists of external nose and nasal cavity. External nose is the visible structure that forms a prominent feature to the face. Most of the external nose is composed of hyaline cartilage, despite the fact that the bridge of the external nose consists of bone. The bone and cartilage are covered by connective tissue and skin. The external opening of the nose is called as Nares (nostrils). The nasal cavity extends from the nares to the choanae (openings into the pharynx). The nasal septum is a partition dividing the nasal cavity into left and right parts. The hard palate forms the floor of the nasal cavity (separating the nasal cavity from the oral cavity). Air can flow through the nasal cavity when the oral cavity is closed or full of food. Three prominent bony ridges (called conchae) are present on the lateral walls on each side of the nasal cavity. The conchae increase the surface area of the nasal cavity (It causes air to churn, so that it can be cleaned, humidified, and warmed). The paranasal sinuses are air filled spaces within bone, which opens into the nasal cavity and are lined with a mucous membrane. The nasolacrimal ducts, which carry tears from the eyes, also open into the nasal cavity. The sensory receptors for the sense of smell are in the superior part of the nasal cavity.

Pharynx: It is the common passageway for the respiratory and the digestive systems. Air from the nasal cavity and air, food, and water from the mouth pass through the pharynx. Inferiorly, the pharynx leads to the rest of the respiratory system through the opening into the larynx and to the digestive system through the esophagus. The pharynx can be divided into three regions such as Nasopharynx, Oropharynx, and Laryngo-pharynx.

- **Nasopharynx:** It is the superior part of the pharynx. It is located posterior to the choanae and superior to the soft palate (incomplete muscle and connective tissue partition separating the nasopharynx from the oropharynx). The uvula is the posterior extension of the soft palate. The soft palate forms the floor of the nasopharynx. The nasopharynx is lined with pseudostratified ciliated columnar epithelium that is continuous with the nasal cavity.

- **Oropharynx:** It extends from the uvula to the epiglottis. Oral cavity opens into the oropharynx. Thus, food, drink and air all pass through the oropharynx. The oropharynx is lined with stratified squamous epithelium, which protects against abrasion.

- **Laryngopharynx:** It passes posterior to the larynx. It extends from the tip of epiglottis to the esophagus. Food, drink and small amount of air swallowed with food and drink pass through the laryngopharynx to the esophagus. The laryngopharynx is lined with stratified squamous epithelium and ciliated columnar epithelium.

Larynx: It is located in the anterior throat and it is involved in breathing, producing sound and protecting the trachea against food aspiration. It extends from the base of the tongue to the trachea. Larynx is passageway for air between pharynx and trachea. The larynx consists of an outer casing of nine cartilages (connected to one another by

muscles and ligaments). Three cartilages are unpaired, and six of them are paired (three cartilages on each side to form three pairs). The largest cartilage is the unpaired thyroid cartilage (or Adam's apple) and it is attached superiorly to the hyoid bone. The most inferior cartilage of the larynx is the unpaired cricoid cartilage (which forms the base of the larynx on which the other cartilages rest). The thyroid and cricoid cartilages maintain an open passageway for air movement. The third unpaired cartilage is the epiglottis (it consists of elastic cartilage rather than hyaline cartilage). Epiglottis helps to prevent swallowed materials from entering the larynx. As the larynx elevates during the swallowing, the epiglottis tips posteriorly to cover the opening of the larynx. The six paired cartilages consist of three cartilages on each side of the posterior part of the larynx. The top cartilage on each side is the cuneiform cartilage, the middle cartilage is the corniculate cartilage and the bottom cartilage is the arytenoid cartilage**.**

Trachea (or windpipe): It is a membranous tube attached to the larynx. It consists of connective tissue and smooth muscle. It reinforced with 16 to 20 C-shaped pieces of hyaline cartilage [1]. The adult trachea is about 1.4–1.6 centimetre's (cm) in diameter and about 10–11 cm long [2]. It begins immediately inferior to the cricoid cartilage (the most inferior cartilage of the larynx). The trachea projects through the mediastinum and divides into the right and left primary bronchi at the level of fifth thoracic vertebra. The C-shaped cartilages form anterior and lateral sides of the trachea and it protects the trachea and maintains an open passageway for air. The posterior wall of the trachea has no cartilage and it consists of a ligamentous membrane and smooth muscle (It can alter the diameter of the trachea. For example, during coughing, the smooth muscle of the trachea contracts, hence decreasing the diameter of the trachea). The trachea is lined with pseudo stratified columnar epithelium (which contains numerous cilia and goblet cells).

2. **Lower Respiratory tract:** It includes the bronchi, lungs and the alveoli.

Bronchi: The trachea divides into the left and right bronchi. Both bronchi's connect to the respective lungs. The left bronchus is more horizontal than the right bronchus, due to the fact that it is displaced by the heart. Once the foreign objects, that enter the trachea usually lodge in the right bronchus (because it is wider, shorter and more vertical than the left bronchus and is more in direct line with the trachea). The main bronchi extend from the trachea to the lungs. The trachea and main bronchi are lined with pseudo stratified ciliated columnar epithelium and are supported by C-shaped pieces of cartilage.

Lungs: Both lungs (left and right) are the principal organs of respiration. The lung is cone shaped organ, with its base resting on the diaphragm and its apex extending superiorly to a point about 2.5 centimetres above the clavicle [1]. The right lung has three lobes (superior, middle and inferior lobes) while the left lung has two lobes (superior and inferior lobes). These lobes are separated by deep, prominent fissures on the surface of the lung. Each lobe is divided into bronchopulmonary segments (separated by connective tissue septa, but these separations are not visible as surface fissures). There are nine bronchopulmonary segments in the left lung and ten in the

right lung. The main bronchi branch many times to form the tracheobronchial tree. Each main bronchus divides into lobar bronchi as they enter their respective lungs. The lobar bronchi (or secondary bronchi), two in the left lung and three in the right lung, conduct air to each lobe. The lobar bronchi in turn give rise to segmental bronchi (or tertiary bronchi), which extend to the bronchopulmonary segments of the lungs.

The bronchi continue to branch many times and finally giving rise to bronchioles. The bronchioles also subdivide numerous times to give rise to terminal bronchioles. The terminal bronchioles subdivide into respiratory bronchioles. Each respiratory bronchiole subdivides to form alveolar ducts. The alveolar ducts are long, branching hallways with many open doorways. The doorways open into alveoli.

Alveoli: It is the small hollow air sac. The alveolar ducts end as two or three alveolar sacs, which are chambers connected to two or more alveoli. There are about 300 million alveoli in the lungs. The alveolar ducts and alveoli are composed of simple squamous epithelium. The gases exchange between the air and blood takes place at the respiratory membrane of the lungs. The respiratory membrane is formed mainly by the walls of the alveoli and surrounding capillaries (a lveolar ducts and respiratory bronchioles also contribute too). The respiratory membrane is very thin to facilitate the diffusion of gases and it consists of six layers:

(i) Thin layer of fluid lining the alveolus
(ii) alveolar epithelium (composed of simple squamous epithelium)
(iii) Basement membrane of the alveolar epithelium
(iv) Thin interstitial space
(v) Basement membrane of the capillary endothelium
(vi) Capillary endothelium (composed of simple squamous epithelium)

The elastic fibers surrounding the alveoli sacs allow them to expand during inspiration and recoil during expiration. The lungs are very elastic. The lungs are capable of expelling the air (when inflated state) and returning to their original (uninflated state). Specialized secretory cells within the walls of the alveoli secrete a chemical, called surfactant that reduces the tendency of alveoli to recoil.

Pleural Cavities: The lungs are connected within the thoracic cavity. In addition, each lung is surrounded by a separate pleural cavity. Each pleural cavity is lined with a serous membrane called the pleura. The pleura consist of parietal and visceral part. The parietal pleura, which lines the walls of the thorax, diaphragm, and mediastinum, is continuous with the visceral pleura (which covers the surface of the lung). The pleural cavity, between the parietal and visceral pleurae, is filled with a small volume of pleural fluid (produced by the pleural membranes). The pleural fluid performs two functions:

- It acts as a lubricant, allowing the visceral and parietal pleurae to slide past each other as the lungs and thorax change shape during respiration
- It helps hold the pleural membranes together. The pleural fluid acts similarly to a thin film of water between two sheets of glass (the visceral and parietal pleurae);

the glass sheets can slide over each other easily, but it is difficult to separate them.

Lymphatic Supply: The lungs have two lymphatic supplies. The superficial lymphatic vessels (are deep to the visceral pleura, they drain lymph from the superficial lung tissue and the visceral pleura) and the deep lymphatic vessels (follow the bronchi, they drain lymph from the bronchi and associated connective tissues). There are no lymphatic vessels are located in the walls of the alveoli. Both the superficial and deep lymphatic vessels exit the lungs at the main bronchi. Phagocytic cells within the lungs phagocytize most carbon particles and other debris from inspired air and move them to the lymphatic vessels.

1.2 Physiology of Respiratory system

The physiology of the respiratory system refers to the flow of air exchanged between the atmosphere and the alveoli. One complete respiratory cycle involved in one phase of inspiration and expiration.

Inspiration: The movement of air from the atmosphere to the alveoli refers as inspiration. During this phase the pressure inside the lungs must be smaller than the atmospheric one, in order to create a pressure gradient so that the air would flow from atmosphere to the alveoli. To do so, the lungs volume should increase thanks to skeletal muscles and diaphragm. This latter one contracts and drops down, while ribs and sternum are pulled upward and toward the outside thanks to the contraction of the external intercostal muscles [1].

Volume of the thoracic cage increases → Intrapulmonary pressure decreases of 1 mmHg → Air flows into the lungs down to its pressure gradient → Intrapulmonary pressure = 0 (760 mmHg).

Expiration: The movement of air from the alveoli to the atmosphere refers to the expiration. During normal breathing, expiration is passive, thus involves mainly the elastic recoil of the lungs. Internal intercostal muscles and the abdominal muscles are involved during expiration. This phase occurs once the inspiration has occurred, so that the pressure inside the lungs has to be higher than the atmospheric one. Thus, the volume of the thoracic cage decreases [1].

Inspiratory muscles relax → Ribs and sternum are depressed as the external intercostal muscles relax → Thoracic cavity volume decreases and intrapulmonary pressure increases of 1 mmHg → Air flows out of the lungs down its pressure gradient Ventilation.

The lungs move in association with the thorax, since they are not able to expand or contract on their own. This occurs thanks to the pleural sac, composed by two layers: the visceral pleura (covers the surface of the lungs) and the parietal pleura (attached to the inner surface of the thoracic cavity). There is a pleural fluid between these two layers. The cohesive force of pleural fluid causes the lungs to adhere to the thoracic cage. To be sure the combination of outward pull exerted by the thoracic cage and the inward one caused by the elastic recoil of the lungs tends to create a subatmospheric intrapleural pressure of about -757 mmHg

(smaller of 3 mmHg with respect to the intrapulmonary one) [1]. This difference with the intrapulmonary pressure creates a tiny pressure gradient, causing the lung to adhere the thoracic cage, also preventing their breakdown due to their natural elastic recoil. Another compound that reduces the effect of muscle during respiration is the surfactant, produced by the type II alveolar cells. It reduces the surface tension of the alveolar fluid, decreasing the lungs resistance to the stretch. Since the pressure arising from the cohesive force depends on the radius, surfactant is more concentrated in smaller alveoli, making their surface tension smaller than the one in larger alveoli. Hence, the function of surfactant is to make homogeneous the surface tensions among alveoli of different sizes, making easier the smaller alveoli to inflate. The gas exchange and transport mechanism is depicted in the figure 2.

