POLITECNICO DI TORINO

Master Degree in Biomedical Engineering

Master Degree Thesis

Development of a cuff-less Blood monitoring device

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Abstract

In an era where technology is advancing at an unprecedented rate, surpassing itself day by day, it is inevitable that this progress involves the health area too. This evolution is mainly represented by the constant increase in user-friendliness, functionality, miniaturization of devices and the possibility of collect a wide amount of data about a subject. In these devices the increment of computational power and the easiness of the integration with complex algorithms encourage their application on health technologies. The study of new methods for evaluating different vital signs falls within this scope.
The objective of this thesis work consists in the use of a wearable device for evaluation of Blood Pressure (BP) in a non-invasive cuff-less based way. In fact, BP is one of the alerts for cardiovascular disease (CVD). In the last few years, some of major causes of death worldwide are cardiovascular disease (CVD).
The negative trend of unhealthy lifestyles, together with the rising age in today's world, is closely related to the rising of number of people suffering of CVD and, one of the risk factors, is chronic hypertension, characterized by high blood pressure retained for a long period of time.
Therefore, the continuous monitoring of blood pressure (BP) allows to provide a valid tool for observing patients in significant health conditions (e.g. for those who have CVD such as hypertension avoiding a degeneration into heart attack and stroke) but it is also an important instrument of diagnosis.
Wearable Health Devices are every year more present in daily use, progressively helping people to monitor their health condition both at a sporty level, for optimization of sport activity, and at a medical level, with a monitoring and prevention value.
The rise in the fabrication and use of wearable devices in daily life, along with the development of their reliability and precision, promote the perspectives of development of this market in the coming years. Blood pressure measurement enters in this field have been explored physiological parameters that allow to measure blood pressure in a roundabout way.
The main one is the Pulse Wave Velocity (PWV) that encloses most of connections with BP. In PWV values are contained the variation of velocity in the propagation

of the pressure wave generated by the passage of blood flow in vessels. In particular, PWV is strongly connected with variation of vessels diameters and so it can be used to estimate pressure.

In this thesis work, a statistical model was implemented to estimate pressure from data collection (ECG, PPG and ABP signals) taken at first from online databases (MIMIC III) and then recorded with State of the art devices (Shimmers and Omron HeartGuide). From electrocardiogram (ECG) and photoplethysmography (PPG) the Pulse Transit Time (PTT) and Heart Rate (HR) are identified in order to train a linear regression algorithm that allows to estimate, after calibration, the systolic and diastolic pressure.
The aim of this study is to develop an algorithm capable of accurately predict continuous BP using a Mathematical auto regressive approach that can be integrated in a cuff-less, no-invasive devices more comfortable compared to those currently used. The results obtained show an effective correlation between PTT/HR and systolic and diastolic BP. The main issue of this approach is that it is person-specific and could change with aging. Besides, this problem could be easily overcome with periodic calibration.

Contents

Chapter 1

Introduction

Cardiovascular diseases (CVD), such as myocardial infarction and stroke, are considered the principal causes of death all over the world. One of the principal factors that can lead to serious CVD, is the hypertension that consists of a state in which systolic blood pressure (SBP) or/and diastolic blood pressure (DBP) are chronically elevated.
Even though the awful lot of evidence on the risk of high blood pressure and benefits of blood pressure lowering accumulated until now, elevated blood pressure remains the main risk factor for illness and disability.[1] A worldwide estimate of people suffering from hypertension may be about 1.13 billion[2], with 7.6 million deaths every year. Approximately 54% of stroke and 47% of coronary heart disease are referable to elevated blood pressure.[3]
It is therefore natural that, in the last decades, a large increase in monitoring of hypertension has occurred. The introduction of machine learning (ML) techniques have shown the potential of exploration of efficient methods to effectively measure BP with minimal invasiveness and in dynamic conditions.
In general, hypertension is an important health issue with prevalence increasing with people aging. The wall of large arteries, notably the aorta, thicken and became less elastic in time. This phenomenon causes an increase in pulse wave velocity (PWV), a significant and dependable measure of stiffness of the arteries.
Several studies have shown the theoretical and practical correlation between cardiac activity and the speed with which blood travels in the different compartments. [4] - [5] This correlation is not direct, due to several influencing features, that has to be calibrated on every specific person. Despite this, the relatedness between PWV and BP remains strong however.
Another point to focus on is the importance of monitoring people apparently in health condition. In fact, there are various kinds of phenomena, effects and conditions that can be found in specific situation o moment of the day. The most famous are "white coat hypertension"[6], "masked hypertension"[7] and some particular morning and night cyclic pattern that are complicated to track. In addition

there are some risky conditions resulting from secondary diseases that can aggravate the health of the hypertensive patient like diabetes, strokes and chronic kidney diseases.[8] In all the phases of hypertension study, diagnosis and treatment, the monitoring of BP is decisive and it is important to have a reliable measure of SBP, DBP.

Another important point that underline the importance of find an innovative method for BP prediction is the discomfort that both method, invasive and not-invasive, have for people that must measure continuously their blood pressure. One example for what concern the non-invasive way of pressure measurement is the 'pressure holter', an automated intermittent measure of SBP and DBP every 15 to 30 minutes for a period of about 24 hours. The device allows the subject to perform normal daily activities while saving the registered data. The continuous monitoring can provide a larger amount of data in an everyday circumstances, help in identification of "white coat" and "masked hypertension", giving a check out of the efficacy of anti-hypertensive drug treatment throughout the day. [9]
With a strong discomfort for people treated given by the swelling of the cuff especially during the night.

1.1 Objective of work

Today, the evolution of demographics dynamics combined with the increase in the average age and the unhealthy diets, brings population to the development of chronic diseases. Chronic diseases are becoming one of the most common cause of reduction of quality of life and death. Hypertension, as described above, is the principal cause of chronic diseases and, prevent or cure it, is one of the best strategies against cardiovascular diseases (CVD), this could be possible with continuous blood pressure measurement. For these reason, medical technology has encouraged the development of comfortable and reliable devices for blood pressure monitoring that, through detecting of signals and interpretation of data using different approaches, could improve person's health.

The aim of this thesis project is to use state of the art, synchronized devices in order to develop a method for no-invasive, cuff-less evaluation of SBP and DBP. The developed of these kinds of wearable device will help to increasing the number of people that constantly monitor their blood pressure. It could be possible with a comfortable device that monitor patients constantly, without impede or limit their normal lifestyle.

1.2 Wearable devices impact

The role of Wearable Health Devices (WHDs) are increasingly changing the relationship between patient and doctor and the usability of continuous monitoring in respect also of non hospitalized patients. These technologies could also help health people to better monitor their activity or fitness level for self-health tracking. Moreover, by having more data to clinicians is possible to have an earlier diagnostic for more effective treatment.

Another important aspect is the wearing comfort that is necessary for reach more people possible willing to wear it. For this goal, the miniaturization of electronic devices, plays a key role, it is enabling to design more adaptable wearables, maintaining their reliability.

To underline the relevance of WHDs, it could be useful to analyse this specific market to predict market values and trends. The market value of wearable devices is in strong increase year after year, this year it is assumed to reach a value of almost $44.43 billion (as shown in Fig. 1.1). With an increment in the last years of approx 200 hundred percent. [10]

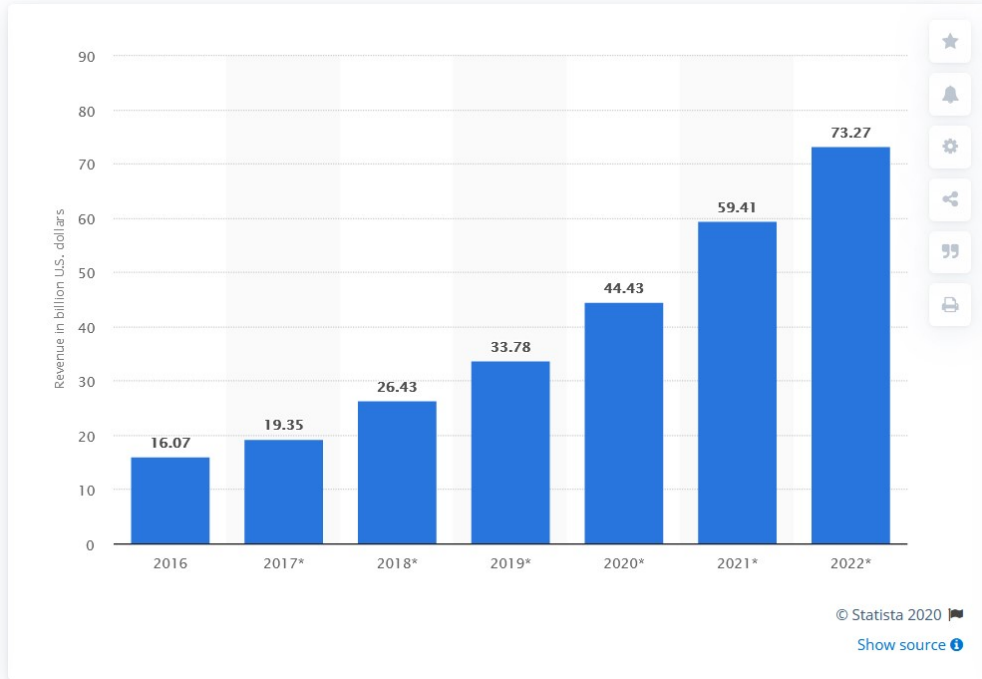

Figure 1.1. The statistic shows wearable device revenue worldwide from 2016 to 2022. [10]

According to a 'ABI Research' study [11], from 2017 to 2019 the wearable devices usage in health applications is been steady increase also thanks to the market

value of sports wearable devices for activity aims. This could give a push WHDs companies to improve and invest in these kinds of products. [11]

The galloping increasing of elderly population and the consequently growing of chronic illnesses result in a stronger attentiveness in wearable measurements devices for physiological data.

Moreover, the improvement of these devices and the development of smaller wearable devices, lead of a less cost and better usability during data collecting. It could enable the change and support of the conventional health-care system with wearable health-care systems, person-specific. [12]

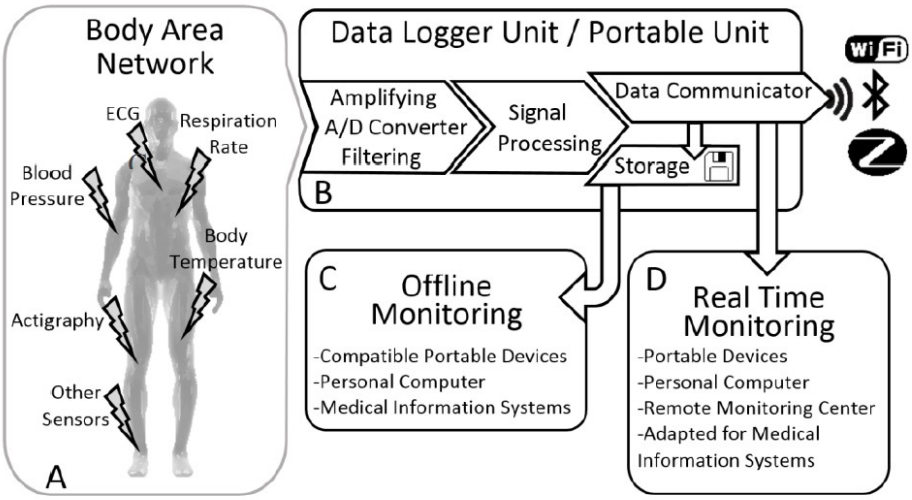

Figure 1.2. Generic architecture of wearable health devices system. [13]

In figure 1.2 an example of architecture made by different modules (A) Body Area Network; (B) Data Logger that include all the electronic; (C) Data Analysis, which enables an offline visualization of records; (D) and Real Time Monitoring that allows to display and analyse live data.

The goal in blood pressure measurement is to have a wearable device that allows real time measurement and that consent a continuous monitoring. With this kind of technology, it will be possible a strong improvement of national health-care system, for what concern all patient that could have benefits with continuous monitoring of BP.

This work has been developed within SINTEC Project, a European project that will provide soft, sticky and stretchable sensor patches that can be used for physiological signals record and elaboration. SINTEC sensors will be applied it in clinical environment and in athletics performance evaluation e.g. in preventive care, sports and fitness, and medical technology.

Chapter 2

Physiological Signals

2.1 Heart physiology

The cardiovascular system enables all that exchanges of nutrients and unwanted materials, that are the absolute requirement of life. The nutrients come from the external environment and need to be bring to all body cells. Diffusion alone cannot deliver to all cells what they require as quickly as they need it. The cardiovascular system provides a much more efficient transport mechanism.

This system is composed by three elements:

- **heart**: the heart is a muscular organ which pumps blood through the blood vessels of the circulatory system;
- **blood vessels**: ducts by which blood rushes;
- **blood**: a fluid that carries oxygen and nutrients to the body, while carrying metabolic waste such as carbon dioxide to the lungs.

2.1.1 Heart

The heart is a muscle that leads the impulse necessary to circulate blood in the blood vessels. It also carries out sensory and endocrine functions that are necessary to regulate cardiovascular variables i.e. blood volume and pressure. The heart is a muscle that generates the force that pushes blood through blood vessels. It is situated in the thoracic cavity, just over the diaphragm, which divides the thoracic cavity from the abdominal ones. [14]
It is divided into right and left sides, that are separates by a longitudinal wall called septum that avoids the oxygenated and de-oxygenated blood from mixing together. Chambers, in turn, are divided in two areas, in fact another wall separates the upper and lower portions. As illustrated in Figure 2.1, the heart is divided in four

chambers: two in the top part, called atria, which receipt the blood that come back from the vascular system to the heart, and two in the lower part, called ventricles, ventricles receipt blood from atria and produce the impulse that drives the blood away from the heart through vasculature. [14]
A series of unidirectional valves divide atria from ventricles, the atrioventricular valves (AV), and ventricles from external arteries, the semilunar valves (SV), avoiding the blood from returning backward once ejected. These valves open and close in a passive way, forced by the flowing blood, so controlled by the ventricles contraction.
The heart transmission of electrical impulses is generated by pacemaker cells (these specialized cells are called auto-rhythmic cells) and transmitted through the bundle of His to the rest of muscle of the myocardium. This muscle is called myogeny and is not dependent of the central nervous system.

