POLITECNICO DI TORINO

Master degree course in Biomedical Engineering

Master Degree Thesis

Ubiquitous unobtrusive blood pressure estimation from photoplethysmographic signal acquisition

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Contents

Abstract

Blood pressure (BP) is one of the most important and meaningful vital signs for determining the health conditions of a person, but at the same time, one of the most difficult to collect in a continuous way and especially with a non-invasive portable device.

The long-term monitoring of blood pressure is very important for patients in serious health conditions, in particular for those who have cardiovascular diseases, currently allowed by invasive catheterization only in Intensive Care Units (ICU) and operating rooms. On the other hand, there is an increasing demand for the acquisition of this vital sign from healthy people doing physical activity. In that sense blood pressure together with other parameters are important indicators to avoid excessive fatigue or cardiovascular diseases.

Studies regarding the blood pressure estimation using other physiological parameters have been highlighted a relationship between BP and photopletismographic (PPG) signal. Despite this, wide research activities have been conducted in the field for years, but no reliable solution is available on the market yet.

Two algorithms have been developed in Matlab environment, in order to allow a continuous estimation of systolic and diastolic blood pressure values (SBP and DBP), by means of a PPG signal.

In the first method it has been performed a linear regression analysis for modeling the relationship between BP values and a specific PPG waveform feature. Therefore, after a calibration phase, a linear predictor function estimates SBP and DBP from PPG signal.

The second algorithm, using PPG and electrocardiographic (ECG) signals, calculates the pulse transit time (PTT) and estimates the BP values through the Moens-Korteweg equation, which models the relationship between the PTT and BP.

Both approaches have been developed, referring to signals coming from the MIMIC internet database, included in PhysioNet archives. Finally, the algorithms have been validated on signals coming from real patients of the San Giovanni Bosco hospital ICU in Turin. A clinical trial, with procedures that had to be compliant to a protocol approved from an ethical committee, has been carried out. Results of these experiments have been then compared in graphical plots and statistical evaluations.

Chapter 1

Introduction

Nowadays it is clear that wearable technology represents one of the most promising pillars of electronic devices development. The statistics speak for themselves, the increasingly diversified wearable technology market is expected to reach over $150 billion by 2027, according to IDTechEx report *[1]*. The main driver for this level of interest is the capability of wearable products to lie at the intersection of important modern trends such as healthcare and fitness. Among the wide variety of wearable devices, wrist wearables, such as smartwatches and wrist bands, seem to have become mainstream.

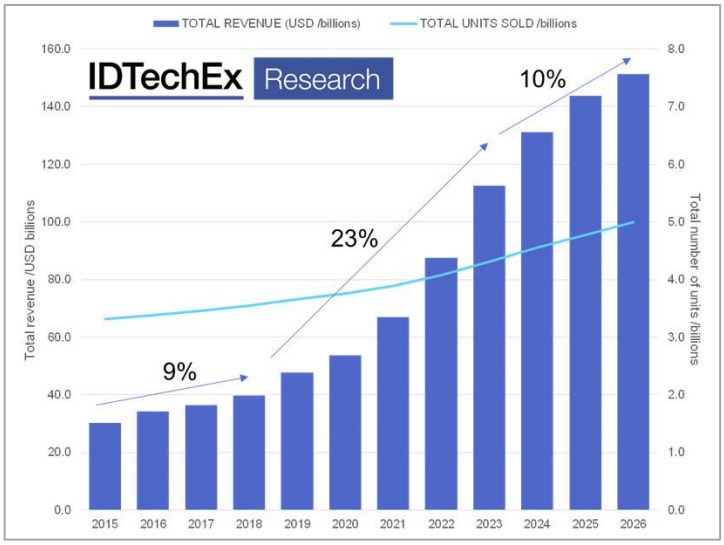

Figure 1.1 Global forecast regarding wearable technology by IDTechEx. [2]

The term "wearable device" refers to electronic and computer technologies that can comfortably be worn on the body, incorporated into clothing items and accessories. Wearable devices go beyond the computing tasks of laptop computers and smartphones with sensors and features scanning, such as biofeedback and tracking of physiological functions. Usually, they have also a wireless communication capability that allows the user to access the data in real time *[3]*.