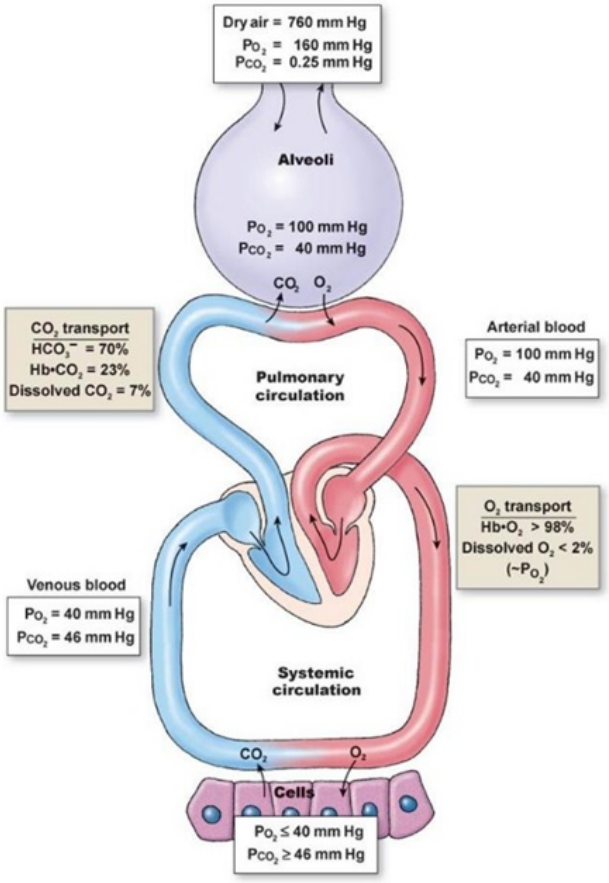

Figure 2: Gas Exchange and transport

The aim of the gas exchange is to regulate three fundamental physiological variables [1]:

1. **Oxygen level:** Where arterial oxygen delivery to the cells must be adequate to support aerobic respiration and ATP production.
2. **Carbon dioxide level:** Waste product during Krebs's cycle, excretion of CO_2 from the lungs is important for two reasons: high levels of CO_2 are a central nervous system depressant and elevated CO_2 causes a state of acidosis (low pH).
3. **Plasma pH:** (maintaining pH homeostasis is critical to prevent denaturation of proteins. The respiratory system monitors plasma pH and uses changes in ventilation to alter it).

Starting from the blood in to the veins (rich CO_2), it arrives to the alveoli. The alveoli will have the PO_2 is 100 mmHg and PCO_2 is 40 mmHg. The veins will have the PO_2 is 40 mmHg and PCO_2

is 46 mmHg. As inspiration begins, atmospheric air comes inside (it becomes warmed to body temperature). The humidified inspired air becomes saturated by water vapor. It exerts a partial pressure and dilutes the total pressure, with pH_2O = 47 mmHg. On the other hand, Arterial blood will arrive to the cell bodies. The arterial blood will have the PO_2 is 100 mmHg and PCO_2 is 40 mmHg. The cell bodies will have the PO_2 is 40 mmHg and PCO_2 is 46 mmHg. Thus, oxygen (O_2) from the arterial blood is now oxygenating cells. There are three variables that influence the efficacy of O_2 exchange are: Alveolar PO_2 (less oxygen available to the blood - air rarefaction), Perfusion (slow blood perfusion affects gas exchange) and Gas solubility (the dynamics of gas molecules that dissolve in the plasma is regulated by the Fick's law). Fick's law states that, for a given particle M, its dissolution from a compartment to another through a permeable membrane is proportional to the pressure gradient ΔpM by the superficial extension of the membrane A, the thickness T, and its permeability D (named also diffusion constant): d[M]/dt = AD. (ΔpM/T). Fick's law explains the reason of high pressure gradient for O_2 at alveolar level. Due to the low solubility coefficient of O_2 in water, a strong pressure gradient drives in O_2 with a fast increase of its concentration in blood.

Gas transport entails two physiological pathways [1]: 1) oxygen flow from its dissolution in plasma in the pulmonary capillary to body cells for oxidative phosphorylation, and 2) CO_2 flow from its production in cell metabolism to the alveoli.

1. Oxygen: It is transported in two ways: 2% remains free in plasma, dissolved units, and 98% bind hemoglobin (Hb). In the Hemoglobin, thanks to the central Fe atom, can bind up to four molecules of O_2, giving rise to oxyhemoglobin (HbO_2).

$$Hb + O_2 \leftrightharpoons HbO_2$$

   Above reaction is shifted to the right ($\rightarrow$) at alveolar level, when more O_2 binds to the Hb. The reaction is shifted to the left ($\leftarrow$) at systemic capillaries level, releasing the O_2 previously bound to Hb. With only diffusion, due to low O_2 solubility, an individual would have only 3 mL O_2 per liter of blood, while with hemoglobin one arrives to 200 mL O_2 per liter of blood.

2. Carbon Dioxide: It is transported in three ways: 1) 7% is dissolved in blood, 2) 70% enters the red blood cells (RBC) then it is converted into bicarbonate ions ($CO_2 + H_2O \rightarrow H_2CO_3$) and, 3) remaining 23% enters the RBC and bind to Hb, forming $HbCO_2$.
   CO2 flows from the cell into the capillary, 7% is dissolved in plasma, while 93% enters the RBC. About 23% of it binds reversibly to Hb, forming the carbominohemoglobin:

$$Hb + CO_2 \leftrightharpoons HbCO_2$$

The remaining 70% is transported to the lungs as bicarbonate ions (HCO_3^-): it provides an additional mean of CO_2 transportation from cells to lungs, where bicarbonate acts as a buffer for metabolic acids, stabilizing their pH:

$$H_2O + CO_2 \leftrightharpoons H_2CO_3 \leftrightharpoons HCO_3^- + H^+$$

Where the first reaction is catalyzed by the enzyme carbonic anhydrase, and H_2CO_3 is carbonic acid. At this point, HCO_3^- diffuses out the RBC, in exchange for Cl^-, in a process known as chloride shift, which serves to maintain the cell osmotic equilibrium. If the reaction is shifted to the right ($\rightarrow$), it is used to produce more HCO_3^- in response to more CO_2 entering the blood from tissue; if shifted to the left ($\leftarrow$), it means that CO_2 is exhaled in the lungs, within the RBC, binding Hb ($H^+ + Hb \leftrightharpoons HbH$). Buffering of H^+ is critical for keeping the reaction moving towards the synthesis of HCO_3^-.

1.3 Respiration signals

The respiration signals contain the respiratory information. In Humans, The respiratory rate is measured by manual counting the number of breaths per one minute through counting how many times the chest rises. Typical respiratory rate for a healthy adult at rest condition is between 12 to 18 breaths per minute [3]. Respiration is an important physiological parameter and it has both diagnostic and prognostic value. There are several ways to measure the respiration which includes the Spirometry, pneumography or plethysmography and fiber optic breath rate sensor can be used for monitoring patients during a magnetic resonance imaging scan [4]. These procedures are also called as direct measurement of respiration.

Spirometry is an electronic device with a mouth piece hooked up. It is the most common of the pulmonary function tests (PFTs). PFTs are noninvasive tests that show how well the lungs are working. Particularly it can measure lung volume, capacity, rates of flow, and gas exchange [5]. The lung volumes and capacities are depicted in the Figure 3.
The following measurements can be measure from the PFT.

- **Tidal volume (TV):** It is the amount of air inhaled or exhaled during the normal breathing (500 mL).
- **Inspiratory Reserve volume (IRV):** It is the amount of air additional volume over the TV (3000 mL).
- **Expiratory Reserve volume (ERV):** It is the amount of air forcefully exhaled after the end of a normal expiration (1100 mL).

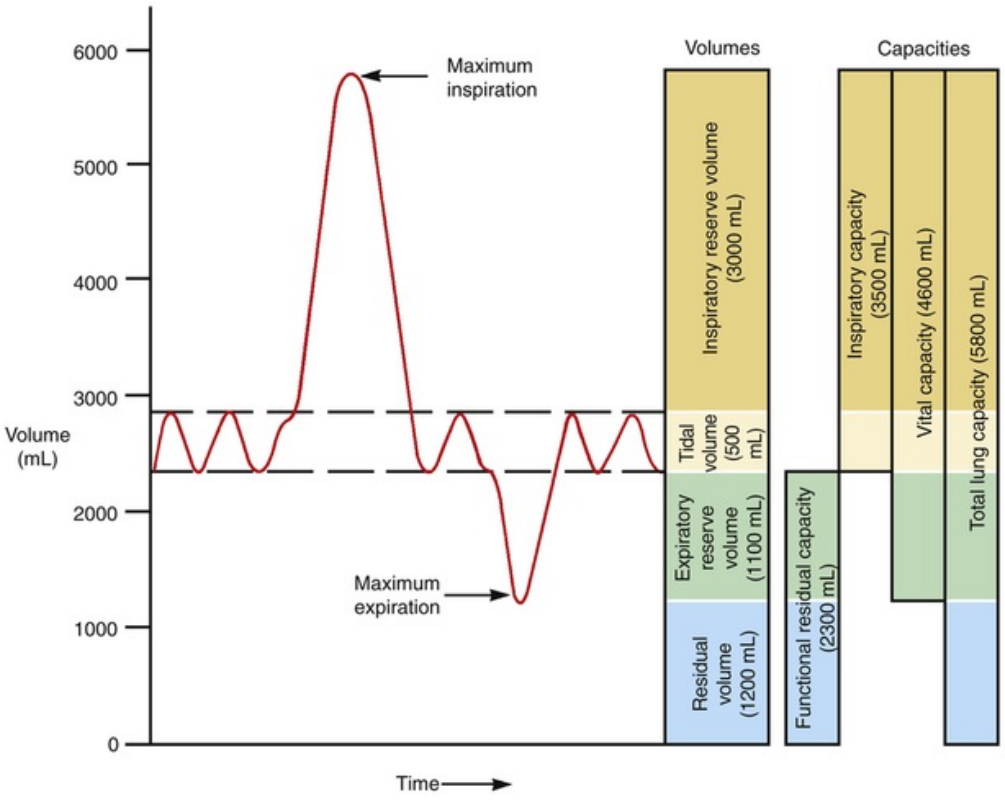

Figure 3: PFTs measures

- **Residual volume** (RV)**:** It is the amount of air left in the lungs after the maximum exhalation (1200 mL). It cannot be measured directly and equals the amount of air that cannot be drawn out from the lungs after reaching the expiratory reserve muscle. Most of this residual volume exists because the lungs are held stretched against the ribs by the pleural fluid.
- **Minute volume (MV)**: This is the total amount of air exhaled per minute.
- **Functional residual capacity (FRC):** This is the amount of air left in lungs after exhaling normally. In other words, it is the sum of the ERV and RV (2300 mL).
- **Inspiratory capacity (IC):** it is the amount of air that can be inhaled after the end of a normal expiration. In other words, it is the sum of the tidal volume and inspiratory reserve volume (3500 mL).