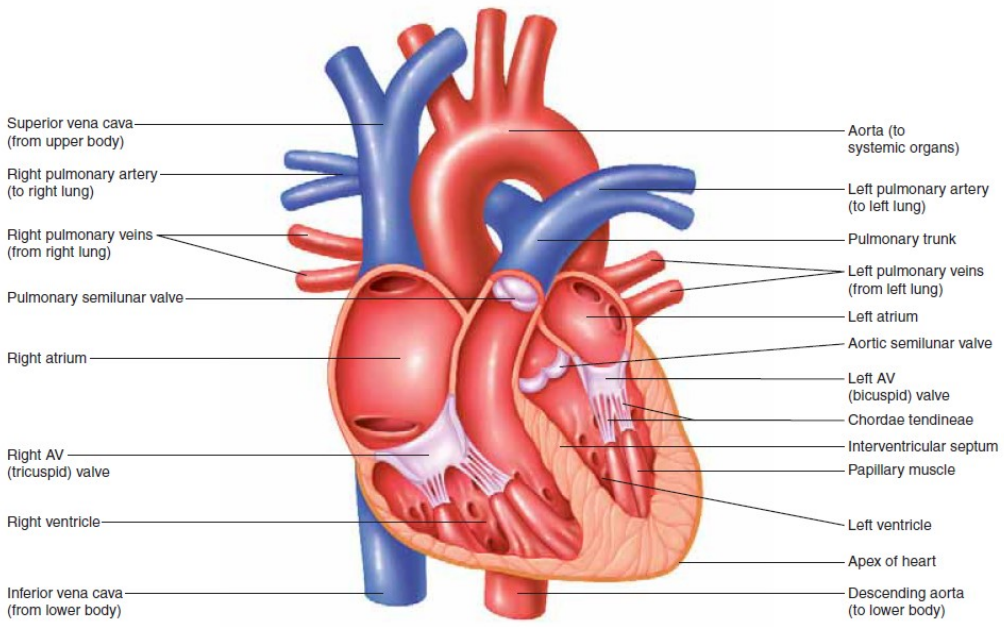

Figure 2.1. Section of the heart showing atria, ventricles, valves, and connections to principal blood vessels. [14]

The conduction system generates a conduction wave that guides the impulse first through the atria, which contract simultaneously, then thought ventricles. This wave causes ventricles depolarization and subsequently contraction, allowing the flow of blood in the blood vessels. Ventricular contraction is called systole, while the release phase is called diastole.
The ability to generate independently an action potential of the pacemaker cells

is given by the unstable membrane potential, that slowly increases from -60 mV until a threshold value. This is the "pacemaker potential", and it is unstable due to the presence of I_f channels (funny current), open at -60 mV. The depolarization velocity of the auto-rhythmic (or pacemaker) cells determines the heart rate (HR), so the frequency which the heart contracts. [15] The permeability of the ions Na_+ and Ca_2+ channels influence the time interval between two successive generated action potentials (Fig.2.2).
A stimulation on the pacemaker cells by the sympathetic nervous system, causes the increasing of the ionic flux in Ca_2+ and I_f channels by using adrenaline and noradrenaline, that accelerates the cardiac frequency.
The acetylcholine, that is a parasympathetic neurotransmitter, instead, increases the permeability of K_+, causing a hyperpolarization of the cell, while the permeability of Ca_2+ decreases decelerating the depolarization process. That decelerates the cardiac frequency.[15] Electric impulse starts with an action potential generated

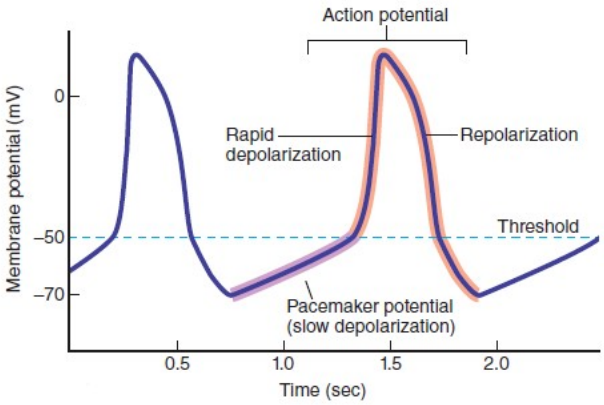

Figure 2.2. **Electrical activity in a pacemaker cell** A recording of the membrane potential showing action potentials, threshold and pacemaker potentials. [14]

by auto-rhythmic cell, placed in the Sinoatrial Node (SA), and propagate through an internodal tract until to arrive at the Atrioventricular Node (AV). Then the depolarization follows the Bundle Branches and Purkinje fibres arriving, at the contractile cells of the ventricles. The SA node imposes the rhythm of the heart beats (Fig. 2.3).

2.1.2 Blood Vessels

The blood moves through the body traveling by a system of vessels. This trip starts from the cardiac muscle until you get to all the organs, then it goes back to the heart. The term used to describe this system is 'vasculature'. The blood vessels

branch over and overflowing away from the heart, growing in number and becoming more small in diameter. The smallest between all blood vessel are capillaries; they provide an exchanging site between blood and interstitial fluid. [14]
When oxygenate blood moves away from heart, it is moved to all the organs and tissues starting from large vessels, called arteries, which branch inside the organs and tissues. The littlest arteries ramify into littler vessels, the arterioles, which transfer blood to the smallest vessels, the capillaries.

From capillaries, blood carries into more large vessels, the venules, which lead to still larger vessels, veins, the veins move blood back to the heart. After passing through the capillaries, blood flows back to the heart, to reject waste materials and to be re-oxygenate (Fig. 2.4).

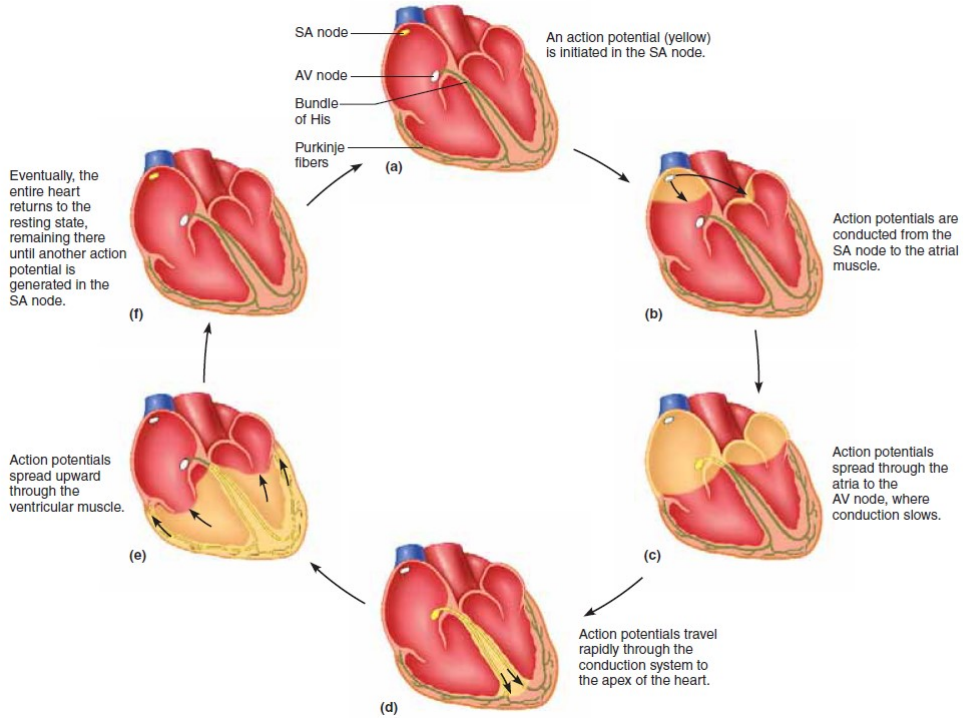

Figure 2.3. **Spread of action potentials through the heart** A single heart-beat sequence of electrical excitation, starting with (a) depolarization of the SA node and ending with (f) the return of the heart to the resting state. [14]

2.1.3 Blood

Blood is a fluid, it is composed of cells by nearly half of its volume, and the other half by plasma. The most numerous cells are erythrocytes or red blood cells, them contain hemoglobin that confers them their typical red colour, it is a protein essential for oxygen carry. The other numerous cells are leukocytes,

they are also called white blood cells, which help the body protect itself against external microorganisms. There are also the platelets, that are cell fragments that are involved in blood clotting. The other half of blood volume consist of plasma, composed by water containing dissolved proteins, electrolytes, and other solutes.

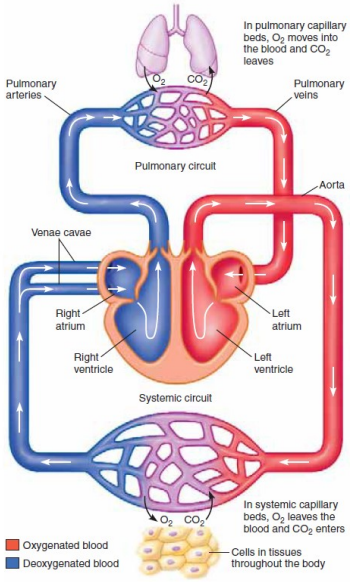

Figure 2.4. **Path of blood flow through cardiovascular system** Pulmonary and systemic circuits and principal blood vessels connecting with the heart. [14]

2.2 Electrocardiography

The electrocardiogram (ECG) is a non-invasive method for monitoring the electrical activity of the heart. It is a record of the diffusion of electrical current through the heart, recorded during the cardiac cycle as a function of time. The heart electrical activity is extremely synchronized, since if the activity is synchronized more larger is the amplitude of signals registered remotely from the source. So, the electrical potentials amplitude (that match with different electrical phases of the cardiac cycle) can be taken over by the skin surface.
So, the ECG typically is recorded by electrodes placed on the skin, it is also possible thanks to body fluids that acting as conductors, so the electrical activity produced by nervous or muscle tissue diffuses through the body. The ECG typically has an amplitude of the order of mV, in particular it is larger than 0.5 mV, the upper limit of the amplitude is about 2.5 - 3.0 mV.

2.2.1 ECG monitoring devices

Willem Einthoven was the inventor of most used technique for ECG recordings, it consists in an equilateral triangle that encircles the heart. The triangle has its corners fall on the right and left arm, and left leg. This pattern is known as Einthoven's triangle. (Fig.2.5) Electrodes placed on the skin are connected in pairs to a device that measures voltage (i.e. oscilloscope or chart recorder). Determined pairs of electrodes are mentioned as leads and indicated by Roman numerals. One electrode in each lead is appointed as the positive one and the other as negative one. Each specific lead calculates the difference in the surface electrical potential between the positive electrode and the negative one.
In detail:

- ***lead I*** detects the potential at the left arm minus the one at the right arm;

$$I = LA - RA \tag{2.1}$$

- ***lead II*** detects the potential at the left leg minus the one the right arm;

$$II = LL - RA \tag{2.2}$$

- ***lead III*** detects the potential at the left leg minus the one at the left arm.

$$III = LL - LA \tag{2.3}$$

A depolarizing wave causes an upward deflection moving towards the positive electrode; while, on the contrary, a depolarizing wave moving towards the negative electrode causes a downward deflection.[14]

2.2.2 ECG waveform

The ECGs are recorded on chart paper at a rate of 25 mm/sec and with an amplitude of 1 mV/cm.
The most three characteristic waveforms of ECG are:

- **The P wave** is an upward deflection caused by atrial depolarization.
- **The QRS complex** is a succession of ascending and descending waves caused by ventricular depolarization; it corresponds to the phase 'zero' of the action potential of ventricular contractile cell.
- **The T wave** is an ascending deflection due to repolarization of ventricles; it corresponds to the phase 'three' of the action potential of ventricular contractile cell.

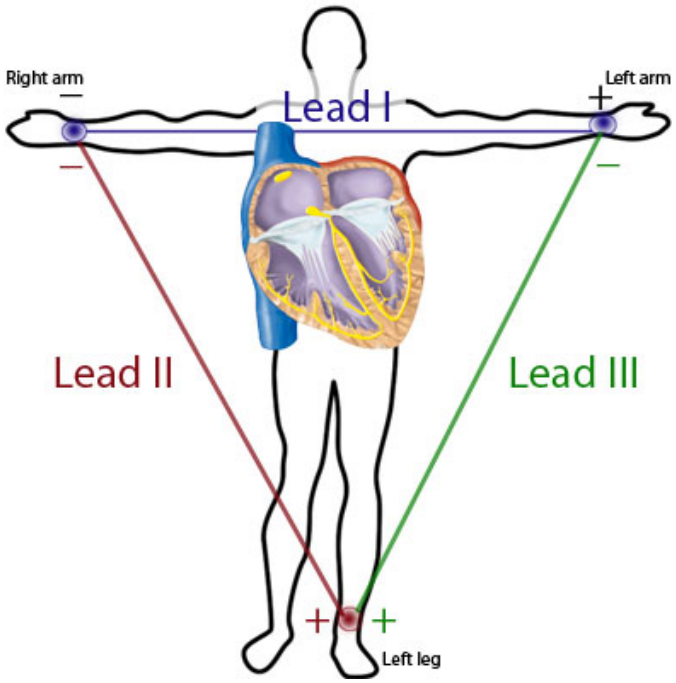

Figure 2.5. Einthoven's triangle. [16]

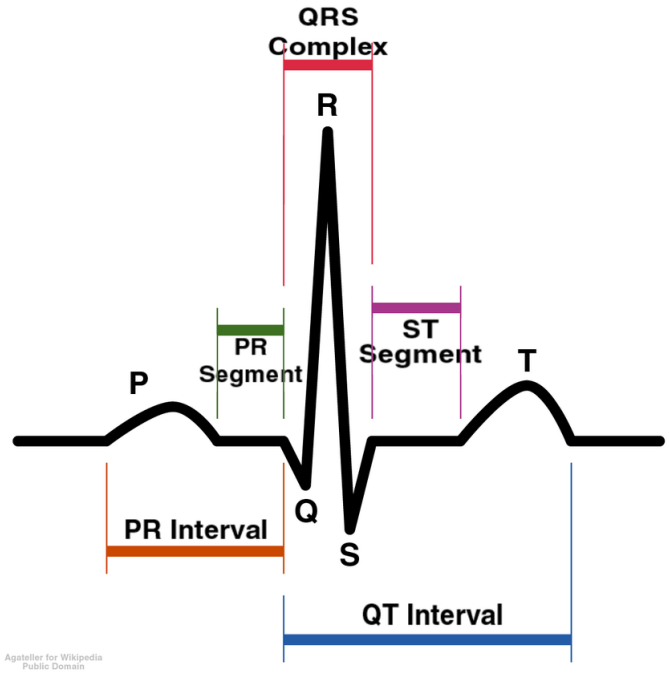

Figure 2.6. Schematic representation of normal ECG waveform. [17]

During each heartbeat, cells triggers action potentials at different times, the Electrocardiogram reflects patterns of action potential of the entire heart muscle. Determined segments and intervals can give important information about some purposes of the heart.
The P-Q (or P-R) interval happens between the P wave and the beginning of QRS complex, this interval gives an approximation of the time of conduction through the AV node.
The Q-T interval is the time from the beginning of QRS complex to the end of the T wave, this interval gives an estimate of the time of ventricles contraction (systole).
The T-Q segment is the time from the end of the T wave to the start of QRS complex gives an estimate of the relaxing of ventricles (diastole).
The R-R interval is the time between the peaks of two consecutive QRS complexes. Thought this interval is possible to calculate the heart rate:

$$HR = \frac{60\ seconds}{RR\ interval} \tag{2.4}$$

2.3 Photoplethysmography

The photoplethysmography (PPG) is another instrument of analysis that has been developed recently. It is a non-invasive technology that uses a light source directed towards the skin surface and a photodetector. The combined use of these two instruments measures the volumetric variations of blood circulation.
Moreover, the low cost of optoelectronic chip, and their high reliability, reproducibility and stability have encouraged the use of this technology in daily medical practice. Just like ECG, PPG can help to diagnose cardiac arrhythmias such as irregular heartbeat.
In fact, photoplethysmography is often used for heart rate monitoring. Recently, researchers have developed a keen interest to extract new and precious features from PPG signal not only the heart rate estimation and pulse oximetry readings. In particular the second derivative wave of PPG signal that contains important information for what concerns health-related. [18]
So, the study of this waveform can help to evaluate different cardiovascular-related diseases, i.e. arterial stiffness, atherosclerosis and so on. In literature there is some evidence that investigating the second derivative wave of PPG signal can also help in quick detection and diagnosis of some cardiovascular diseases that could appear in future. [18]
The continuous and real-time monitoring is an important approach to take advantage of this kind of measure, it has been enabled thanks to the technological advances in sensor technology (i.e. miniaturization of sensor) and wireless communications.

2.3.1 PPG monitoring devices

In the last years, a lot of studies investigated about the optimal position of the sensor and the optimal light frequency band able to cross the tissues and reach the point of interest in order to get the best information possible.
In particular, for what concern the best wavelength, a combination of red and near infrared has always been used for blood mobility monitoring and also for oximetry estimation. [19]
IR-LEDs are most commonly used for measuring the blood flow located in particular parts of body like muscles, instead green light is typically used for calculating the oxygen absorption. However, in recent studies, other sources of light were studied, and it has been found out that the green light gives a better stability for what concerns accuracy and possible motion with respect to the red light. [20]-[21]

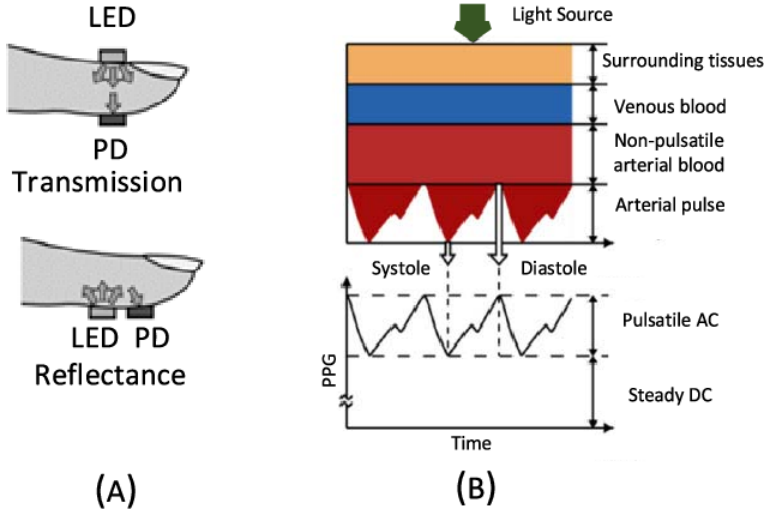

Figure 2.7. PPG (A) two possible configuration of monitoring devices and (B) waveform [22]

A typical PPG device contains a light source and a photodetector as shown in Fig 2.7. The light source emits light in direction of tissue and the photodetector measures the reflected light coming from the tissue. The blood volume variation is estimable because it is proportional to the reflected light. There are two possible valid configurations for PPG recording, the *transmission* configuration and the *reflectance* configuration (Fig. 2.7 (A)), depending on monitoring devices.
In the first configuration the target tissue is placed between light source and photodetector; the signal captured by the photodetector is the light passed through the target tissue.
The second configuration is obtained placing both photodetector and source on the same side: in this case the signal detected is the light reflected by the target tissue. Wearable PPG sensors can be placed only at certain locations on the body,

in fact there are different degrees of accuracy based on different measurement sites. Usually it is preferred to use specific body locations such as earlobe, finger, and forehead.
In this work were used signals collected from finger for what concern the algorithm training from online database and signals collected from earlobe in the migration phase of use of SoA device Shimmer (which will be discussed in the next chapters).

2.3.2 PPG waveform

There are some characteristic points in the signal waveform [23]:

- The foot point (or minimum) and the maximum point (which corresponds to the systolic peak); their difference, indicated with "x" in the Figure 2.8, gives an information on the cardiac output; different factors influence the cardiac output, such as the heart rate, peripheral resistance and the blood pressure;
- The pulse width, that is an index of peripheral resistance;
- The amplitude of the diastolic peak indicated with y in the figure. The study of this shape can assess some information related to the health of peripheral circulation;
- The pulse interval that represents HR can be defined as the distance in time between 2 consecutive foot or two consecutive systolic peaks.

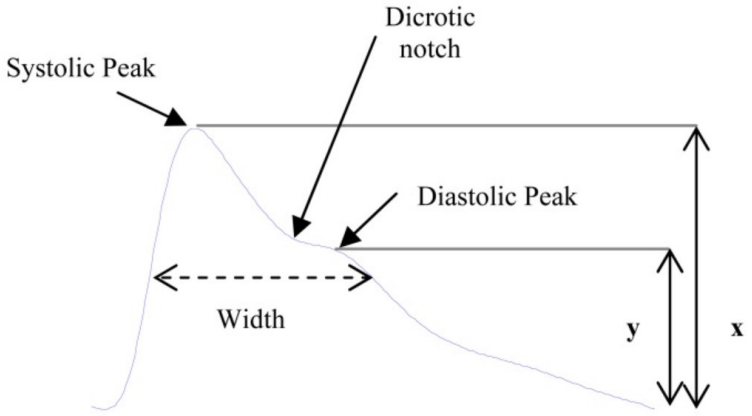

Figure 2.8. A typical waveform of the PPG and its characteristic parameters [23]

The limits of this technique are represented by light interference caused by external sources, in fact the amount of light that is usually studied is much smaller of the incident one, it oscillates between 1 % and 5 % of the initial radiation.[24]

So it is easy, for the sensor, to confuse the significant light for the one derived by external sources.

In addition, the light relevated by photodetector is influenced by different factors:

- skin properties: skin structure (that produces a dispersion of light equal to the 6% of the total reflected) and composition;
- blood properties: oxygen saturation, temperature and blood flow variation; number of red blood cells in circulation (other substances which affect the absorption spectrum are hemoglobin, fibrous proteins, collagen, fat, bilirubin and carotene), orientation and agglomeration;
- vessel properties: speed of contraction and dilation of arterioles and their capillaries.

A mathematical law that estimate the physical correlation with the biological behaviour of light diffusion through the body is the Beer-Lambert's law (Equation)[25]:

$$I_{out}(z) = I_{in}e^{\mu_a z} \tag{2.5}$$

Where:

- I: is the expression of light intensity;
- z: is an axis parallel to the direction of the beam;
- μ: is the attenuation (Napierian) coefficient.

This law is influenced by different factors like intensity of the light, the wavelength of the incident light, the length of the path and the composition of the structure in which pass the radiation.

2.4 Arterial Blood Pressure

The Arterial Blood Pressure (ABP) signal is the representation of a pressure wave, which moves through the arteries, it has different diffusion speed and morphology according to the section crossed. Physically a pressure wave that diffuses through a viscoelastic pipe is progressively attenuated with a speed exponential reduction, but if the tube has different diameters because of branches in which divides, an amplification of the signal is caused by reason of reflection phenomena. These phenomena change according to the vessel, for ABP recording, is used the less rigid one, the aorta, where the reflection is negligible.
Starting from the ejection of the blood from the ventricle into the aorta, pressure in the aorta starts its increase to nearly the one of ventricle. Anyway, aorta pressure does not remain high, because during the diastolic phase, blood quits flowing into

the aorta with a consequent and slow decline in pressure until the minimum just before the next systole.
The elevated pressure in the arteries during diastole is due to the elastic draw back property. The increasing of pressure is caused by arterial walls recoil inward that causes an effort on the blood. The maximum pressure occurs during systole and is called systolic pressure, the minimum pressure, instead, occurs during diastole and is called diastolic pressure. A significant value is represented by average arterial pressure during the cardiac cycle called MAP.
Pressure is usually measured in the brachial artery; blood pressure generally is lower in upper regions of the body and higher in lower regions because of the gravity force that acts on blood. When a technician records blood pressure, is used a sphygmomanometer, which consists of an inflatable cuff and a pressure-measuring device that displays the air pressure inside the cuff; the technician also uses a stethoscope placed over the brachial artery to listen for sounds produced by turbulent blood flow. After the increasing (until it is greater than systolic arterial pressure) and a decreasing (until it is lower than diastolic arterial pressure) of cuff pressure, blood flowing creates audible vibrations (Korotkoff sounds). This happens because of blood turbulence, which can be heard by the use of stethoscope. When the Korotkoff sounds first appear, is possible to record the systolic arterial pressure, when these sounds first disappear is possible to record the diastolic arterial pressure. It is shown on Fig. 2.9.

Normal values for a healthy individual are SBP equal to 110 mm Hg and DBP equal to 70 mm Hg. From the blood pressure measurement pulse pressure (PP) and mean arterial pressure (MAP) can be determined. The PP is calculable as the difference between systolic and diastolic pressure:

$$PP = SBP - DBP \tag{2.6}$$

For a healthy adult, the pulse pressure is approximately 40 mm Hg. [14] In elders a PP abnormally high may indicate an increase of stiffness of vessels, that causes a decrease of their ability to stretch.

The MAP can be evaluated by the following expression:

$$MAP = \frac{SBP + (2 \times DBP)}{3} \tag{2.7}$$

For a healthy adult, this is approximately 83.3 mm Hg. [14] Notice that the MAP is a weighted mean, in which diastolic pressure has a greater weight respect the systolic one. This because during a single cardiac cycle, aortic pressure is near its maximum for a shorter period than the minimum (for which is about twice as long).

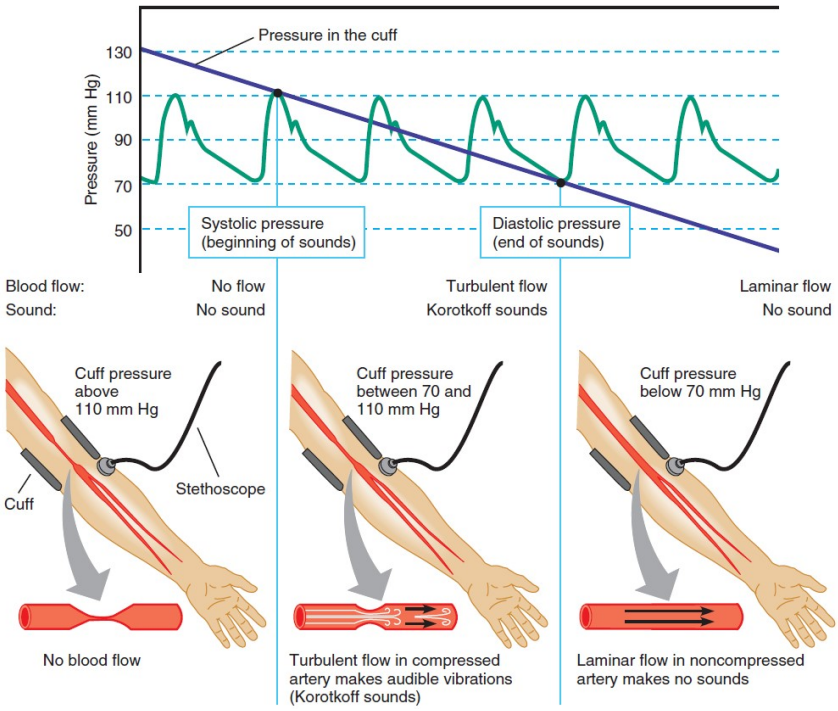

Figure 2.9. Arterial blood pressure measurement and waveform. [14]

2.4.1 Hypertension

We talk about Hypertension when resting blood pressure is persistently elevated, threshold values are greater than 120 mm Hg for SBP and over than 80 mm Hg for DBP (Fig. 2.10). Hypertension remains one of the major risk factors for the development of cardiovascular disease (CVD), that are one of the major causes of mortality in the world. Even though the awful lot of evidence on the risk of high blood pressure and benefits of blood pressure lowering accumulated until now, elevated blood pressure is still the leading risk factor for disease and disability.[26] In fact, there is an annual increase of patient suffering CVD.
Chronic hypertension is typified by elevated baseline blood pressure for long periods of time. [27]
Two forms of hypertension are distinguished:

- Primary hypertension (or essential) provides about 90–95% of all hypertension cases. This condition is associated with certain risk factors, unhealthy lifestyles worsen this condition, but it is also influenced by genetic disposition. [14]
- Secondary hypertension is characterized by elevated blood pressure caused by a secondary disease. For example, renal hypertension where the primary cause is a disorder of kidney function.

Blood pressure is a risk factor that derives highly from lifestyle. More of the 90% of the cases of arterial hypertension depends on an unhealthy diet, obesity and lack of physical activity. The habit to smoke increases the risk as well as increase of age. The rising of blood pressure in elders is associated with structural changes in the arteries and with large artery stiffness. Moreover, there is a close correlation between increase of blood pressure and cardiovascular risk and all evidence indicates that treating the elderly hypertensive patient will reduce the risk of cardiovascular events such as stroke. [28] Hypertension is closely involved with atherosclerosis, where a fatty plaque is accumulated in arteries walls, it causes a decreasing of elasticity of arterial walls and a restriction of lumen. This causes an increase in resistance of the blood vessel, that leads to hypertension. This activates a vicious circle because hypertension damages the arteries walls, triggering atherosclerosis, each facilitate the development of the other. Hypertension has several other bad effects on the cardiovascular system, in fact it increases the heart workload and can lead to heart failure. Luckily nowadays treatments for hypertension are largely used and include diuretics and specific antihypertensive drugs, like beta-blockers and calcium channel blockers.

Blood Pressure Stages

Blood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower #)
Normal	less than 120	and	less than 80
Elevated	120-129	and	less than 80
High Blood Pressure (Hypertension) Stage 1	130-139	or	80-89
High Blood Pressure (Hypertension) Stage 2	140 or higher	or	90 or higher
Hypertensive Crisis (Seek Emergency Care)	higher than 180	and/or	higher than 120

Source: American Heart Association

Figure 2.10. Blood pressure stages according to American Heart Association.