- **Vital capacity (VC):** This is the total volume of air that can be exhaled after inhaling as much as you can. In other words, it is the sum of the IRV, TV and RV ((4600 mL)).

- **Total lung capacity:** It is the total volume of the lungs when filled with as much air as possible (5800 mL). In other words, it is the sum of the TV, IRV, ERV and RV.

- **Forced vital capacity (FVC):** This is the amount of air exhaled forcefully and quickly after inhaling as much as you can.

- **Forced expiratory volume (FEV):** This is the amount of air expired during the first, second, and third seconds of the FVC test.

- **Forced expiratory flow (FEF):** This is the average rate of flow during the middle half of the FVC test.

- **Peak expiratory flow rate (PEFR):** This is the fastest rate that you can force air out of your lungs.

Normal values for PFTs vary from person to person. The amount of air inhaled and exhaled in test results are compared to the average for someone of the same age, height, gender. Results are also compared to any of previous test results. PFTs may require in healthy people as part of a physical routine, employees who work in certain types of work environments (such as graphite factories and coal mines) to ensure employee health. Another use of PFTs is to assess treatment for asthma, emphysema, and other chronic lung problems. PFT is not an invasive procedure. It is safe and quick for most people. But this procedure may have some risks (which may include: Dizziness during the tests, Feeling short of breath, Coughing and Asthma attack brought on by deep inhalation). In some cases, PFT is not recommended for the patients including: Recent eye surgery (because of increased pressure inside the eyes during the procedure), recent belly or chest surgery, Chest pain, recent heart attack, or an unstable heart condition, bulging blood vessel (aneurysm) in the chest / belly / brain and Active tuberculosis (TB) or respiratory infection. PFT procedure is less accurate for the patients including the degree of patient cooperation and effort, Use of medicines that open the airways (bronchodilators), Use of pain medicines, Pregnancy, Stomach bloating that affects the ability to take deep breaths and Extreme tiredness or other conditions that affect a person's ability to do the tests [5].

Plethysmography is the equipment with air tight box that looks like a short, square telephone booth. It can measure changes in volume within an organ or whole body (usually resulting from fluctuations in the amount of blood or air it contains). To do the tests, patient can sit or stand inside it [6].

Pneumography is the device for recording the velocity and the force of chest moments during respiration [7]. There are various types of pneumographic devices are available, which have different principles of operation.

- Some pneuomgraphs are based on a flexible rubber vessel (equipped with the sensors) is attached to the chest.

- Others are based on impedance. In this type of procedure, High frequency (usually tens to hundreds of kHz), low amplitude current is injected across the chest cavity. Voltage resulting from the injected current is measured and the resistance is derived from the Ohm's law (Resistance = Voltage divided by Current). As the lung fills, current flows less through the chest, so the resistance rise with the increasing lung volume.

However, these techniques require use of unwieldy devices, which may interfere with the natural breathing and which are unmanageable in certain applications like ambulatory monitoring, stress testing, and sleep studies [8]. For this reason, an accurate automated measurement of respiration was necessary for the ambulatory patients. Despite, there are several ways to extract the estimation of respiration from Electrocardiogram (ECG), Photoplethysmogram (PPG) and Blood Pressure signals. There are several literatures available on ECG-Derived Respiration (EDR), PPG-Derived Respiration (PDR), BP-Derived Respiration (BDR) [8]. This thesis focused on the EDR, which has been discussed in the Chapter 3.

Chapter 2

Cardiovascular System

Cardiovascular system (Vascular System) is also known as circulation system. Cardiovascular system includes the heart, blood and its circulation.

2.1 Anatomy of cardiovascular system

The cardiovascular system anatomically appears as a series of interconnected blood vessels (interconnected tubes), filled with blood (streaming fluid) and connected to the heart (pump), which generates a pressure that drive blood through closed system of blood vessels. The blood vessels that carry blood away from the heart are called arteries. The blood vessels that carry blood to the heart are called veins.

The heart is a muscular organ which lying in the thoracic cavity, in particularly between lungs and behind the sternum and above the diaphragm. The heart is encased in the pericardium (tough membranous sac), More precisely, pericardium can be divided in to Fibrous pericardium (which protects, anchors the heart and prevents from overstretching) and Serous pericardium (which is a thin delicate membrane), which contains a parietal layer (outer layer), pericardial cavity with pericardial fluid and visceral layer (epicardium, which lubricates the heart to prevent friction). The heart itself is composed mostly of cardiac muscle. Myocardium (cardiac muscle layer is the bulk of the heart), which covered by thin outer and inner layers of epithelium and connective tissue. Endocardium is the most inner layer of the heart which contains chamber lining and valves.

The heart is divided by a central wall (septum), into left and right. Each septum is divided in to an atrium and a ventricle. These are depicted in the figure 4. Blood moves through the cardiovascular system, a system of valves in the heart and veins ensures the blood flows in one direction only. In particular, there are two sets of heart valves: Atrioventricular valve (between atria and ventricles) and semilunar valve (between the ventricles and the arteries stemming from heart). The atrioventricular valves are formed of thin flaps of tissue, connected on the ventricular side with collagenous tendons. There are two atrioventricular vales: tricuspid valve (right side) bicuspid or mitral valve (left side). The chordae tendineae, which are anchored to mound like extension of the ventricular basin called papillary muscles

(retainer of the valvular flaps, which could be pushed back to the atrial cavity after the rush of blood invades the ventricle). The semilunar valves are pocket like structures attached at the point at which the pulmonary artery and the aorta leave the ventricles. There are two semilunar valves: aortic and pulmonary valve. These valves are in the arteries leaving the heart.

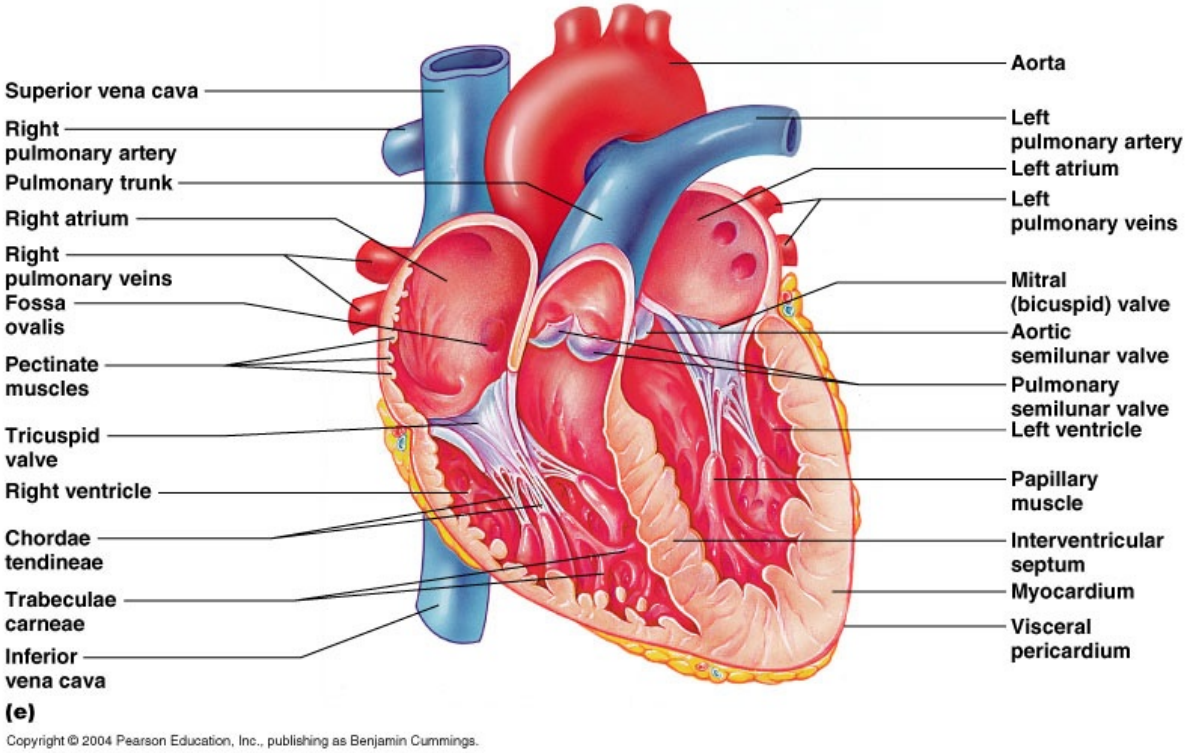

Figure 4: Heart

Blood flows from right atrium into right ventricle of the heart. Blood in the left ventricles is pumped to the lungs for the oxygenated purpose, through the pulmonary arteries (Hence, deoxygenated blood in the right side of the heart). Blood travels from the lungs to the left side of the heart through the pulmonary veins. Blood from the lungs enters the heart at the left atrium and passes into the left ventricle. Blood pumped out of the left ventricle enters the large artery known as the aorta. The aorta branches into a series of smaller and smaller arteries. The first branch of the arteries represents the coronary arteries (which nourish the heart muscle itself). Blood from these arteries flows into capillaries. From the capillaries blood flows into the coronary veins (which empty directly into the right atrium at the coronary sinus). Ascending branches of the aorta go to the arms, head, and brain. The abdominal aorta supplies blood to the trunk, the legs, and the internal organs such as liver (hepatic artery), digestive tract, and the kidneys (renal arteries). Each of these arterial vessels begins continuously bifurcating and thinning in small vessels interconnected in a wide net called capillaries (which are the site of exchange of nutrients, oxygen and wastes to all body's cells). Leaving the capillaries, blood flows into the venous side of the circulation, moving from small veins into larger and larger veins. Those from the upper part of the body join to form the superior vena cava, while those from the lower part of the body form the inferior vena cava . The two venae cava empty into the right atrium.

The heart is made up of two pumps disposed in series: the first one pushes venous blood throughout the lungs to ensure the exchange of O_2 and CO_2 in a process called pulmonary circulation, while the second one pushes the arterial blood in all the other tissues of the body by the process called systemic circulation. This one-way circuit steers the blood along a specific route, making circulate always the same amount of blood, and ensures systematic distribution of gases, nutrients, signal molecules, and wastes. In fact, blood picks up oxygen at the lungs and nutrients in the gastrointestinal tract, and then delivers these substances to the whole pack of body's cells; at the same time, it picks up wastes continuously and removes them through lungs and other excretory systems.

2.2 Physiology of cardiovascular system

The primary function of the cardiovascular system is to transport the blood to and from all parts of the body. In myocardium, most cardiac cells are contractile, but about 1% of them are autorhythmic cells. In fact, the functioning of the cardiovascular system would happen due to the autorhythmic cells, which are specialized to generate action potential spontaneously. The electrical propagation is depicted in the below figure 5.