Chapter 3

Materials and methods

This thesis work has been subdivided in two phases, the first phase was focused on the verification of proper functioning of algorithms, the second phase was oriented on the application of these algorithms on signal recorded with SoA devices. The training phase has been carried out by using signals from MIMIC III database.

3.1 MIMIC database

The first phase of this thesis was focuses on the collection of physiological parameters recorded concomitantly in detail PPG, ECG and ABP, from a large number of subjects. For this purpose, the MIMIC III database was employed, it is an extensive database with an huge number of subjects where signals are taken at the same time, with a sufficient sampling length.

The MIMIC database has been created by MIT Lab; it is an open access online database that collected different kind of physiological information. [29] It contains data taken from intensive therapy from approximately 60,000 hospitalizations. Thanks to this database different studies in clinical fields have been brought forth.

It is available from PhysioBank ATM, shown in Fig. 3.1 where is possible to visualize signals for a first evaluation (Fig. 3.2). [30]

One of the main problems related to MIMIC database is that this model can be influenced by some bias. In fact, even though it contains a large number of different types of data recorded during hospital admissions, the median age of adult patients is 65.8 years, where 55.9% of patients are male and 44.1% are female. [31]
Moreover, another disadvantage of this database is the lack of additional information about on each single patient from whom the data comes. The accessible data related just signal recordings, not taking into account of information like age and

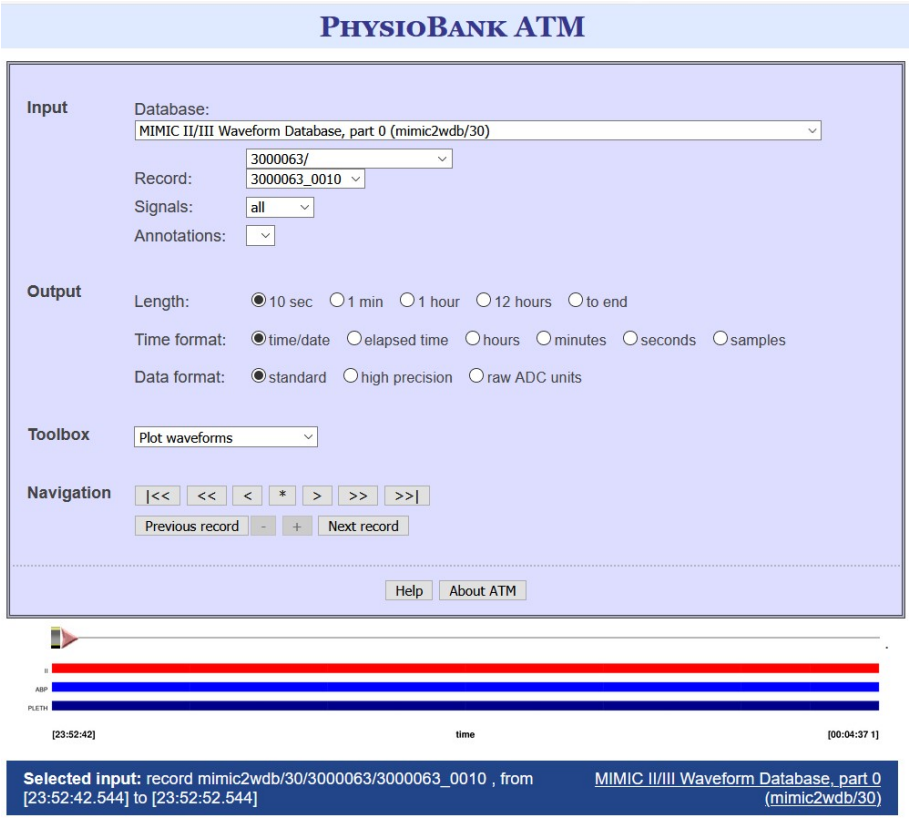

Figure 3.1. PhysioBank ATM. [30]

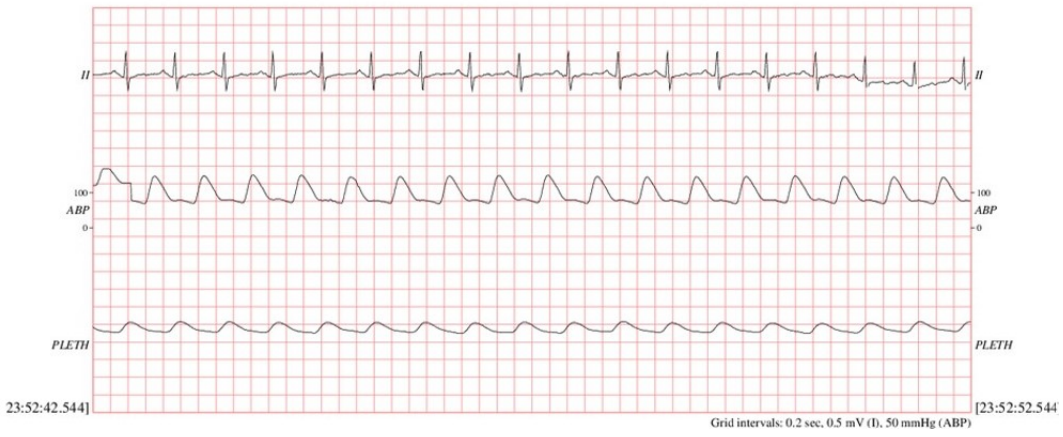

Figure 3.2. i.e. signals in MIMIC III database. [30]

gender. These information influence blood flow. In fact, the existing correlation between aging and higher stiffness of vessels is traduced in a reduction in the time interval between the systolic peak and the diastolic peak of the PPG signal waveform. [32]
The wall of large arteries, principally aorta, thicken and lose elasticity in time, this process causes an increase in pulse wave velocity (PWV), an important and dependable measure of arterial stiffness. [33] The increased arterial stiffness reduce reservoir/buffering function of the conduit arteries near the heart and increase PWV, both of which increase systolic and pulse pressure.[32] In addiction studies demonstrate gender-specific differences for what concerns vessels stiffness and ventricular deformation, both at rest and during stress test. [34]

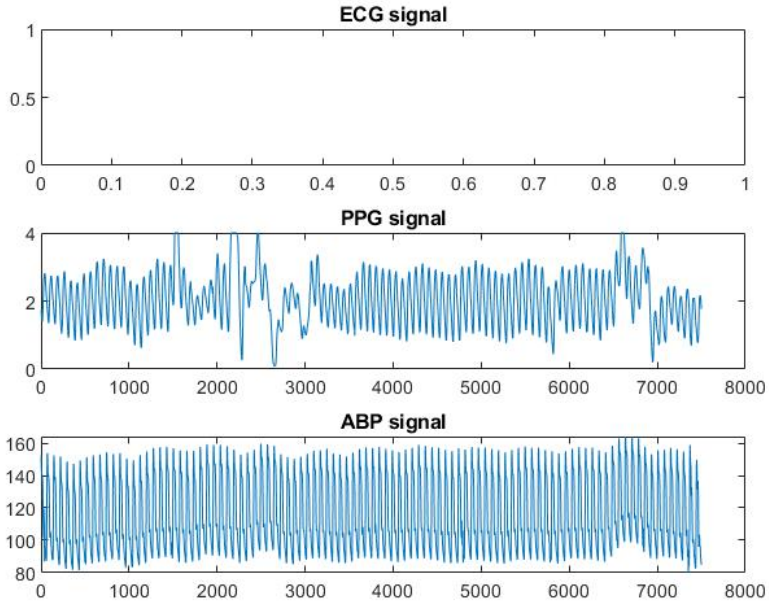

Figure 3.3. i.e. disturbed signal in MIMIC III database (detachment of ECG sensor and PPG signal artefacts). [29]

Since the collected data come from the Intensive Care Unit (ICU), the quality and reliability of the signals are not very high, in addition, most of the subjects have undergone drugs administration that alter their pressure values.
So, the most relevant issue for algorithms implementation is the poor quality of signals. The signal waveform usually suffers a not negligible alteration of the measurement, so signals present abnormal and noisy recordings, as missing peaks, pulsus bisferiens, interference to the sensor (sensor-off), flat lines, shown in Fig.3.3,

and flat peaks most likely attributed to a sensor issue. [31]
This does not allow the use of large windows that are required in order to train the algorithm.

However, MIMIC database is the only database with a such large number of signals recorded and for that reason is the most used so far, despite it causes evaluation error in formative models.
In order to limit these issues, it is necessary to pre-process the signals, consisting in a segmentation of signals and deleting noisy components with consequent reduction of observation window to achieve brief segments of good quality signals.
For reliable results, a very long acquisitions would have been required in order to train the algorithm but the length of the acquisitions available in the database was not always enough. Thanks to the use of these techniques, results obtained were encouraging for what concerns the correlation between cardiac activity and blood pressure. From that the need of a new database with quality signals taken from a representative sample of population with different age, gender and medical condition recorded with specifics protocols and state of the art sensors.
These features together with a better quality of signals could strongly improve the customization and the accuracy of this algorithm.

3.2 State of the Art sensors

The respect of guidelines on medical devices requires that new devices must be compared with State of the art devices, so devices that reached the highest level of general development. In order to do this, is necessary a clinical evaluation that is a methodologically well founded procedure to recorder, estimate and evaluate clinical data of the new medical device and to analyse if there is enough clinical evidence to confirm compliance of the product when it is using according to the producer's instructions. [35] State of the art (SoA) techniques in the development of software it is a well tested method applicable to high-integrity devices (such as medical devices). To complement this software test techniques there is a abundance of test tools available to prove them. These tools are necessary and commonplace in the development of applications.[36]
For what concerns this thesis work we will focus on Blood pressure that can be measured in invasive and non-invasive way. In the following sections both methods will be reported. In this study are used two SoA devices, Shimmer sensors, in particular two different sensors for ECG and PPG signals recording, and Omror HeartRate for measuring the systolic and diastolic blood pressure.

3.2.1 Invasive methods

The first studies that aimed the possibility of blood pressure estimation were conducted in the second half of the XVIII century. The discovery was reached by

Stephen Hales (1677 - 1761), who firstly measure the average BP by placing a tube, opened at the extremity in a horse's carotid artery, and measuring the height reached by the horse's blood. [37] The discover gave the opportunity to measure BP and it has perfected and implemented year after year to reach a major accuracy, safety and comfort. To date, invasive methods remain the gold standard for BP measures, for its precision and for the possibility of continuous blood pressure measurement.

All the existing instrument for blood pressure mensuration are based on these basics elements as shows in Fig.3.4:

- a catheter inserted in an artery;
- a transducer that translate a mechanical value in to an electric one;
- a complex of valves that control the fluidic system and allow to measure the blood pressure or to take blood samples.

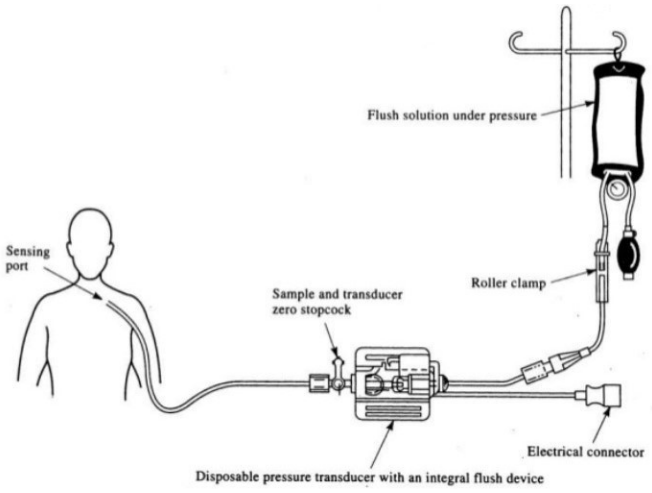

Figure 3.4. Invasive blood pressure measurement.

The measurement is executed using a needle inserted in an artery, generally the radial artery because of its limited depth and so accessibility, but also the brachial and the aortic one. The needle is connected through a catheter to a pressure transducer, that converts a physical quantity in input, in an electrical one as output. The device computes the wave of blood that hit the needle and the blood pressure waveform is amplified and filtered and then visualized on a monitor. This measuring system needs to have as a reference the atmospheric pressure to be well calibrated. Since its accuracy, it has always been used as the gold standard for all the devices that declare to measure the blood pressure. [38] Despite this,

invasive (intravascular) monitoring has potential risks to patients such as infection and various vascular damage. There are also clinical situations where invasive arterial monitoring may be difficult or impossible to be performed safely, such as in patients with obesity.

3.2.2 Non-invasive methods

The second class of blood pressure devices consist of the ones that evaluate BP in a non-invasive way. There are various methods to non-invasively measure BP; monitoring techniques can be classified on the basis of their capacity to measure BP intermittently or continuously. [39] These devices can do it because there are some physiological events that are closely related with blood pressure; these events are used and evaluated. Anyway, measure the BP in non-invasive way remain the best way in term of safety and comfort; in addition is possible to use them autonomously outside hospitals.
Techniques for monitoring BP can be classified on the basis of their capacity to measure BP intermittently or continuously, the validated and consolidated instruments and technologies are listed in the sections below.

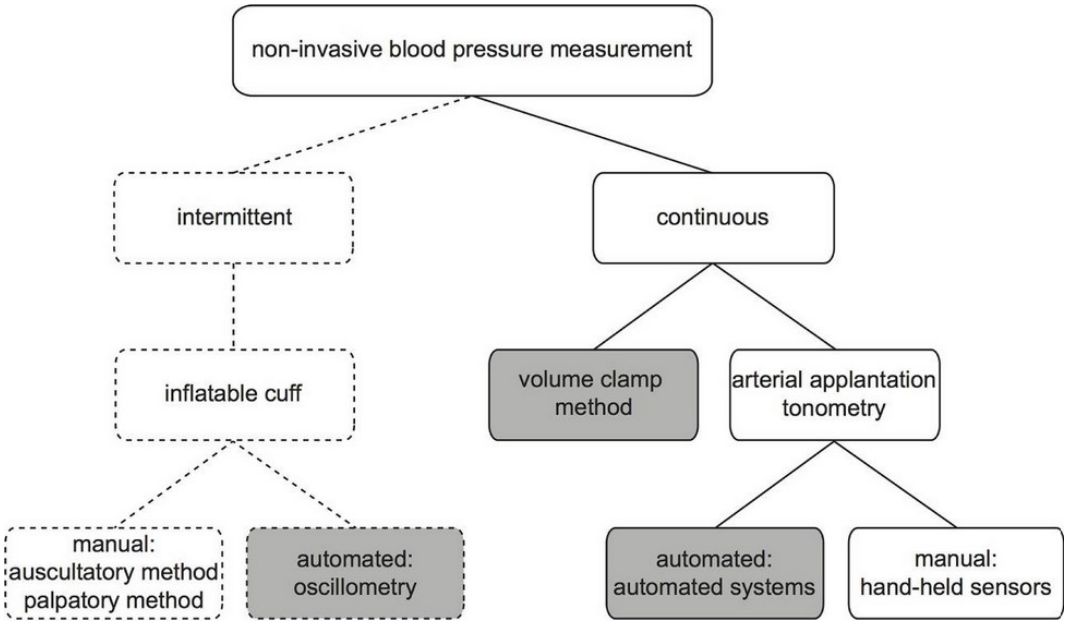

Figure 3.5. Non-invasive blood pressure monitoring techniques. [39]

Non-Invasive Intermittent Techniques

For non continuous blood pressure measurement, can be used an air-filled occluding cuff that allows to measure BP manually or automatically. Manual measurement of BP using an occluding cuff can be done by palpation or auscultation. [40] The auscultatory method uses an inflatable cuff, the subject has to be relaxed and sits with the lower arm supported, the cuff is placed on the right arm, allowing 2.5 cm between the bottom of the cuff and the elbow. [41] Then the cuff is inflated to a pressure higher the systolic pressure, with consequential vanished of radial pulse. For this procedure is necessary to have a stethoscope that can detect the typical Korotkoff sounds during slow deflation of the cuff (Fig.3.6). The first sound it is audible in correspondence of the systolic arterial pressure. Instead, the last sound it is audible in correspondence of the diastolic arterial pressure. The disadvantages of this technique include the need for training for use correctly the device and the need of a stethoscope and a quiet environment. [40]

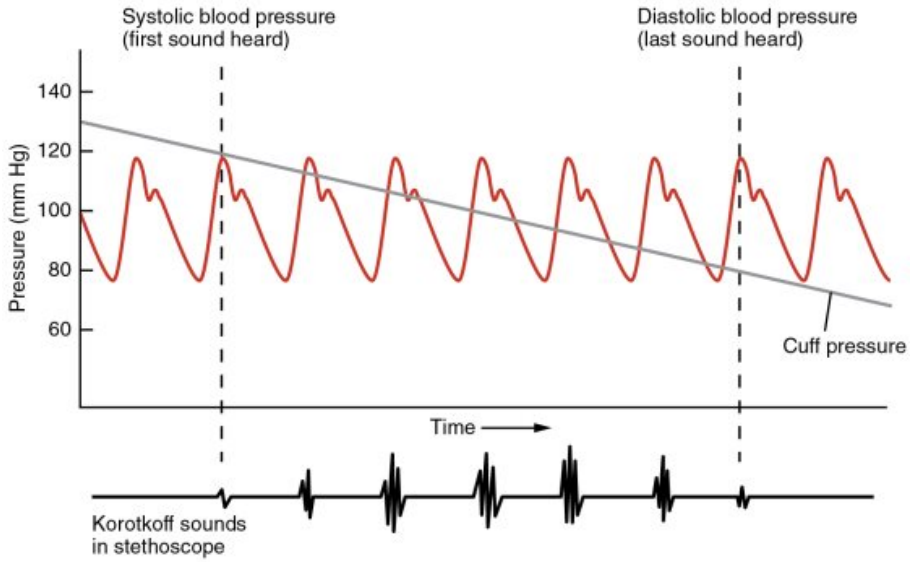

Figure 3.6. Korotkoff sound explanation. [42]

The palpatory method uses an inflatable cuff wrapped around the arm of a patient in correspondence of elbow. The manometer connected to the cuff by a tube shows the pressure applied. The cuff is rapidly Inflated to 70 mmHg, and increased by 10 mm Hg increments, the physician inflates the cuff until the brachial artery collapses, and there is no blood flow. [43] The level of pressure at which the pulse disappears and reappears during deflation will be systolic blood pressure. The advantages of this technique include that it no need stethoscope and it is possible to use this device also in noisy place, but this method only provides the systolic

arterial pressure. [40]
Another intermittent method is the automated one, also for this method is necessary an occluding cuff employs the oscillometric technique. The cuff is inflated to a predetermined value, then the pressure is slowly reduced. The oscillations in the vessel are translated in pressure wave by the cuff. The maximum of oscillations corresponds to the mean arterial pressure (MAP) [44] then an algorithm estimates the systolic and diastolic arterial pressure. [45] The advantages of this method are the reliability of MAP, in physiological values range, and the possibility of having an unsupervised device to record BP in a predetermined interval. In literature are reported as disadvantages the overestimation of low values and underestimation of high one [44] and the possibility to falsify measurements by movement or every input that can be read as oscillations. [46]

Non-Invasive Continuous Techniques

Continuous non-invasive BP monitoring techniques, with direct BP measurement, became available in the last few years. These techniques enable the recording of a real-time BP curve and numerical BP values. The two techniques are the volume clamp method and arterial applanation tonometry.
The volume clamp technique collects by a sensor the signal of blood volume pulse and then converts light into a weak current. This kind of transmission can be easily disturbed. [47] The BP is measured by the combination of an inflatable cuff and a photodiode that measures the diameter of artery in the finger; the pressure in the cuff is regulated in every instant to keep the diameter of the artery constant. The pressure changes in the cuff is traduced as a BP curve correspond to brachial artery BP (Fig.3.7).

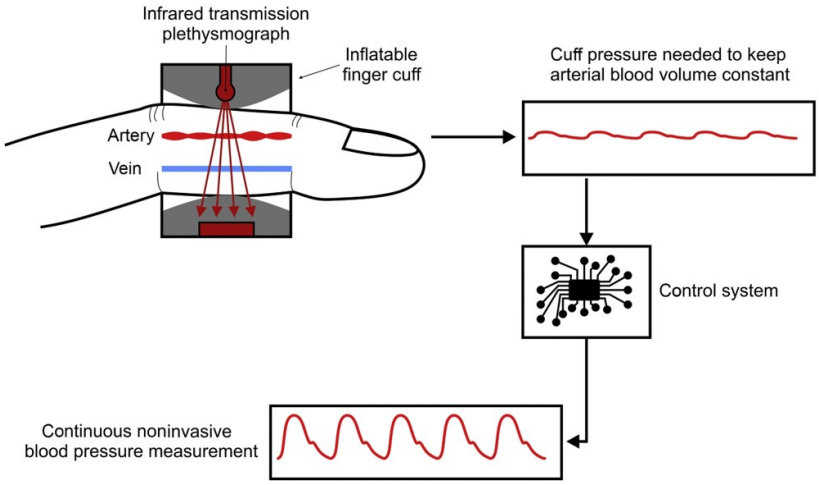

Figure 3.7. Principle of volume clamp technique. [47]

The applanation tonometry (AT) is the second method for non-invasive continuous BP measurement it is an accurate representation of the aortic pressure waveform that can be easily replicated. Waveform highlights the systolic and diastolic pressure but also the influence of pulse wave reflection on the central pressure waveform (Fig.3.8). This technique can be divided into two subsets an automated one and one that have to be supervised by physicians. For the second one there is the disadvantage that the continuous monitoring with this method is possible but difficult to be done because the device has to be handheld by the physician.

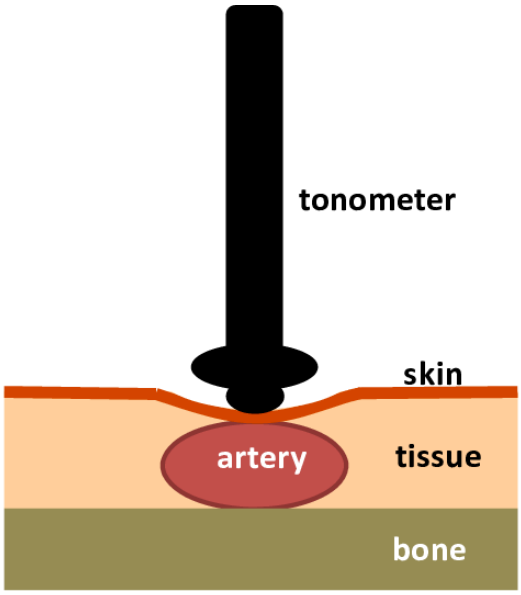

Figure 3.8. Principle of work of arterial applanation tonometry. [48]

3.2.3 SoA devices used in this study

Until today, most of the researches on BP estimation were done using online database for training and testing the algorithms, specifically MIMIC database. MIMIC is an open access online database containing a large amount of biomedical data collected by the MIT Lab for Computational Physiology. [49] It collects data from intensive care of 60,000 hospitalizations approx. The most relevant issue for algorithms implementation is the poor quality of signals. The signal waveform usually suffers a not negligible alteration of the measurement, so signals present abnormal and noisy recordings, as missing peaks, pulsus bisferiens, interference to the sensor (sensor-off), flat lines and flat peaks most likely attributed to a sensor issue. [50] This does not allow the use of large windows that are required in order to train the algorithm. For the purposes of overcome these issues the goal is to build a new database using state-of-the-art (SoA) devices. In this thesis have been

used:

- Two Shimmer units: used to record in a synchronized way the ECG and the PPG signals;
- OMRON HeartGuide: a cuff based wearable blood pressure monitor used to obtain the gold standards of the analysis, systolic and diastolic blood pressure.

Shimmer devices

Shimmer is a wireless sensor platform which can be used for biomedical research applications. Specifically, shimmer's modules could be used for physiological signal acquisition. Moreover, thanks to their compact form factor, Shimmer's sensors are very suitable also for kinematic sensing applications (Fig.3.9).

Figure 3.9. Shimmer modules. [51]

In this study two shimmer's module are old, one used for Electrocardiogram and the other one for photoplethysmogram recording. [52] The one used for ECG retrieve need to use electrodes for signal recording. In this study has been used three electrodes, placed on the chest. Two in direction of the arms (right and left), and one on the leg as reference (in this study the right) placed as in the figure 3.10.

To obtain the PPG signal an Optical Pulse Sensor at green light was placed on the left ear-lobe. The lobe was chosen because in literature is the recommended position; additionally, trying also other positions, has been observed that the best one in terms of signal quality is the lobe.

Omron HeartGuide

HeartGuide is a wearable blood pressure monitor cuff based. In a first moment the cuff inflates then slowly deflates, so the device senses the pressure pulsations of the artery in the wrist. The disadvantage of this device is that to collect the data the

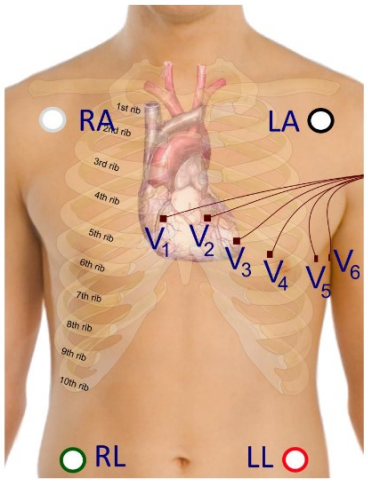

Figure 3.10. Possible positions of electrodes for ECG measurement. [53]

subject must be standstill and bring the arm to which the watch is applied at chest, keeping it for few seconds.
The declared accuracy is +/− 3 mmHg [54] therefore it has been chosen like SoA device to quantify SBP and DBP both used like gold standard for algorithm implementation.

Figure 3.11. Omron HeartGuide. [54]

Chapter 4

Mathematical approach and algorithm

The electro-mechanical signal that is generated by ventricular contraction in cardiac muscle, produces into the circulatory system a systemic wave of pressure, this wave is the SBP. Instead of the pressure recorded between two beats that is the DBP. The dilation of the arterial walls is the direct cause of the periodically variation between these two waves. The photoplethysmography brought the possibility to detect the back propagation wave generated by ventricular contraction. Given a measure of velocity of propagation in all the vessel tree complex. By studying the delay time between R-peak (detected by ECG) and Systolic-peak (detected by PPG), the most common parameter studied is the Pulse Transit Time (PTT). So, the time necessary for a single pulse to travel from one point to reach a more distant site (ear-lobe). The combined use of an electrocardiograph and a photoplethysmograph enables to carry out an in-depth study of the physiological responses of the arterial tree.
The arrival of the pressure wave is visually clear thanks to the photoplethysmograph, it is represented by the highest peak of the PPG waveform (systolic component). This peak is the response of pressure transmission from the aortic root to the ear lobe in which it is measured. The diastolic component is caused by pressure waves transmitted along the aorta up to small arteries in the distal and lower body. There these waves are transmitted back and then are recorded to the ear lobe.

4.1 Bramwell–Hills and Moens–Kortweg's equation

The blood flow is possible thanks to the continuous expanding and contracting during systole and diastole of the vessels.[55] The elasticity of arteries has a strong influence on the propagation speed, this influence is underlined by the Bramwell–Hills and Moens–Kortweg's equation, that represents the relationship between pressure (P), Pressure Wave Velocity (PWV) and Time Delay for an artery with a length L. [56] In this study the Time Delay and the PTT coincide since a single PPG and ECG sensor have been used.

Bramwell–Hills and Moens–Kortweg's equation:

$$PWV = \frac{L}{TimeDelay} = \sqrt{\frac{hE}{\rho d}}$$

where:

- L: length of the vase
- h: thickness of the vase
- d: diameter of the vase
- E: elasticity of the vase
- ρ: blood density

This equation highlights the direct proportionality between pressure and PWV (with other parameters constant), and an inverse one with PTT. The elasticity E of arteries has a strong effect on the propagation speed. For all these correlation is possible to writ the equation by expressing PWV in terms of fluid Pressure (P), blood density (ρ), artery diameter (d), artery thickness (h), Euler number (α) that is a vessel parameter and the Young's modulus estimated by considering zero arterial pressure elasticity (E_0).
In 1991 Leslie A. Geddes discovered that there was an exponential relationship between the elasticity E and the pressure P [57], specifically:

$$E = E_0 e^{\alpha P}$$

By replacing in the Bramwell-Hills and Moens-Kortweg's equation, it can be written to show better the relationship between PWV and:

$$PWV = \frac{L}{PTT} = \sqrt{\frac{hE_0 e^{\alpha P}}{\rho d}}$$

Here the direct and inverse relation between pressure-PWV and pressure-PTT respectively is well shown by obtaining e:

$$e^{\alpha P} = \frac{\rho d L^2}{h E_0} \frac{1}{PTT^2}$$

then receiving the logarithm:

$$P = \frac{1}{\alpha} \ln \left(\frac{\rho d L^2}{h E_0} \right) - \frac{2}{\alpha} \ln PTT \tag{4.1}$$

For a subject is possible to assuming constant:

- L: length of the vase (distance at which the Time Delay is obtained);
- h: thickness of the vase;
- d: diameter of the vase;
- E_0: elasticity parameter;
- ρ: blood density.