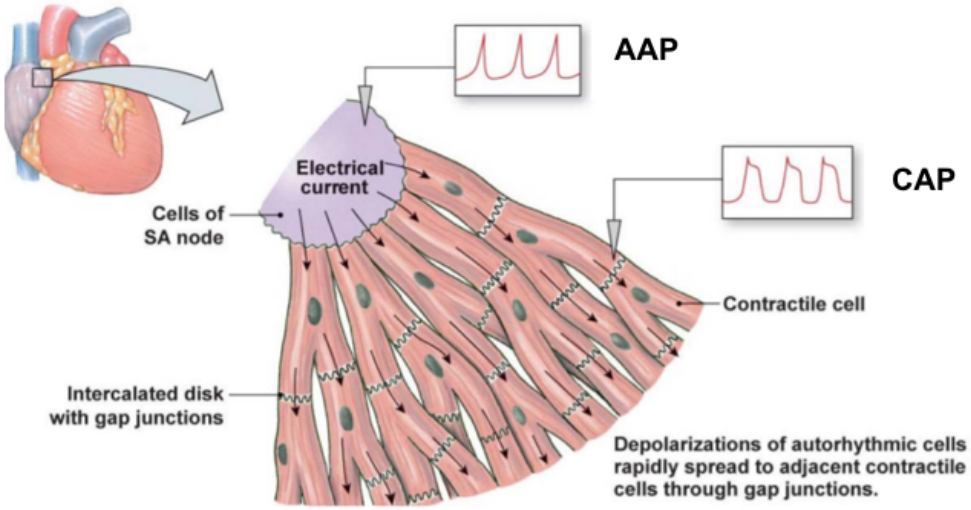

Figure 5: Electrical propagation

The trigger is given by electrical propagation through gap junctions and conductive fibers of the autorhythmic action potential (AAP) generated by the autorhythmic cells. These pulses spreads from a heart pacemaker, a wave of depolarization called contractile action potentials (CAP), which is generated on the sarcolemma of every cardiac muscle cell and it is responsible of the contraction. This process can be described as the following cascade of events:

- CAP arrives from an adjacent cell.
- Depolarization wave opens the voltage gated L-type calcium ion channels in the membrane.
- Calcium ion enters the cell and opens Ryanodine receptor channels in the Sarcoplasmic Reticulum.

- Stored Sarcoplasmic Reticulum Calcium ion flows out into the cytosol, populating it with a high concentration of calcium (necessary condition to the formation of cross-bridges in the contractile fibers).
- Calcium released from the Sarcoplasmic Reticulum provides about the 90% of Calcium ion needed for muscle contraction, remaining 10% entering from the Extra Cellular Fluid (ECF).

Note that, the relaxation is the reverse process.

The cascade is triggered by the arrival of an AAP, which pulls in ECF's calcium (in addition to Na^+) through its dedicated channels. For this reason, the process is also called $Ca2^+$ induced $Ca2^+$ release (CICR).

The rapid depolarization phase of the action potential is the result of Na^+ (sodium) entry, and the steep repolarization phase is due to K^+ (potassium) leaving the cell. The depolarization wave has the following trend: From the resting membrane potential of about –90 mV (4), the increase of membrane's permeability to Na^+ due to the opening of voltage gated Na^+ channels, generates an abrupt overshoot called "depolarization – 0". During the rising edge of the wave, Na^+ channels starts to close till all are closed at a membrane potential of 20 mV. Then the cell begins to repolarize as K^+ leaves through open K^+ channels, in a phase called "slight repolarization – 1". This phase is very brief.

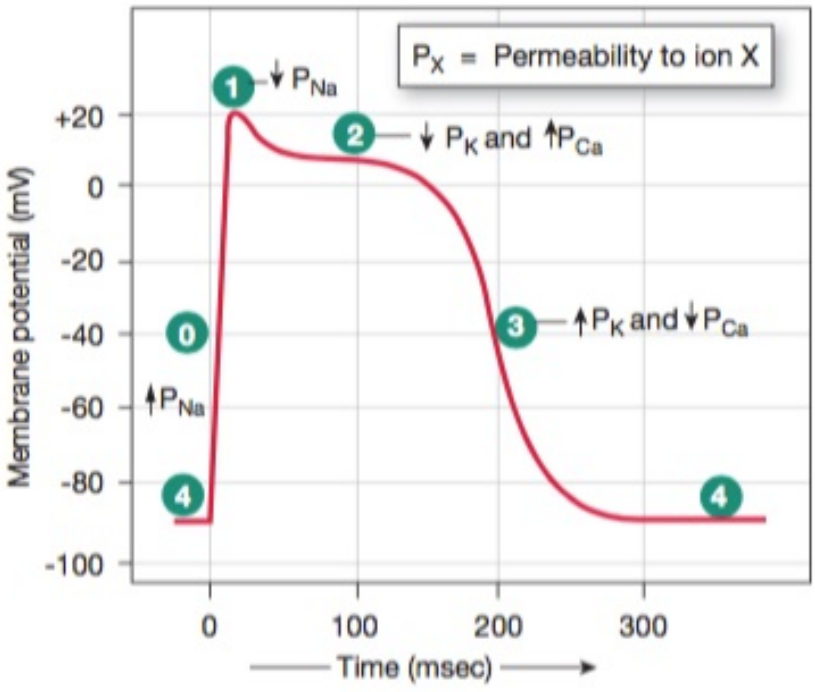

Figure 6: Cardiac action potentials

The action potential then flattens into a "plateau – 2" as the result of two events: a decrease in K^+ permeability and an increase in $Ca2^+$ (calcium) permeability. Voltage gated $Ca2^+$ channels activated by depolarization have been slowly opening during "phases 0 and 1". When they finally open, $Ca2^+$ enters the cell. At the same time, some "fast" K^+ channels close. The

combination of $Ca2^+$ influx and decreased K^+ efflux causes the action potential to flatten out into a plateau. This stalemate phase ends with the occurrence of “rapid repolarization – 3”, due to $Ca2^+$ channels closing and K^+ permeability increasing once more. When the slow K^+ channels open, K^+ exits rapidly, returning the cell to its “resting potential – 4”. All these cardiac action potentials stages are depicted in figure 6.

The influx of $Ca2^+$ during “phase 2” lengthens the total duration of a myocardial action potential. A typical action potential in a neuron or skeletal muscle fiber lasts between 1–5 ms. In a contractile myocardial cell, the action potential typically lasts 200 ms or more [1]. This is due to the fact that the “refractory period” is the time following an action potential during which a normal stimulus cannot trigger a second action potential.

In the heart, electrical communication begins with an action potential in an autorhythmic cell. The depolarization begins in the Sinoatrial node (SA node), a cluster of autorhythmic cells in the right atrium that serve as the main pacemaker of the heart. From the SA node, depolarization wave spreads rapidly through intermodal pathway to atrioventricular node (AV node), so a group of autorhythmic cells stays near the floor of the right atrium. AV node delay’s the impulses ensuring that the atria have ejected their blood into the ventricles first before the ventricles contract. The AV node has its own firing rate (which is suppressed till the SA node works properly and shifts to be the proper heart rate if the SA node interrupts its firing). From the AV node, depolariz ation moves into the ventricles through bundle of his. The bundle of his divided in to left and right bundle branches. The bundle branch fibers continue the depolarization wave to the apex of the heart through the purkinje fibers (specialized conducting cells, transmit impulses very rapidly, with speeds up to 0.004 sec, so that all contractile cells in the apex contract nearly simultaneously). Cardiac conduction system is depicted in the following figure 7. This complete process is called as a cardiac cycle.

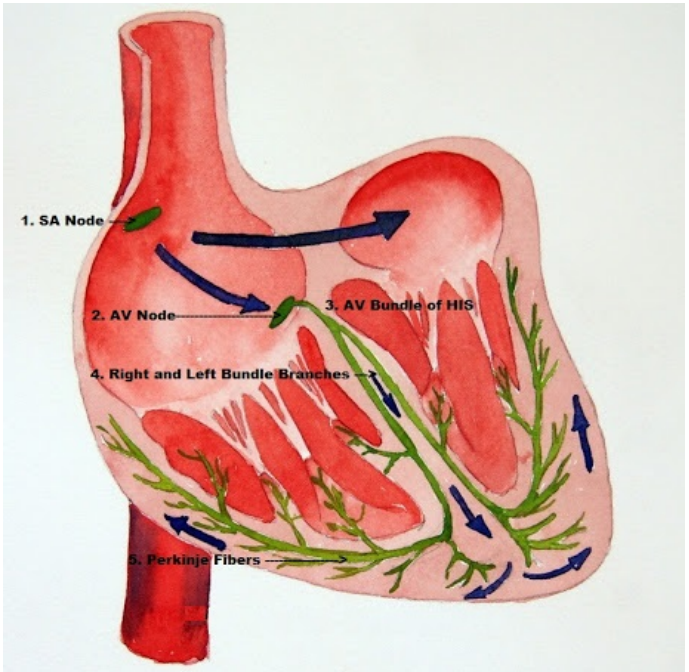

Figure 7: Cardiac conduction system

A cardiac cycle (heartbeat) represents one period in which autorhythmic cell fires to push blood on the system circulation through the aorta. Each cardiac cycle has two phases: diastole (cardiac muscle relaxes) and systole (cardiac muscle contracts). Because the atria and ventricles do not contract and relax at the same time, the cardiac cycle consist of series of five consecutive steps:

1. **Late Diastole:** During this step both atria and ventricles are relaxing. The atria's are filling with blood from veins. The AV valves are open, blood flows by gravity from atria into ventricles.

2. **Atrial Systole:** During this step SA node starts to depolarize the atria. So, atrium starts to contract. The pressure increases, contraction pushes blood into the ventricles. A small amount of blood is forced backward into the veins because there are no one-way valves to block backward flow, although the openings of the veins do narrow during contraction.

3. **Isovolumic ventricular contraction:** As the atria are contracting, the depolarization wave is moving slowly through the conducting cells of the AV node, then rapidly down the Purkinje fibers to the apex of the heart. Ventricular systole begins, the blood pushing against the underside of the AV valves forces them to close so that blood cannot flow back into the atria. The vibrations following closure of the AV valves create the first heart sound (LUB). During this step the blood in the ventricles does not change.

4. **Ventricular ejection:** As the ventricles contract, they generate enough pressure to open the semilunar valves and push blood into the arteries. The pressure created by ventricular contraction becomes the driving force for blood flow. High-pressure blood is forced into the arteries, displacing the low-pressure blood that fills them and pushing it farther into the vasculature. During this step, the AV valves remain closed and the atria continue to fill.

5. **Isovolumic ventricular relaxation:** At the end of ventricular ejection, the ventricles begin to repolarize (relax). So, the ventricular pressure decreases. Once ventricular pressure falls below the pressure in the arteries, blood starts to flow backward into the heart. This back flow of blood causes the closure of the semilunar valves. This vibrations created by semilunar valve closure create the second heart sound (DUB).