In this way The Bramwell–Hills and Moens–Kortweg's equations give a relationship between BP and the Pulse Transit Time:

$$BP = a \ln PTT + b \tag{4.2}$$

Later Chan et al. postulated that if the variation of d respect to the variation of blood pressure is negligible, and if the change in the arterial wall tone (E_0) is slow enough, then the first term of the right-hand side of eq.(4.2) can be regarded as constant during the observation window, so is possible to write:

$$\Delta BP = -\frac{2}{\alpha PTT} \Delta PTT \tag{4.3}$$

By a linear approximation for (4.3) was proposed:

$$BP = aPTT + b \tag{4.4}$$

Since several studies highlights the improvement caused by adding in the equation the heart rate (HR). So, the mathematical relationship between BP and PTT used is a Linear Model with as a second variable the HR:

$$BP = aPTT + bHR + c \tag{4.5}$$

The coefficients a, b and c can be obtained through a regression analysis between the gold standard BP and the corresponding PTT. [58] for doing that is necessary

a procedure of calibration.
Since principal interest in blood pressure analysis is to predict systolic and diastolic blood pressure (SBP, DBP), the model (4.5) can be split in the following way, Linear model with HR:

$$\begin{cases} SBP = a_s PTT + b_s HR + c_s \\ DBP = a_d PTT + b_d HR + c_d \end{cases}$$

4.2 Regression analysis

The most used statistical procedure for calculating the value of a dependent variable from an independent variable is the linear regression, it provides the measure of the association between two variables.
In order to estimate f = f(x_1, ..., x_k), is possible to assume that a set of data y depend on a k number of variables, then is necessary to fit data with a regression model. This model can be described in the following equation:

$$\hat{y} = \beta_0 + \beta_1^T x + \epsilon \tag{4.6}$$

With:

- β_0: scalar parameter to be chosen;
- β_1^T: vector parameter to be chosen;
- ϵ: random error that represent the mismatch between data and model;

So, the regressive model enables to minimize the residual error or the quadratic error between prediction and target. Then are applicable two different techniques to evaluating the fitting, the mean square approach (4.7) and the Pearson correlation coefficient (4.8). [59] For the first approach the residual error L could be calculate by this equation:

$$L = \sum_i \epsilon^2 = \sum_i (y - \beta_0 - \beta_i^1 x_i)^2 \tag{4.7}$$

The smaller L represent the best circumstance.
The other possible method is the Person correlation coefficient:

$$R = \frac{(y - E[y])(\hat{y} - E[\hat{y}])}{||y - E[y]||_2 \; ||\hat{y} - E[\hat{y}]||_2} \tag{4.8}$$

In this case the better result is when R is close to 1.
In this study the regression analysis is made for the individual data set of each subject, in order to perform an individual calibration.[59]

4.3 Calibration issues

The approach used requires a person-specific calibration, is needed a different calibration for each user. With calibration is possible to centre the measure around the Pulse Transit Time value of the subject and its systolic and diastolic BP.
It is a one-time procedure, it consists in measuring the PPT and HR, it asks the user to input the SBP and DBP, measured by a SoA device in that moment.
Then the next step is to process signals with the algorithm, it receives these parameters and subsequently it adds an offset to the two constants: a_s and a_d. These constants intrinsically contain personal-physiological parameters of the specific user. So, when the model obtains as input PPT and HR, it has asserts as result the real values of SBP and DBP measured by SoA device during the calibration.
The need of calibration represents the disadvantage of the mathematical approach. It needs, at first, the calibration that will be done in a healthcare facility with physician support for the patient monitoring of their own BP. The ideal is to identify the most general models for the BP estimation for associate a specific model to each user, without the need of a calibration procedure.

Chapter 5

Results and Criticisms

After data cleaning and synchronization control, the effective work of adjustment of the data and blood pressure prediction was started.

5.1 Cleaning of the signals

To make signals easier to be studied a deep process of signals cleaning was carried out. This process was necessary both for MIMIC III database signals and shimmer ones. Specifically, to identify the interest frequencies, the MATLAB function 'periodogram' has been performed by estimation of the power spectral density. Subsequently, in relation to the previous results the cut frequencies have been chosen. Different cut frequencies have been used for ECG and PPG, depending also the sources of the signals, i.e. taken from the online database or from the SoA devices. In the recorded signals, noise strongly affects the time series with unknown statistics, causing a more difficult sinusoid detection. To remove this noise, pass-band filters have been used both for ECG and PPG signals. To determine the correct cut frequencies the signals frequencies have been shown by two periodograms. Then visually the four frequencies have been chosen. In particular for ECG signal taken from MIMIC III database a band-pass filter has been chosen, with those cut frequencies:

- $f_L = 0.1\ Hz$
- $f_H = 30\ Hz$

To determine these values, it was used the 'periodogram' function of MATLAB, as shown in figure 5.1.

Instead for what concerns the PPG signal taken from the online database a band-pass filter has been selected, with those cut frequencies:

- $f_L = 0.5\ Hz$

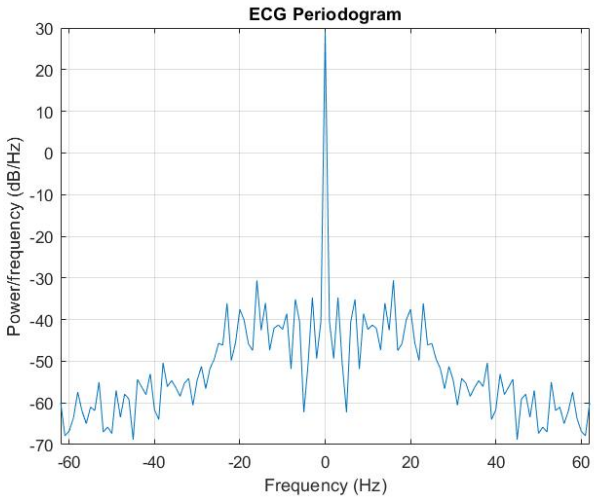

Figure 5.1. ECG periodogram.

- $f_H = 7\ Hz$

Also for PPG to determine these values it was used the 'periodogram' function of MATLAB, as shown in figure 5.2.

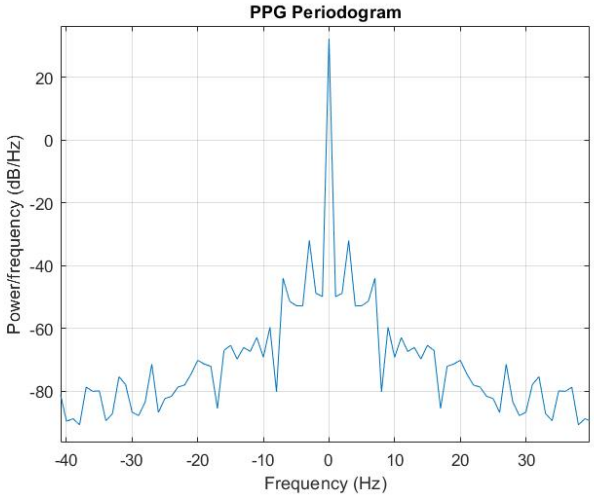

Figure 5.2. PPG periodogram.

After this filtering process the two signals are morphologically distinguishable, in the figure 5.3 an example of filtered signals is shown.

Regarding signals taken with Shimmer devices, in addition to the cleaning of the signals was necessary the synchronization of the two signals recorded. This step

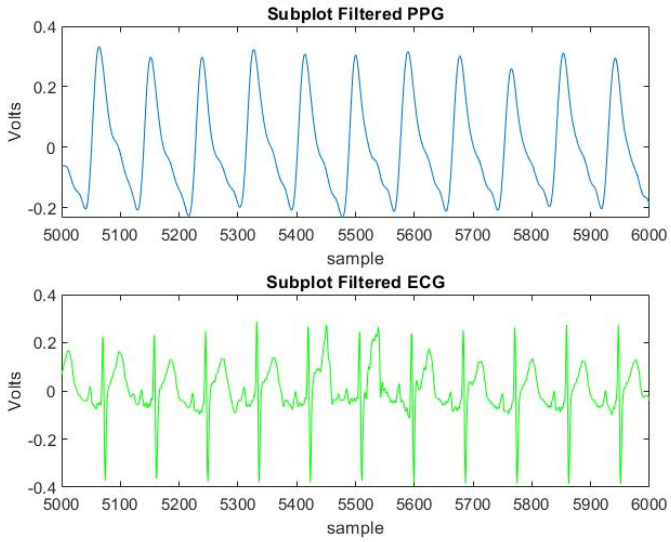

Figure 5.3. ECG and PPG after the filtration process, of mimic III database patient 3500015_0002m.

required a purchase of an additional device, causing some delays in this study. For ECG signal taken with Shimmer a band-pass filter has been chosen, with those cut frequencies:

- $f_L = 0.1\ Hz$
- $f_H = 20\ Hz$

As already done before, to determine these frequencies the 'periodogram' function of MATLAB was used, as shown in figure 5.4.

Instead, for what concerns the PPG signal taken from the shimmer, it was more difficult because an elevated number of disturbing frequencies are present. This involves the choice of a narrower band. Thus, it was used a band-pass filter, with those cut frequencies:

- $f_L = 0.3\ Hz$
- $f_H = 5\ Hz$

Also for PPG to determine these frequencies it was used the 'periodogram' function of MATLAB, as shown in figure 5.5.

After this process the improving of signals quality was evident, especially for PPG signals as shown in figures 5.6 and 5.7.

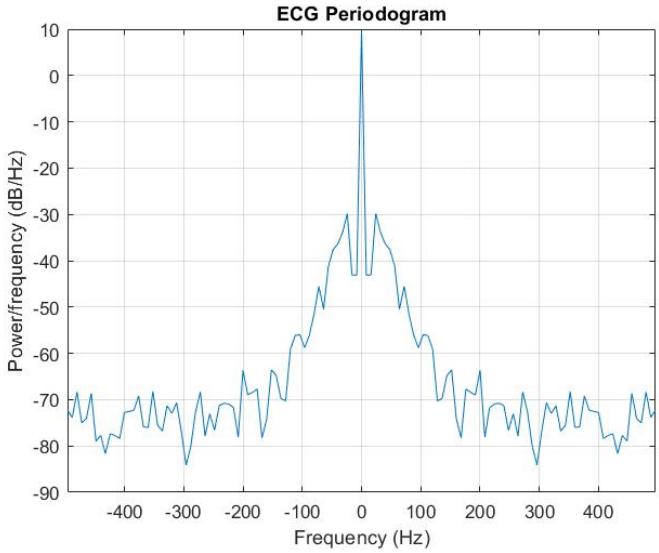

Figure 5.4. ECG shimmer periodogram.

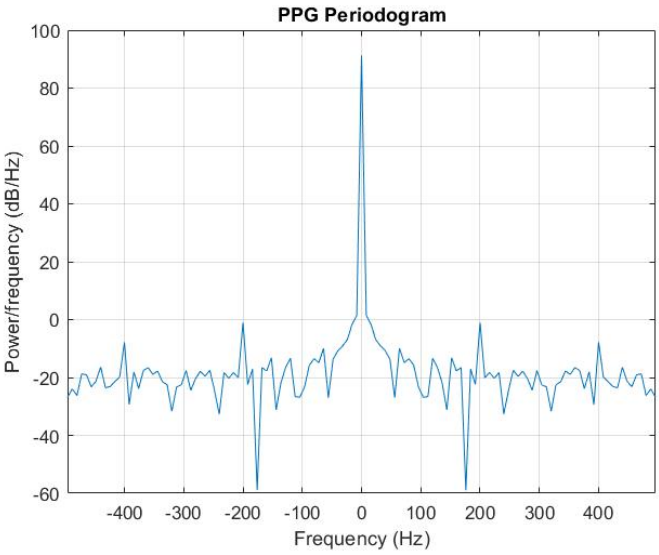

Figure 5.5. PPG shimmer periodogram.

5.1.1 Search of interest points

The objective of this section is to locate the point of interest, so the significant features. Specifically, these features are:

- PTT

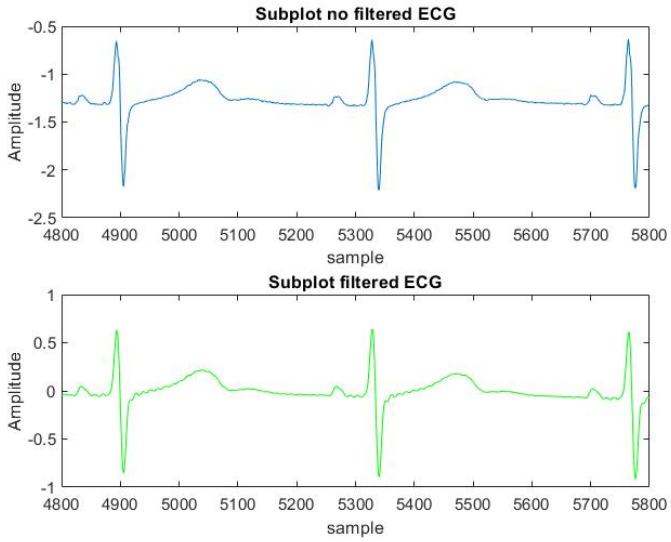

Figure 5.6. No filtered and filtered ECG signal from shimmer devices.

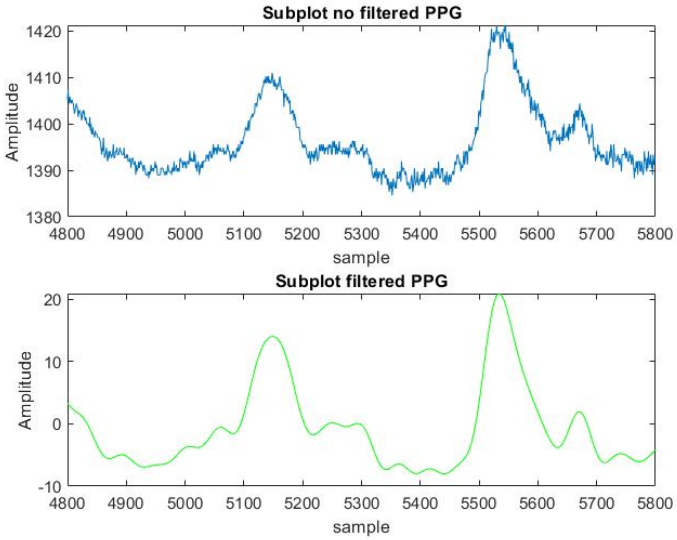

Figure 5.7. No filtered and filtered PPG signal from shimmer devices.

- HR
- SBP
- DBP

For the first two items it was necessary to locate the R peak for ECG and the systolic peak for PPG. The R peak of ECG was identified by using 'find-peak' function of MATLAB with a threshold that changes in relation of signals used. It is shown in figure 5.8.

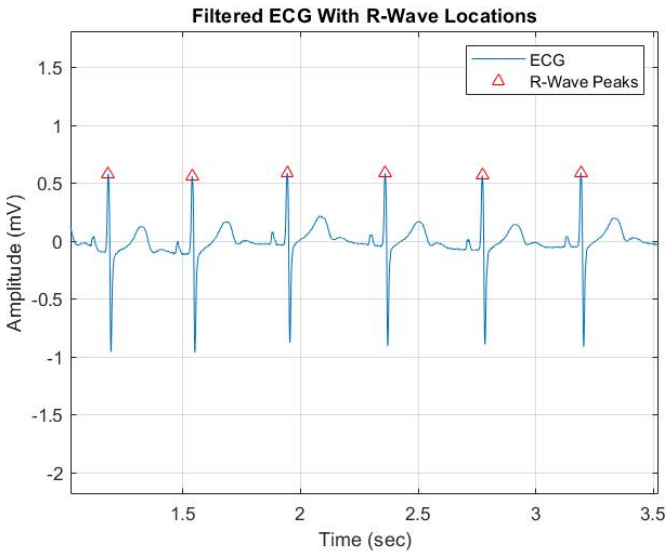

Figure 5.8. R peak location with 'find-peak' function of MATLAB.

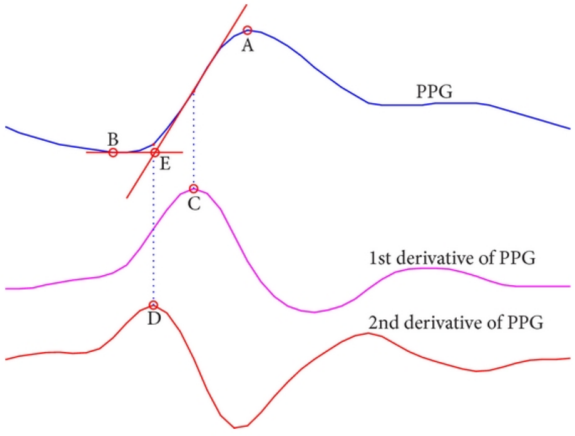

Figure 5.9. Different PPG points determined with derivation of the signal. [60]

For what concerns the PPG signals many ways were tested. In literature different points were used to determine the PTT between R-peak and a significant point of

PPG. This point could be determined using directly the maximum of signal (the systolic peak of PPG) or by using one of the two derivatives of PPG.
With the first derivative of the signal is possible to identify the point of ascent as shown in the purple wave of the figure 5.9. By using this derivative, results obtained have revealed that it causes a lack of specificity in detection. In fact, this method located several false positives, by highlighting ascendant points even if they are not present.
The second derivative, on the other hand, gives information about the position of the minimum of PPG as shown in the red wave of the figure 5.9. Eventually, after testing all three methods, it was decided to use directly the maximum point of PPG. In fact, this provides a better result and a lower computational load.
Despite this, the second derivative of PPG signal was used to define the cardiac cycle, in fact the 2^{nd} derivatives maximum corresponds to the start of cardiac cycle as show in figure 5.10.

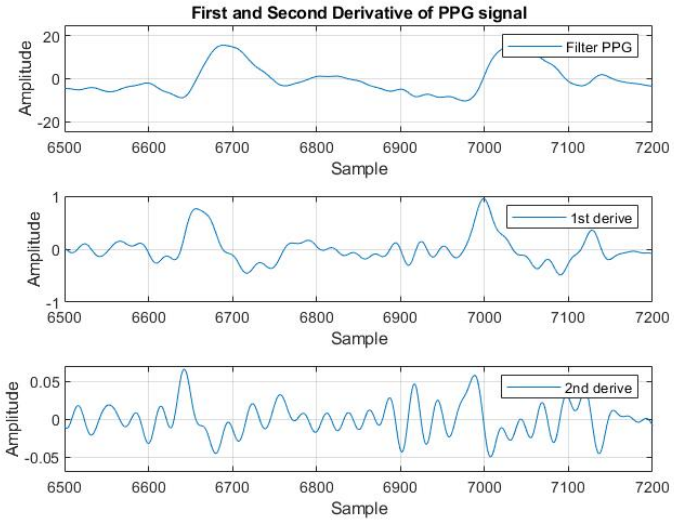

Figure 5.10. First and second derivatives of PPG signal.

The Systolic-peak of PPG was identified by using the 'find-peak' function of MATLAB with a specific threshold that change in relation of signals used. It is shown in figure 5.11.

Also for ABP signal, it was necessary an elaboration of signal to determine the systolic and diastolic pressures. As said before the ABP is an analogical signal recorded usually in an invasive way. To determine the two values of pressure, it is necessary to locate the maximum, that corresponds to the systolic value, and the minimum, that corresponds to the diastolic value. An example of ABP wave with interesting points highlighted is shown in figure 5.12.

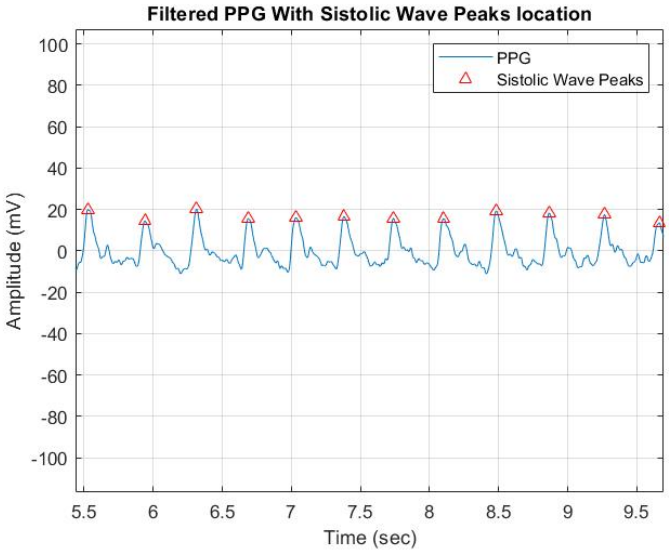

Figure 5.11. Systolic-peak location with 'find-peak' function of MATLAB.

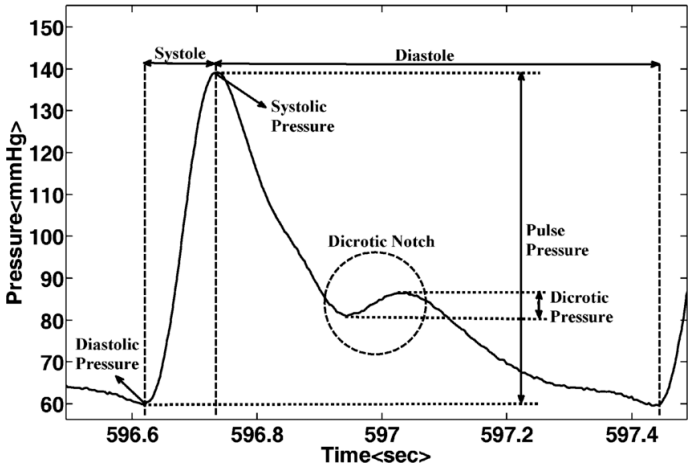

Figure 5.12. An ABP waveform including systole and diastole regions and systolic and diastolic peaks. [61]

After have obtained all the necessary points, it was possible to calculate the PTT and HR values.

$$PTT = time_{PPG}(Systolic\ PPG\ peak) - time_{ECG}(R-peak) \tag{5.1}$$

$$HR = \frac{60}{R_{peak}(i+1) - R_{peak}(i)} \tag{5.2}$$

Before PTT estimation, some validating criteria have to be applied. First of all, the first and second PPG derivatives are calculated to define the cardiac cycle. Furthermore, the second PPG derivative shall be seated between two consecutive R-peaks. The following steps are applied:

- Identification of R-peaks of the ECG signal;
- Identification of S-peaks of the PPG signal;
- Verification that the first R-wave peak is before the systolic peak of PPG signal, if not, the estimation starts from the subsequent point;

$$t_{Rpeak}(i) < t_{PPGpeak}(i) < t_{Rpeak}(i+1) \tag{5.3}$$

- Eventually, calculation of the distance between the R peak and the Systolic peak of PPG.

5.1.2 Regression Analysis and Validation Process

After this pre-processing procedure, it is started the real predictive process. Some mathematical models have been trained and the one that gave the best results is the logarithmic model with PPT and HR:

$$BP = a \ln PTT + b\ HR + c \tag{5.4}$$

$$\begin{cases} SBP = a_s \ln PTT + b_s HR + c_s \\ DBP = a_d \ln PTT + b_d HR + c_d \end{cases}$$

To evaluate the BP estimation some error evaluations have been done. Among the quantities used to assess the reliability of the system there is the Root Mean Squared Error (RMSE). It is the square root of the mean square error (that is a measure of how close a fitted line is to data points). It has the same units as the quantity studied, so the $mmHg$. The RMSE is the average of distance of data points from the fitted line. It gives a measure of goodness of fit, then a correlation coefficient. In addition, the squaring is done so negative values do not counterbalance positive values.[62]

$$RMSE = \sqrt{MSE} = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}} \tag{5.5}$$

with:

- y_i = real value
- $\hat{y}_i$ = prediction

- n = number of data points

Systolic blood pressure					
Dataset	*RMSE*	*MAE*	R^2	Err_{std}	$p-value$
Trainset	10.271	8.397	0.287	10.259	0.534
Testset	10.969	8.604	0.225	10.907	0.297
Diastolic blood pressure					
Dataset	*RMSE*	*MAE*	R^2	Err_{std}	$p-value$
Trainset	4.907	3.877	0.295	4.904	0.667
Testset	4.746	3.704	0.304	4.740	0.644

As shown in the tables above the RMSE of systolic blood pressure is bigger than the diastolic one. It is probably caused by a higher variability in systolic BP values. This could be also caused by the variance of error magnitudes of frequency distribution. For what concerns the diastolic RMSE results are great. According to the current ANSI/AAMI/ISO requirements, it is tolerable a maximum error (MAE) of 10 mmHg with an approximate probability of the 85% that this error occurs. [63] Although the RMSE values are above 10 mmHg, the performances respect the requirements. In fact, it is the MAE value that gives an idea of this algorithm performances and they are all above the threshold. The MAE is the average over the sample of the absolute differences between prediction and observation, in this measure for all individual differences the weight is equal.

$$MAE = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}} \tag{5.6}$$

with:

- y_i = prediction
- $\hat{y}_i$ = real value
- n = number of data points

Both for systolic and diastolic pressure evaluation this algorithm is under the threshold chosen by ANSI/AAMI/ISO.
Another indicator evaluated is R^2 or R-squared. It represents the variance's proportion for a dependent variable, that is explained by the regression model. It gives an idea of the weight that the variance of one variable has on a second variable. So, if the R^2 of a model is 0.50, almost the 50% of the noticed variation can be explained by inputs of the model. However, this works only for linear model. By this indicator it was possible to say that this model is not linear, in fact for this algorithm R^2 is always under 0.5. In particular, this affirmation is also proved by the p-value as it will be described afterward.

$$R^2 = 1 - \frac{RSS}{TSS} \tag{5.7}$$

with:

- RSS = sum of squares of residual
- TSS = total sum of squares

Another studied parameter is the Err_{std} or Standard error.

$$Err_{std} = \frac{\sigma}{\sqrt{n}} \tag{5.8}$$

with:

- σ = standard deviation of sample
- n = number of samples

This value gives an indication about the representativeness of the sample in respect of the overall population. The smaller it is the more representative is the sample of the population. In particular, for regression analysis, it mentions to the standard error for a particular regression coefficient.
The last one statistical value evaluated is the $p - value$. In statistics, the p-value or the probability value, is the probability to obtain equal results, or less likely, respect to the one observed during test, assuming that the null hypothesis is correct. Shortly the p-value helps to know if the difference between real results and observed ones is caused by the introduced causality due to sampling or if it is statistically significant. The p-value represents the observed significance level, it is the probability that the rejection of the null hypothesis is only due to causality. It is the probability that the possible refute of the null hypothesis could be only due to the low representability of the chosen sample. In this case it is been studied if the data population approximated by the algorithm is statistically significant in respect of the one obtained with ABP. A significant p-value exceeding the $\alpha < 5\%$ threshold does not imply that the null hypothesis is rejected. It means that the invasive and the non invasive method performed carry statistically similar information. This could be considered an evidence of the well performing of this algorithm.

5.1.3 Meaningful charts

In the following bar charts the effects of the Ridge Regression performed are shown, both for training and test set for SBP and DBP evaluation. It is a technique for analysing multiple regression data that are affected by multicollinearity. Multicollinearity occurs when there are near-linear relationships between the independent variables. Multicollinearity causes several disadvantages, it could cause inaccurate estimates of the regression coefficients, it could increase the standard errors of the

regression coefficients, it could give incorrect p-values, and so affect the forecast of the model. [64]

In the figures 5.19, 5.20, 5.16 and 5.14 the relation between $\hat{y}_i - y_i$ (real-predicted values) and the *instances* are plotted, or observation, respectively for DBP and SBP train-set and for SBP and DBP test-set.

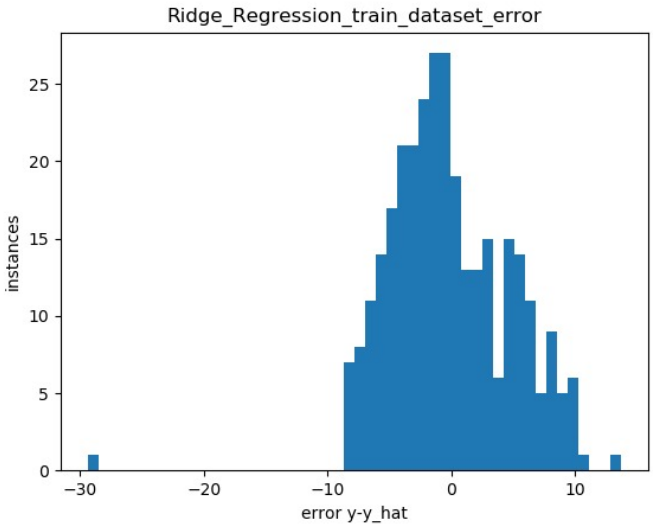

Figure 5.13. DBP trainset error.

In all this graphs the most frequent occurrence of errors is around '0' but for SBP the values further from the average the occurrence is less frequent but the bell widens. Probably it is caused by a most strong variability that affects the SBP values.

With scatter plot it is possible to have a visual idea of the correlation between real and predicted values ($\hat{y}_i$ and y_i). A scatter plot indicates the correlation between variables, this correlation may be positive, negative, or null and indicates respectively the case of variables with a rising correlation, falling correlation and uncorrelated. In this case the pattern of points slants from lower left to upper right, it underlines a positive correlation between the variables.

The point cloud of all the graphs clearly approximates a straight line for both the SBP and the DBP. This gives a positive idea about the predictive capabilities of the algorithm.