2.3 Electrocardiogram

Electrocardiogram (ECG) is the wave produced by the electrocardiograph (machine). The wave represents the voltage versus time, in particularly which represents the electrical activity of the heart using electrodes places on the skin. These electrodes detect the small electrical changes during each cardiac cycle (consequences of the cardiac muscle depolarization followed be the repolarization). ECG pattern changes occur in a numerous cardiac abnormalities including cardiac rhythm disturbances (atrial fibrillation and ventricular tachycardia), inadequate coronary blood flow (myocardial ischemia and myocardial infarction) and electrolyte disturbances (hypokalemia and hyperkalemia) [1]. Normal ECG

wave as depicted in the figure 8.

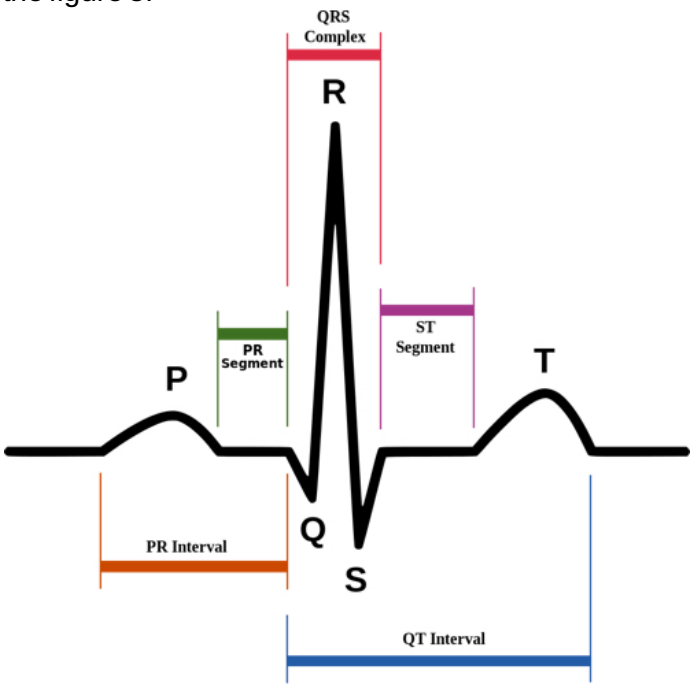

Figure 8: ECG wave

The P-wave represents the depolarization for the atria (atrial systole in the cardiac cycle), QRS - complex represents depolarization of the ventricles (isovolumic ventricular contraction and ventricular ejection in the cardiac cycle) and the T-wave represents repolarization of the ventricles (isovolumic ventricular relaxation in the cardiac cycle) [1]. Sometimes U-wave may appear after the T-wave. U-wave hypothesized that caused by the repolarization of papillary muscles of the interventricular septum. Normally, U-wave will have low amplitude and is most often completely absent. Generally, the durations between the waves are denoted as segments or intervals. In fact, segments extend from the end of one wave to the start of another wave, whereas intervals extend from the start of one wave to the start of the next followed wave, which are depicted in the figure 6. The PR interval refers the duration from the start of atrial depolarization to the start of the QRS complex, rather than to R (This is because to determine the R-peak in abnormal ECGs can be difficult). The QT interval refers the duration of a single cycle of ventricular depolarization and repolarization (usually measured from the end of PR interval, rather than from the bottom of the Q wave [9].

The baseline of the ECG is known as the isoelectric line (typically it is measured as a portion of the tracing from end of the T-wave to the beginning of the next P wave in case of absent U wave) [9]. In a normal ECG, the complete duration of one cardiac cycle (one heartbeat, also known as one complete wave) is about 750-800 ms [9].

Chapter 3

Electrocardiogram Derived Respiration

The extraction of the respiration from the electrocardiogram (ECG) is called as an electrocardiogram derived respiration (EDR). Advantage of EDR is no further equipment is needed during ECG recording. EDR signal arise from the movement of electrodes with respect to the heart during respiration. The EDR methods exploit the respiratory induced changes of the ECG to provide a surrogate respiratory signal. For example, signal with varying amplitude corresponding to the different phases of respiration. These surrogate signals should enable the estimation of the respiratory rate and the temporal pattern of respiration [10].

3.1 Literature review on Electrocardiogram-Derived Respiration

There are many methods are available in the literatures for the extraction of a respiratory signal from the ECG (EDR). To derive a respiratory signal from the beat morphology of the ECG, the earliest attempt date back to 1974. Wang et al.[11] proposed a technique for monitoring the respiratory rate, using the respiratory induced variation of the angle of the mean electrical axis (AMEA) of the heart. Although this technique is not strictly an EDR, the ECG can be synthesized from the Frank-lead VCG and vice versa through the Dower transformation matrix [12]. In 1985 Moody et al.[13] presented multiple ECG lead approach (utilized the AMEA). The AMEA was found as the arctangent of the ratio of the areas enclosed by the QRS complex of two orthogonal ECG leads. After subtracting the baseline, areas were measured with ECG leads. The resulting EDR was visually compared to a recording of chest circumference and the similarities between these two signals were reported.

In 1996, Caggiano and Reisman [14] investigated the effect of different QRS area windows (fixed and variable). Two windows with variable window width performed better than a fixed width window, with correlation coefficients the resulting EDR and a respiratory reference signal of 0.521 and 0.521 compared to 0.468. Measuring variations in AMEA have been applied later in sleep studies and Heart rate variability analysis [15, 16].

In 1992, Khaled and Farges [17] was the first to exploit the simple principle of amplitude modulations from the single lead ECG. They found a respiratory surrogate by plotting the amplitude of R wave with respect to baseline as a function of time. They compared the EDR signal and the impedance rheography signal, concluded that the EDR signal was less sensitive to motion and cardiac artifacts.

In 1998, manner Dobrev et al. [18] was used single lead QRS complex peak-to-peak amplitude (In other words, which is the sum of the absolute values of the R peak and the S peak) in apnea detection in infants. The EDR signal was visually compared to the impedance respirogram

from a commercial cardiorespirograph. They concluded that motion artefacts considerably affected the impedance respirogram and the EDR signal remained adequate for apnea detection.

In 2001, Mason and Tarassenko [19] were compared the EDR signal from the R wave amplitude with respect to the baseline and S wave (In this method, S-wave was defined the minimum value in a window of 0.1 seconds after the R-wave). In this method, breath detection algorithm was used to detect respiratory instances. They found and concluded that the R wave to S wave method was superior to the R wave to baseline method with higher sensitivity (76.87% compared to 67.94%) and higher positive predictivity (56% compared to 48.59%).

In 2007, O'Brien et al. [20] modified the R-wave in two versions one with respect to baseline and another one AMEA method. In one method, R-wave amplitude is interpolated at the time instance of R-wave in time. In another method, the amplitudes R-wave amplitudes were interpolated evenly in time spacing's corresponding to the average heart rate of the given series. They compared with a simultaneous inductance plethysmography respiratory signal and founded that the original and the modified yielded similar correlation coefficients ($r = 0.78$ and $r = 0.80$ respectively).

In 2002, Yi and Park [21] presented a method, that did not rely on the detection of the QRS complex or any other important point in the ECG. The major principle for this method was to isolate the components corresponding to the respiratory frequency band in the ECG signal. In this method, a discrete wavelet transform was applied to a lead II ECG signal and the EDR was found as the reconstruction of the detail signal of the 9th decomposition. The ECG was sampled at 200Hz (i.e the detail signal of the 9th decomposition corresponds to 0.2 – 0.4Hz). The instantaneous respiratory rates were extracted from the EDR and a respiratory airflow signal. They founded and reported that the correlation was high ($r < 0.9$).

In 2008, Correra et al.[22] compared three methods (based on R wave area, R peak amplitude and heart rate variability) for estimating respiratory signal through ECG was carried out. For each method, cross-correlation coefficient and spectral coherence in a range of frequencies up to 0.5 Hz were computed between the EDR signals and the three real respiratory signals (oronasal, and two inductance plethysmography's recordings - chest and abdominal). Results were indicated that EDR methods based on R wave area and HRV are better correlated than R peak amplitude method. These methods show a wider spectral coherence with real respiratory signals than the other EDR method based on R peak amplitude.

In 2009, Boyle et al. [23] compared different wavelet decomposition methods (band pass filtering and Heart rate variability-HRV based methods). In this literature, the mean respiratory rate was detected in the resulting EDR signals and compared to the mean respiratory rate detected in a reference signal. The methods that performed the best filtering in the pass band to 0.2 – 0.8Hz (mean error < 20%, No specific characteristic of the filter was mentioned) and combination of the HRV method and the 0 .2 – 0.8 Hz band pass method (mean error < 20%). The EDR methods with the worst performance yielded a mean error of around 50%.

3.2 Electrocardiogram derived respiration methods

There are several EDR methods are available in the literatures [11-23]. These EDR methods includes: based on the Discrete wavelet transform and Band-pass Filtering [21, 23], Vectorcardiography based on variations in angle of mean electrical axis [12], Multiple Lead based on variations in angle of mean electrical axis [13, 14], Single Lead based on R-wave Amplitude or QRS Area [17-21], based on heart rate variability [22] and a combination of both (beat morphology and heart rate variability) [23] are available in the literatures. In this section, differentiate the EDR methods in to three groups for our understanding purpose. These groups include beat morphology, HRV, combination of beat morphology and HRV for understanding in a better way.

1. **EDR based on beat morphology:**

    - **Discrete Wavelet Transform and Band-pass Filtering:** This type EDR method is applicable to a single lead ECG recording. This is the simplest and intuitive approach for the investigation of the respiratory frequency band in the ECG signal content.

    - **Vectorcardiography based on variations in angle of mean electrical axis:** This method proved that it is the superior method than the method based on heart rate variability and two lead angle of mean electrical axis [10]. This method is to exploit QRS-VCG loop alignment (rotation matrix needed to align QRS loops with a reference loop) to produce the corresponding EDR signals.

    - **Multiple Lead based on variations in angle of mean electrical axis:** This method requires at least two approximately orthogonal ECG leads. In this method, tracking the angle between the respiratory induced rotations of the mean electrical axis of the heart with a reference can be used to derive respiratory information.

    - **Single Lead based on R-wave Amplitude or QRS Area:** This method can be carried out on a single lead ECG. This method is the one of the simplest approaches (interpolation of R-wave amplitudes or area of QRS complexes). Different methods may vary mostly in the preprocessing of the ECG signal and in the choice of ECG lead or electrode placement. In this method, the suggested electrodes to extract the respiratory information are Lead II or V4 (due to the fact that these electrodes will have the highest respiratory information).

2. **EDR based on heart rate variability:** In fact, heart rate varies as a function of respiration, so that heart rate variability can be exploited to extract respiration.

3. **Combination of heart rate variability and beat morphology:** Methods deriving respiration from a combination of beat morphology and heart rate variability.

All of the EDR methods have their advantages and disadvantages, but among all these methods have not yet widely adopted into clinical practices [24]. And among all of these methods one of the simplest methods is to extract respiration from the single lead ECG (which is the focussed in this thesis).