Furthermore, the large number of samples to train the system shows a sufficient number of samples for the central values but not for the peripheral ones. This is translated into a different weight of error with respect to the average relative to the

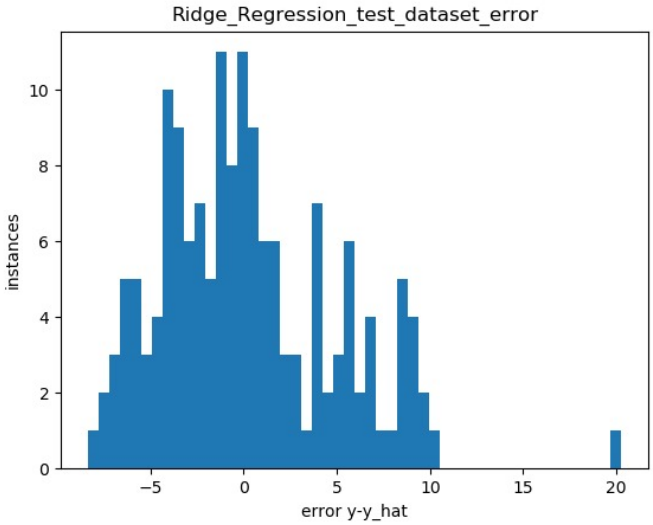

Figure 5.14. DBP testset error.

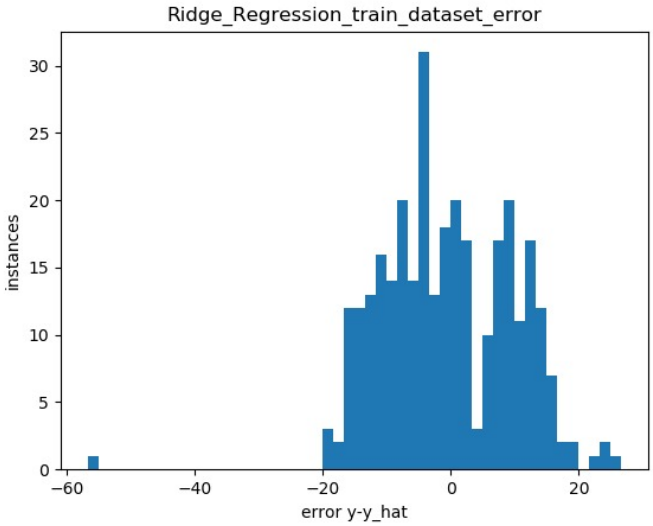

Figure 5.15. SBP trainset error.

central values.

To better figure the continuous trend of the predicted pressures with respect to the real ones the two graphs below have been plotted.
In the first one (Fig. 5.21), putting attention on the ordinate axis, it is evident that the error range is small, therefore it is consistent with what was said previously.

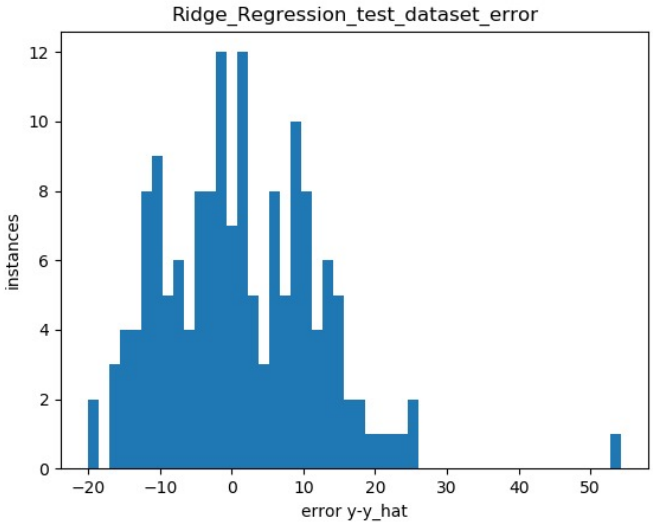

Figure 5.16. SBP testset error.

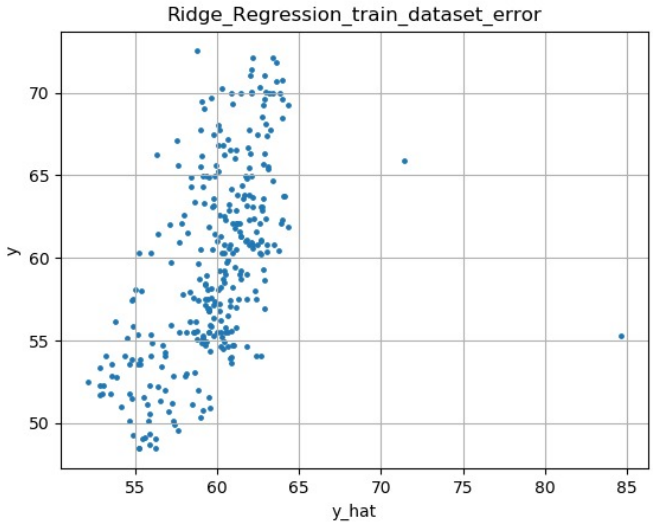

Figure 5.17. DBP scatter training error.

In the second figure (Fig. 5.22), the error range is bigger, anyway the predicted signals follow the real one.

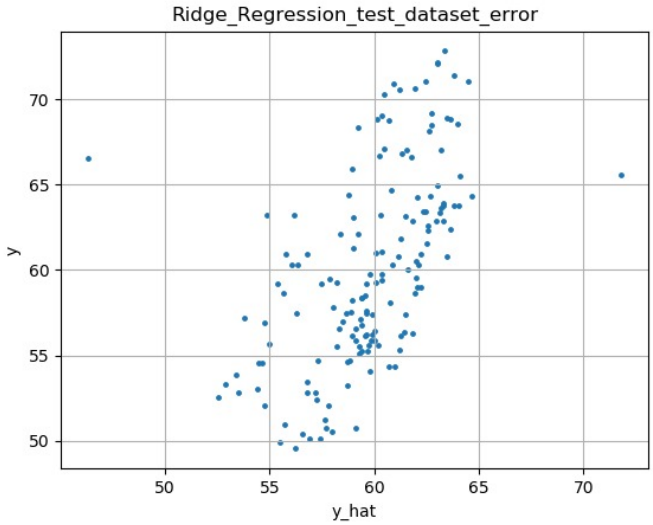

Figure 5.18. DBP scatter test error.

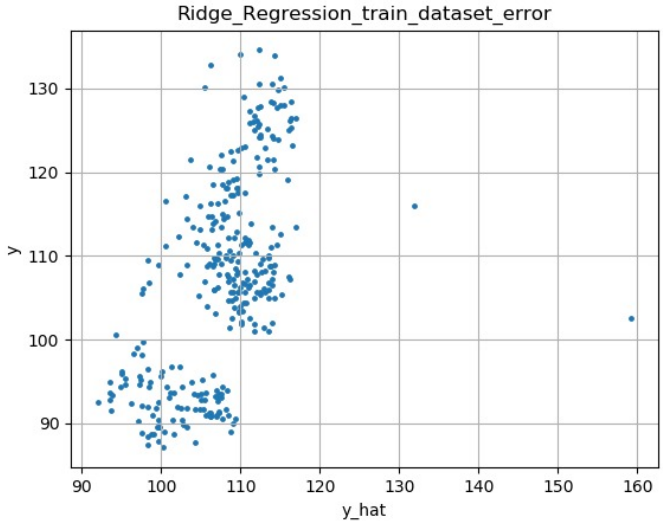

Figure 5.19. SBP scatter training error.

5.1.4 Criticisms

The principal criticism is given by the need of periodic and person-specific calibrations. For these calibrations, when they should be carried out is not known a priori. Furthermore, the calibration process requires a certain amount of time in

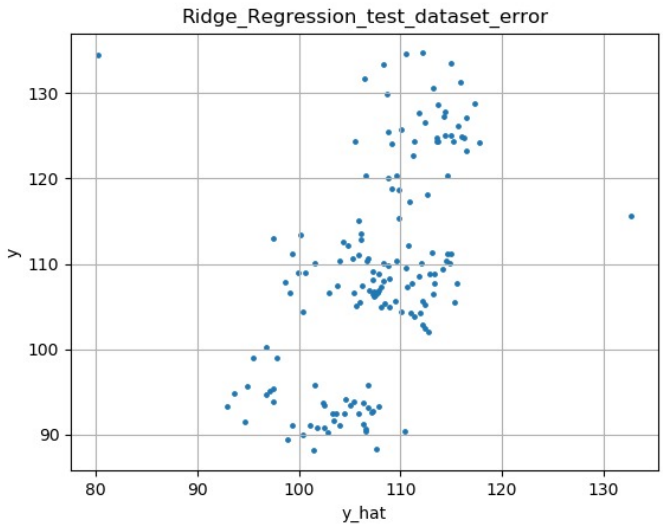

Figure 5.20. SBP scatter test error.

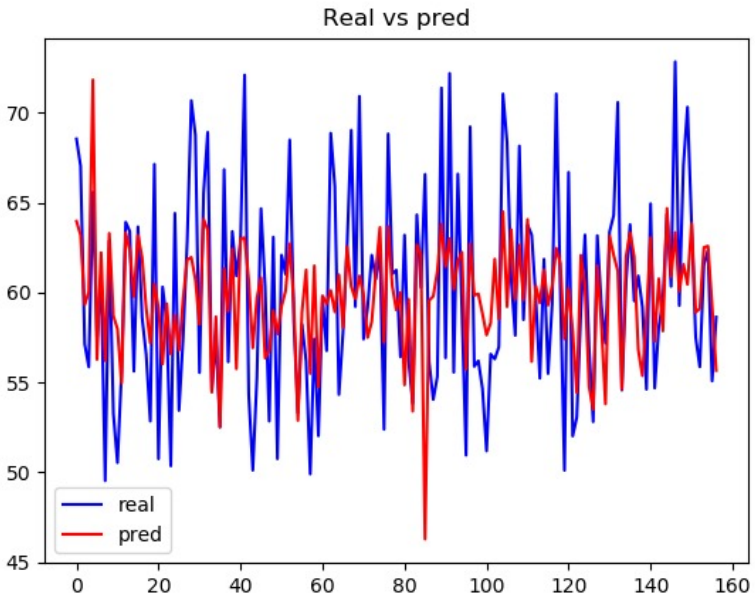

Figure 5.21. Real vs predicted DBP.

which the subject must remain still and measure his BP with a SoA device.
To overcome this limit we are evaluating the minimum training window necessary

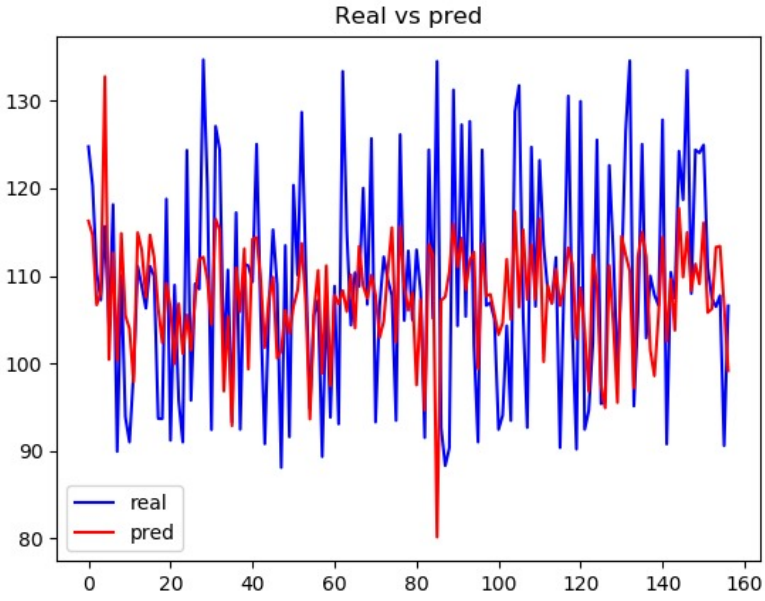

Figure 5.22. Real vs predicted SBP.

to perform the regression. The next step will be then to multiply an observation window of one minute (time required for the acquisition of SBP and DBP pressures with traditional devices) by the time required, thus going to limit the waiting time for the patient.
The need to re-calibrate the device does not affect the results for what concerns the SINTEC sensor. This depends on the fact that the device in question will be worn for limited periods and, by estimating the timing of the variation of the physiological parameters (i.e. the stiffness of the arteries), this occurs on average over a period of years.
Among the difficulties that have been observed was that of finding sufficiently long MIMIC signals. As previously mentioned, the database contains signals from an intensive care unit, which causes a decrease in signal quality and a lack of sufficiently long observation windows. A difficulty which has led to a selection of usable signals and which can be overcome by the use of SoA devices for the acquisition of signals.

Chapter 6

Conclusion

The study of pressure estimation was carried out by calculating Pulse Transit Time and Heart Rate. The calculation of these two characteristics required the implementation of a method for identifying the R-peaks in the ECG, and the S-peaks in the PPG.
The former was chosen to calculate HR, the latter was used concurrently with the ECG for PTT calculation. The innovation of this study is given by the possibility of carrying out measurements without the use of invasive devices and continuously. The algorithm carries out an easy and quick estimate of blood pressure by giving precise numerical results as output. The computational costs of this method are not high, facilitating the future applicability on wearable devices. Furthermore, the algorithm has an excellent ability to analyse the signals processed once they are suitably filtered and edited.
In conclusion, this method proved to be effective and a good starting point for blood pressure monitoring with new non-invasive methods.
This will lead to constant monitoring that can be carried out not only in the strictly medical field but which could also be integrated into everyday devices. In this way it will be possible to intercept the development of cardiovascular diseases before they cause irreversible damages.
As for the migration from MIMIC database to SoA devices, there have been some setbacks due to synchronization problems of the devices on which we are still working. In the meantime, a study of signal cleaning and of identification of the features has been carried out. Once synchronization will be achieved between the ECG and PPG signal sampling devices, the already implemented algorithm can be applied to these signals.
This work is primarily intended to be a contribution to the clinical sector of research. It aims to develop an algorithm for the SINTEC device, which will also be used as a tool for measuring SBP and DBP. Expectations were mostly met in relation to current regulations. Furthermore, the ergonomics of the device would place it above those currently on the market.

6.1 Future work

Based on the results obtained in this thesis work, there are several prospects for improvement that can be pursued:

- Test the algorithm on state-of-the-art devices to improve and prove the reliability of the developed model;
- Applying the implemented algorithm on signals acquired in real time, this is the springboard for the effective application on wearable devices;
- Another innovation that could be carried out is to estimate the values of the person-specific constants by considering information that influences blood pressure values. This information is of a physiological type such as weight, sex and age, all information not present in the available databases.

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