Chapter 4

Principal Component Analysis

Large datasets are increasingly widespread in many disciplines. In order to interpret such datasets, methods are required to drastically reduce their dimensionality in an interpretable way, such that most of the information in the data is preserved. Many techniques have been developed for this purpose, but principal component analysis (PCA) is one of the oldest and most widely used. Its idea is simple—reduce the dimensionality of a dataset, while preserving as much 'variability' (i.e. statistical information) as possible [25]. First, it was introduced by Pearson (1901) and developed independently by Hotelling (1933) [26]. Hotelling method is one of the most familiar methods of multivariate analysis which uses the spectral decomposition of a correlation coefficient or covariance matrix. The PCA is a multivariate method, it was not widely used until the advent of electronic computers, but it is now well established virtually in every statistical computer package.

The central idea of PCA is to reduce the dimensionality (multivariate) of a data set. The data set consisting of a large number of interrelated variables, while retaining as much as possible of the variation. The PCA is achieved by transforming (orthogonally) to a new set of variables called the principal components (PCs). These PCs are uncorrelated but ordered. The first few PCs will retain the most of the variation present in all the original variables [25]. In General, PCA can be used for multiple purposes depends on the application. These applications may include data visualization, data reduction, data classification, trend analysis, factor analysis, and noise reduction [25]. Among these applications of the PCA, In this thesis PCA used for the data reduction in a multivariate data sets and noise reduction. For example, considering a vector of 'n' random variables 'X' for which the covariance matrix is 'Σ', then the PCs can be defined by the following equation:

(1)

Where, 'Z' is the vector of 'n' PCs and 'A' is the 'n × n' orthogonal matrix with rows are the eigenvectors of 'Σ' [XX]. The eigenvalues (of Σ) are proportional to the fraction of the total variance accounted for by the corresponding eigenvectors. So, the PCs can explain the most of the variance in the original variables. If, some of the original variables are correlated then a small subset of PCs describes a large proportion of the variance of the original data.

In summary, depending on the size of N, a correlation analysis of all N/2 +1 energy values with each machining parameter and also finishing surface roughness may not be satisfactory once many power spectra components tend to be auto-correlated. Principal Component Analysis (PCA) can be used to reduce the power spectra vector dimension leaving only the components that carry most of the information. PCA is a linear statistical technique with the objective of reducing data dimension by forming a new set of principal components (PCs), representing the maximal data variability without loss of information [27]. Computation of the PCA data transformation matrix is based on the eigenvalue decomposition and computation of the principal components follows the below procedure:

1. Calculate the covariance matrix of the input data
2. Compute the eigenvalues and eigenvectors of the covariance matrix
3. Retain the principal components whose cumulative explanation of the variance-covariance structure can be at least 90%; the first principal component has the largest possible variance (each succeeding component in turn has the highest variance

possible under the constraint that it is orthogonal to the preceding components) and PCA is sensitive to the relative scaling of the original variables.

4. Project the original data onto the reduced eigenvectors obtaining the scores and thus reduce the dimension of the data. The scores represent the level of relationship and explanation of a variable through the PCA model.

Note that the first principal component has the largest possible variance (each succeeding component in turn has the highest variance possible under the constraint that it is orthogonal to the preceding components) and PCA is sensitive to the relative scaling of the original variables.

4.1 Mathematical formulation of PCA

It is expressed that PCA can be used to extract the common information of observations in the population. Assume that we have N observations and P variables. In PCA we represent the problem as a matrix (O) with N rows (N stands for the number of observations) and P columns (P stands for the number of contributing parameters).

(2)

In order to study the relationships between variables and observations, we construct the covariance matrix for variables () and observations (). is a matrix and is a matrix. In order to construct the Covariance matrix between two variables (), the following equations are used to calculate the:

(3)

(4)

Where, refer to measured data points, , stand for the average of , data points. is the number of observations (data points). is a statistical criteria which indicates the data points' dispersion with respect to the mean value of observations. The more is the variance of a parameter, the more dispersion (which is available between the various values of that parameter). Covariance between two parameters indicates their relationship and dependence. If is positive, they have direct relationship with eachother, i.e. if increases, will increase. Using above mentioned definitions, we have the following matrixes for the covariance matrix for variables or parameters () and observations or measurements ().

(2)

(2)

Thanks to Rouche-Capelli theorem to obtaine can obtain Eigenvalues () and Eigenvectors () of the Square Matrices using the following equations:

(5)

(6)

Below equation (7) represents the covariance matrix between variables and its relation.

(7)

Where is P X N matrix , is P X P matrix and is P X N matrix

Below equation (8) represents the covariance matrix between observations and its relation.

(8)

Where is N X P matrix , is N X N matrix and is N X P matrix

Finally, using equation (9) the PC (matrix) results from the multiplication of E (matrix) and O (matrix).

(9)

4.2 Principal Component Analysis in ECG Signal Processing

The PCA has a widespread application in the Signal processing, particularly in ECG signal processing [28]. In the ECG Signal processing, PCA can be used for the noise estimation [29], source separation applied to fetal ECG [30] and the atrial fibrillation [31].

This thesis, hypothesize that beat to beat changes in ECG features such as QRS complex could be identified by PCA from single lead ECG recordings. This hypothesis is based on the knowledge that beat to beat changes in ECG features result in a change in the correlation between these features at different beats. So, PCA can be able to extract the clean ECG from raw ECG affected by noise and artefacts without losing information about local heart-rate variations [32].

Since the respiration is the main effect that modulates the ECG, in this thesis, our aim was to investigate PCA could detect the respiration and access the PCA as a tool to extract the respiration signal from a single lead ECG.

4.3 Procedure of applying Principal Component Analysis to ECG Signal

The procedure applied PCA to ECG is in 4 steps.

Step 1: Extract the available QRS segments in 1-minute window of the ECG signal

Step 2: Treated the different QRS segments as observations and number of samples in each segment as variables (or degrees of freedom).

Step 3: Find the significant PCA coefficients from each window. Then take the number of PCA coefficients in the decreasing order of variability that capture the 99% retention in the information for variance-covariance structure.

Step 4: Obtain the Auxiliary signal from the reduced data dimensionality through PCA coefficient using cubic interpolation.

Chapter 5

Electrocardiogram-derived Respiration Signal extraction by Principal Component Analysis

In order to extract the respiration for the single lead ECG, the experimental design includes the clinical data, methods and statistical analysis. The standard segmentation procedure was used to extract the respiration.

5.1 Clinical Data

In order to extract the respiration from the single lead ECG, the clinical data used in this thesis consisted in the fantasia database, which is freely available to download from the website of physionet [33]. Physionet is the research resource for the complex physiological signals. All the data available in the Physionet are fully anonymized (deidentified) and can be used without further approval of ethical committee [34]. In this thesis, 33 subjects clinical data (including male and female population with young and old subjects) with the mean length of the signal 118.28±4.15 mins were used. During the measurements subjects were in a resting state (supine position) with spontaneous breathing, sinus rhythm while watching Fantasia movie (Disney, 1940) to help maintain wakefulness. The continuous respirations and single lead of ECG (lead II) were simultaneously captured. Respiration was measured with belt attached around thorax. Originally, ECG signal was sampled at 250Hz.

5.2 Methods

The methodology is accomplished by MATLAB code, equipping the reader with tools to develop, test and serves to extract the EDR from the physiological wave form (ECG). To pre-process the considered data sets, nine consecutive steps were performed. These steps, which include resampling, pre-filtering, identification of the R-peaks, QRS segmentation, P rincipal component analysis, computation of an Auxiliary signal, compute the differences of R-peak positions, compute the spline interpolation and finally extracted the ECG-derived respiration (EDR).

The steps are:

1. **Resampling:** It is the procedure to compress the signals with the resampling rate without compressing the original length of the signal. Originally ECG signals were sampled at 250 Hz. In this thesis, the ECG signal was resampled at 200 Hz, which is the commonly used resampling rate. Resampling step applied for the complete ECG signal.

2. **Pre-filtering:** It is the filtering process. In our case, it was done at 40 Hz low pass bidirectional 6^{th} order Butterworth filter to remove high-frequency components from the ECG, particularly power line noise. Pre-filtering applied for the complete ECG-signal.

3. **Windowing:** In this thesis, windowing procedure was applied for the complete data sets. This procedure will allocate each window size of 1-minute in the complete ECG signal (For example, one ECG signal has the length of 1 hour signal; it means 60 windows can be achieved for this complete signal). The below followed steps (4-9) were applied for the each 1- minute window of the signals.

4. **Identification of R-peaks:** Typically, amplitude of the R-peak is measured with respect to the baseline. This is a simple and widely used method. There are many applications are available to identify the R-peaks. In our case, Pan-Tompkin [35] was used to identify the R-peaks. The below Figure 9 depicted the R-peaks identification in one minute window.

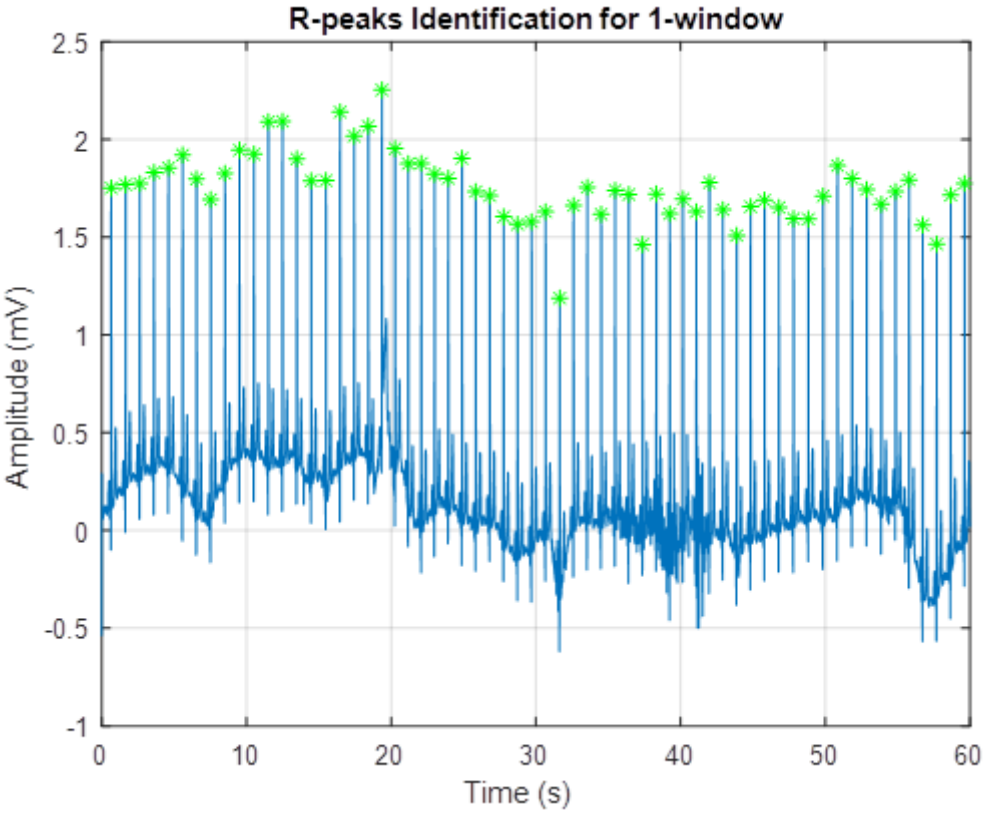

Figure 9: Identification of R-peaks by Pan-Tompkins algorithm

5. **QRS Segmentation:** It is the process considered from 80ms before and after from the R-peaks. So, each QRS segment will have a constant length of 160ms. The below Figure 10 depicted an example of one QRS segment.

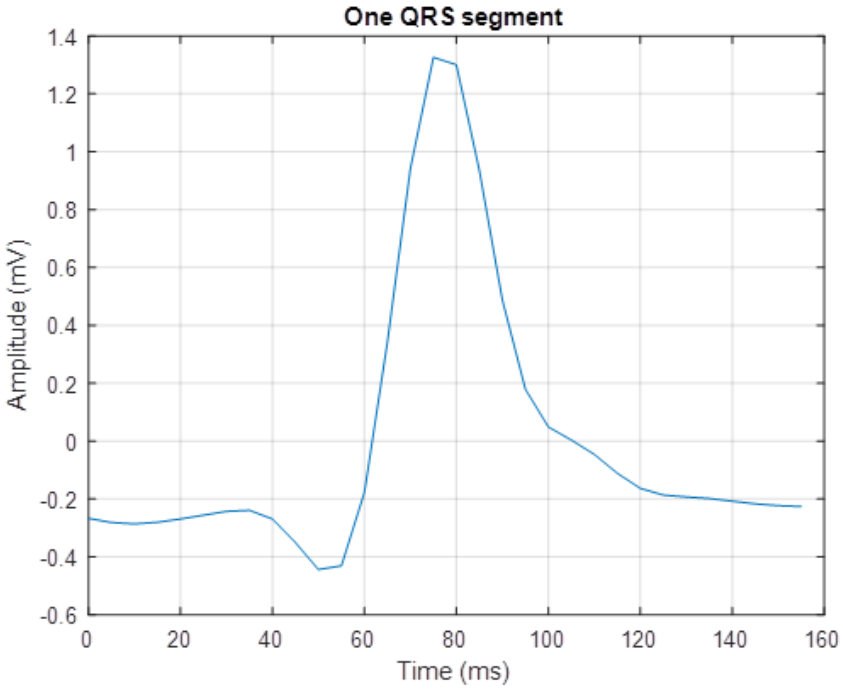

Figure 10: One QRS segment

Below Figure 11 depicted the QRS segmentations in one minute window.

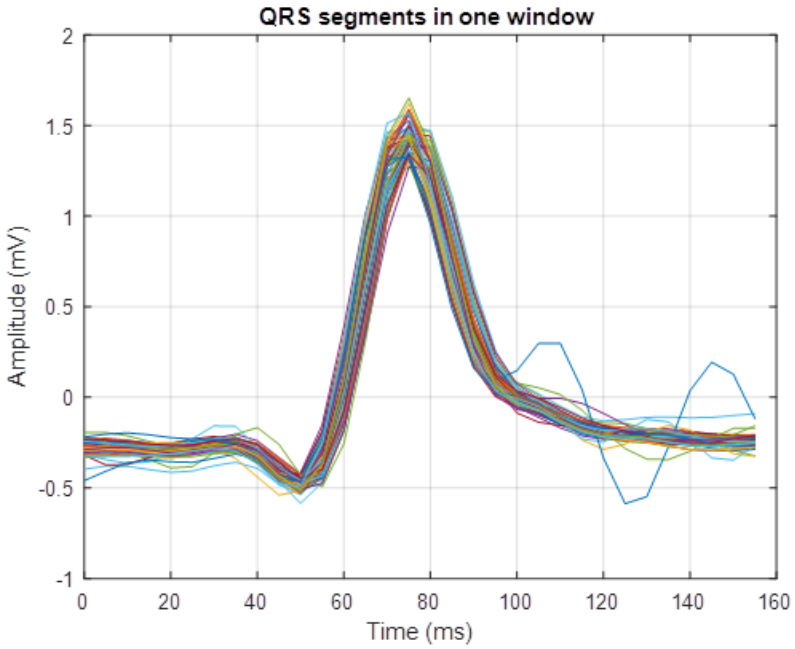

Figure 11: QRS segments in one window

6. **PCA for the segmented Beats:** After obtaining the QRS segments, each QRS segment was processed by PCA. Generally, PCA technique is used for reducing the dimensionality of multivariate datasets; in this case QRS segments [25]. In ECG signal processing, PCA had founded widespread applications, which include noise estimation (in this case) [29]. PCA were applied for the all QRS segments in the signal. Usually, 1 st principal component will have the largest possible variation. For this reason 1 st principal component was analyzed for each window. The below figure 12 depicted an example of 1st principal component of the QRS segment.

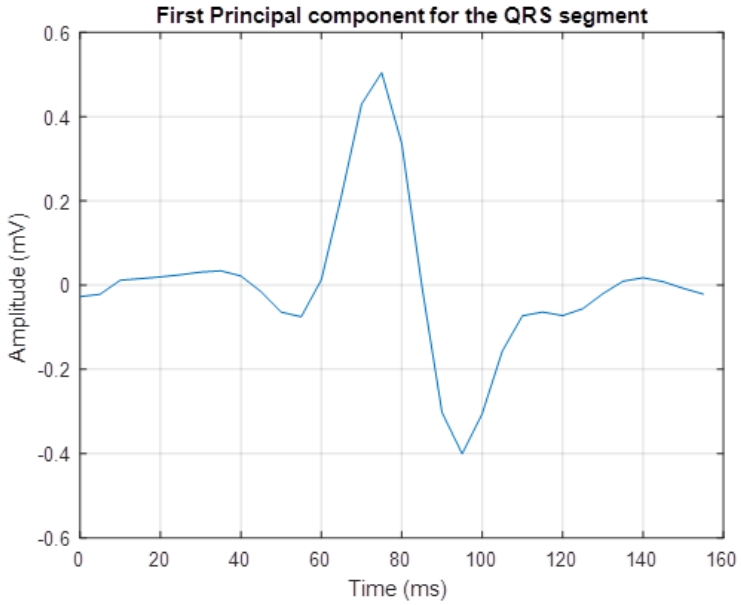

Figure 12: 1st Principal Component of the QRS segment

7. **Computation of Auxiliary signal:** After obtaining the principal components, all the QRS segments were replaced with the principal components of the QRS segments in the original ECG signal.

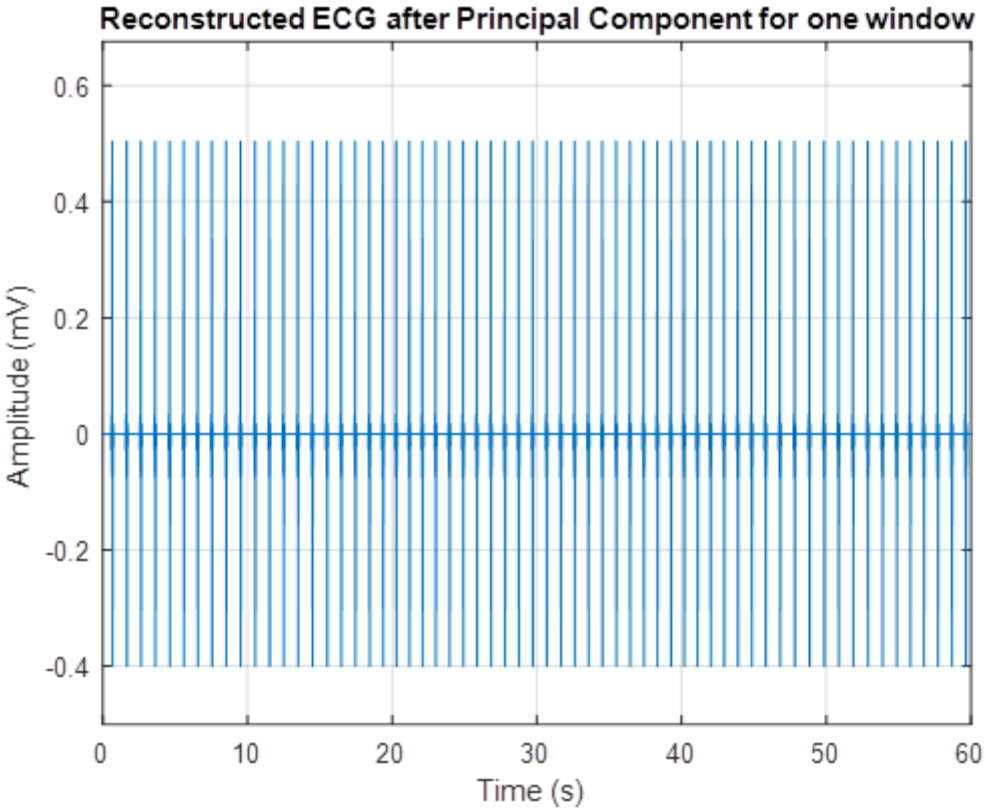

Figure 13: Auxiliary signal

After obtaining the Auxiliary signal it is mandatory to check the R-peak positions of the original ECG and Auxiliary signal. R-peak positions should align in the original ECG and Auxiliary signal, In order to be sure that to do not manipulate the clinical information (signal of interest). The below Figure 13 depicted the Auxiliary signal. The below Figure 14 depicted the overlapped signals original ECG and auxiliary signal.

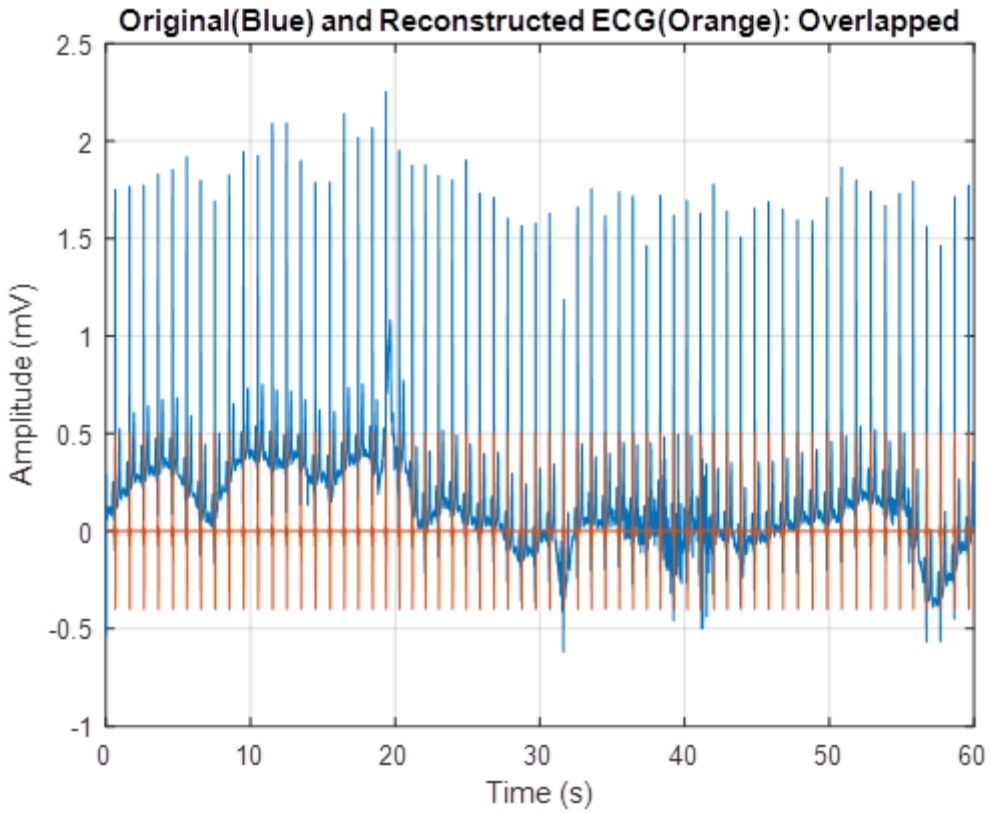

Figure 14: Overlapped signals (original ECG and Auxiliary)

8. **Compute of R-peaks differences:** After obtaining the Auxiliary signal, subtracted the amplitude of an Auxiliary signal on the R-peak positions to the original ECG. Then computed the differences in amplitudes on the R-peak positions.

9. **Compute the Spline interpolation:** After computing the R-peaks differences, obtained the signal which is not homogeneously sampled. Thus, interpolate the sample (using cubic spline interpolation), in order to obtain the signal sampled at the original sampling frequency. Finally obtained the ECG-Derived Respiration (EDR). The below Figure 15 is the example of obtained EDR signal.

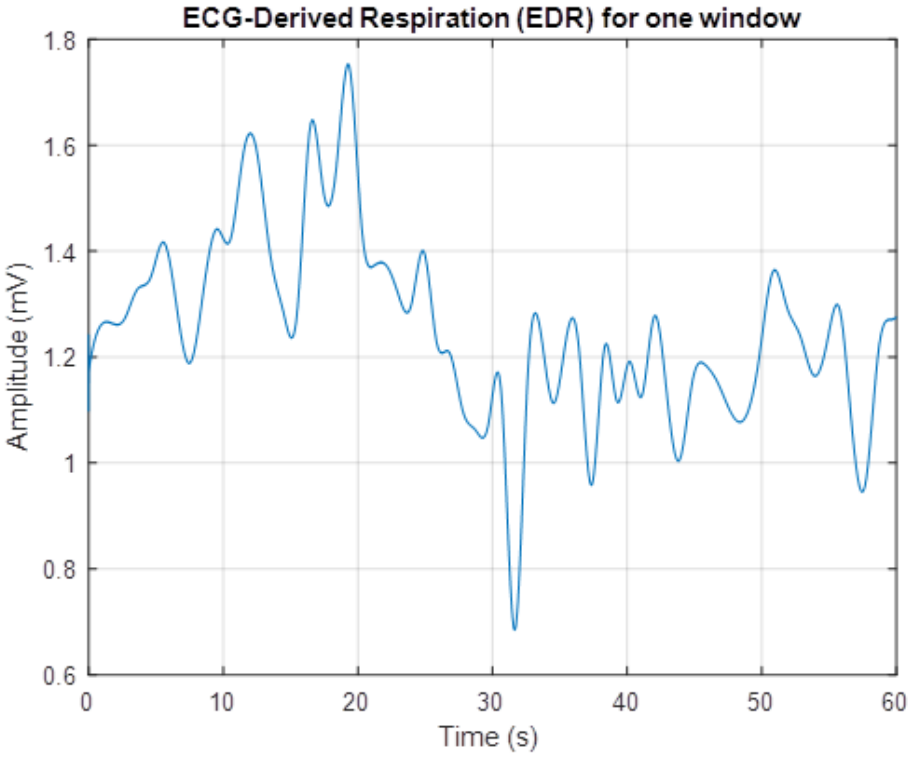

Figure 15: EDR signal

5.3 Statistical Analysis

After extracting the EDR signal from the raw ECG, statistical analysis was performed, in order to evaluate the goodness of the method. Particularly correlation analysis was performed, computing, for each window, the correlation coefficient (ρ) between the EDR and the direct respiration signal. Moreover, the windows were classified in two classes according with the correlation coefficient. In relation to the correlation coefficient the window is classified as incorrectly estimated (|ρ|<0.5) and correctly estimated (|ρ|>0.5).

5.4 Results

Correlation analyses were performed after obtaining the EDR signal. This correlation analyses were performed between the original respiration signal and obtained EDR signals. Resulting groups were divided in to two with EDR<0.5 and EDR>0.5 in order to understand the strongest correlations. The Results are reported in the below Table 1.

	Length of the signals (min)	N° of windows	Correlation coefficient (ρ)			
			N° windows with |ρ|<0.5	N° windows with |ρ|>0.5	|ρ|<0.5	|ρ|>0.5
Mean	**118.28**	**118**	**29 [24%]**	**89 [76%]**	**0.37**	**0.74**
Standard Deviation	**4.15**	**4**	**14 [12%]**	**15 [12%]**	**0.03**	**0.02**

Table 1: Results

Below figure 16 depicted the overlapped signals between the direct Respiration and the obtained EDR.

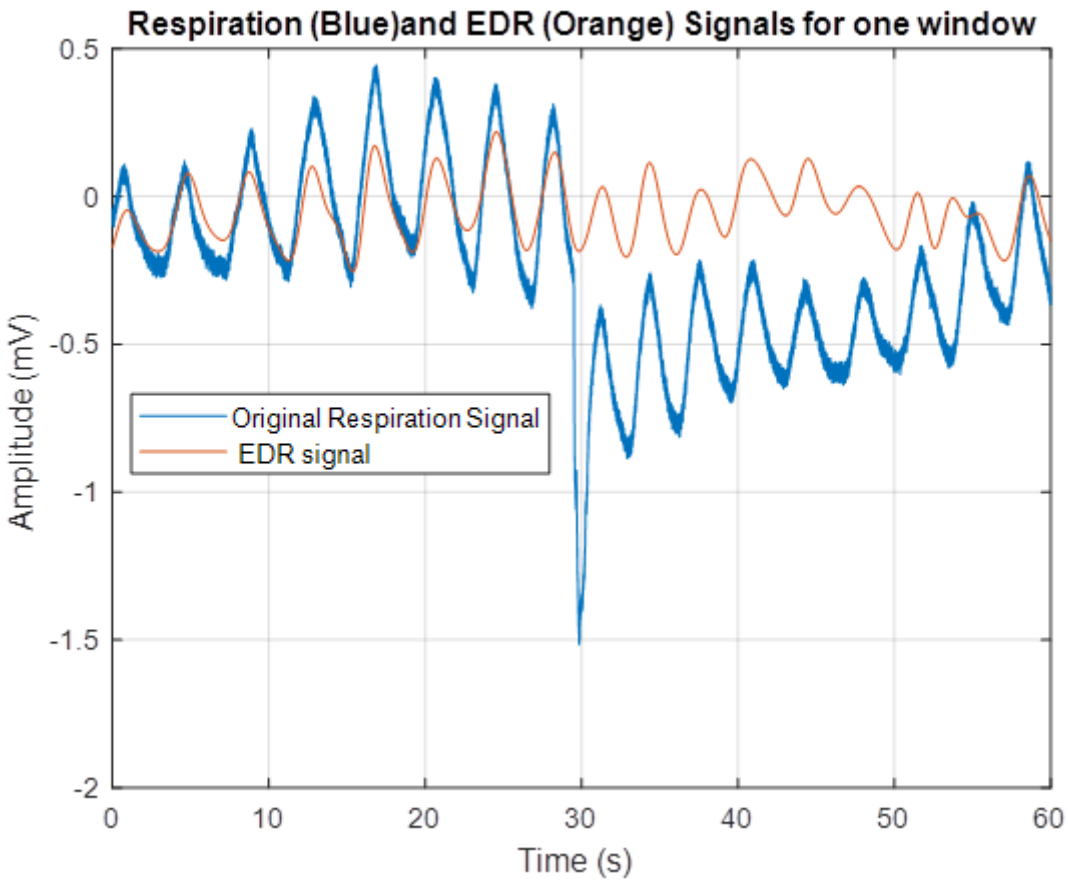

Figure 16: Overlapped between direct Respiration and obtained EDR Signals

5.5 Discussions and Conclusion

The demonstration of experimental EDR method by using Single lead ECG has been described to investigate PCA could detect the respiration and access the PCA as a tool to extract the respiration from a single lead ECG.

There are several methods are available to extract the respiratory signal from ECG have been described in the literatures [11-23]. There are some methods based on respiration induced variations in the beat morphology, others extract respiratory information from variations in instantaneous HR and the combinations of both methods (HR and beat morphology) have been proposed. But none of these methods have been applied in to the clinical settings [24]. In general, EDR algorithms based on beat morphology are more accurate than other EDR algorithms based on heart rate information. Among these EDR methods, one of the simplest approaches is the interpolation of R-wave amplitudes or area of QRS complexes from a single lead of ECG. Studies have shown, that EDR signal based on measure of the R-peak with respect to amplitude of S wave obtained higher sensitivity and positive predictivity compared

to the other EDR model (R-wave amplitude, known as R-peak with respect to baseline) [19]. There is another single lead EDR approach is by calculating the area enclosed by baseline and QRS complex in a certain interval. The QRS area approach is less affected by noise compared to pure amplitude EDR methods (R-wave amplitude or with respect to amplitude of S wave) [13]. The boundaries of QRS area can be either fixed or variable. In this thesis, the standard QRS segmentation method was considered. In this method, QRS were segmented 80ms before and after from each of the R-peaks to extract respiration using PCA.

According to the literatures EDR is inversely correlated to the original respiration [32]. For this reason, in this thesis absolute values of the correlation coefficients were used. Results obtained for the number of incorrectly estimated windows is 29±14 [24±12%] for each subject, associated with a distribution of correlation coefficients equal to 0.37±0.03. On the contrary, the number of correctly estimated windows is 89±15 [76±12%] for each subject associated with a distribution of correlation coefficients equal to 0.74±0.02. Our results clearly saying that there was almost 50% higher values obtained for the correctly estimated windows when compared with the incorrectly estimated windows.

It can be seen that results of PCA in our study differ from the previous results presented in the literatures [37, 38]. This was expected because the study of Langley et al [37] is clearly saying that the respiration data were collected by using different protocols in the laboratory. Moreover, the study of Widjaja et al [38] and Suvi et al [39] also used the Fantasia database, but the data segment selection was different from our study.

Generally, there is a drawback of using PCA but which is an advantage of our study, as it operates on a linear assumption that the ordinal of principal component offers the best surrogate respiration data which improves the performance of the observed EDR waveform with appropriate comparison parameters. This thesis restricted the study to healthy subjects only.

In the conclusion, PCA is a novel based approach to extract EDR, the proposed method may represent a potentially useful tool to extract the respiration from single lead ECG using PCA. As only a single lead was used in our study, however care should be taken to choose the ECG lead for extracting the respiration. Further studies can conduct to the cardiac diseased subjects.

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