The wearable technology can influence a lot of fields like health and medicine, rehabilitation and fitness, but also finance, education, gaming and transportation. Geographically, North America is at the top of the countries list with greater consumer percentage, followed by Europe and Asian countries.

As highlighted, the healthcare sector is a considerable portion of the wearable technologies market. The applications addressed by these devices fall in two main areas: fitness and telemedicine. The current goal in the sports wearables market is to improve and better manage personal fitness and athletic performance, setting health goals and personal sports activity and tracking progress. These devices are able to analyze heart, muscle, breathing and sports endurance parameters and retrieve an information which may also prevent injury. Wearable technology in the telemedicine area are also expected to increase. This kind of devices allows remote patients monitoring which can go home earlier, improving their comfort and reducing the burden on manual hospital checks. In this way the continuous measurement of vital parameters may alert doctors in case of chronic diseases. Moreover, wearable devices are useful to identify early-onset diseases, offering preventive health benefits.

1.1 Purpose of the work and followed methodology

Today one of the vital signs most difficult to measure in a continuous and non-invasive way, but at the same time one of the most important and meaningful, is the blood pressure (BP). The measuring and the continuous monitoring of blood pressure are very important for patients in serious health conditions, in particular for those who have cardiovascular diseases, such as hypertension, heart attack and asthma. On the other hand, monitoring of blood pressure is becoming more and more important also for healthy people doing physical activity. In that sense blood pressure together with other parameters, such as heart and breath rates, are important indicators to avoid excessive fatigue or cardiovascular diseases.

Hence, given the trends and the forecasts expressed in the previous section, it is simple to motivate the direction taken by a company like STMicroelectronics, leader in the segment of semiconductor solution for electronic devices. Relevant efforts have been spent in the past years in the development of MEMS technology and therefore in wearable devices, especially in the healthcare application field.

Therefore, the industrial focus of the thesis is to implement an algorithm for estimating blood pressure in a ubiquitous and unobtrusive way, in order to be able to interface with the bio-potential acquisition devices developed by STMicroelectronics.

"Ubiquitous" points out the continuity over time of the estimated value, not exactly in real time as from an invasive way, but with an output every appropriately short time lapse. On the other hand, the adjective "unobtrusive" refers to a system as less intrusive as possible, especially non-invasive.

More precisely, physiological data chosen to achieve a blood pressure information are photoplethysmographic (PPG) and electrocardiographic (ECG) signals.

Regarding the market target of this project, STMicroelectronics is engaged in the development of both consumer and clinical devices. It was decided to steer the work towards both the markets. Indeed, the algorithm validation by means of a clinical trial at San Giovanni Bosco hospital and the collaboration with the doctors allowed to experience the clinical world perspectives, keeping in mind the very strict guidelines and the related rigorous policies.

The desired goal is to provide an algorithm implemented in Matlab numerical computing environment by initially considering physiological signals from an online database. Subsequently, to estimate the true accuracy and reliability, the algorithm will be validated on real patients' signals acquired at San Giovanni Bosco hospital.

The development of a feasible strategy to extract blood pressure values from ECG and PPG signals has required different enhancement phases, continuous adjustment and setting refinements and several validation steps.

Here is reported a brief summary of the followed steps:

1. **Initial analysis and feasibility study:** in the initial stage of the work a primary analysis of the problems, starting conditions and general information about the application is required. This step also involves a feasibility study of the system. The topics widely investigated in this step are:
    - Study of human physiological aspects in cardiology, especially in blood circulation and blood pressure.
    - Study and analysis of ECG, PPG and blood pressure signals.
    - Research in literature and state of the art about algorithms and devices able to extract pressure estimations from PPG and ECG.
2. **Identification of suitable datasets:** clinical recordings have been identified from internet medical database, on which algorithms development may rely. Then, for a deeper validation, it has been chosen to consider real PPG, ECG and BP signals from patients at the San Giovanni Bosco Intensive Care Unit (ICU).
3. **Algorithms implementation in Matlab environment:** this section covers the algorithms definition. According to the identified methods, the algorithms able to estimate the blood pressure follow two parallel approaches:

- Extraction of BP directly from PPG features
- Estimate of BP values from both ECG and PPG signals, thanks to the correlation between blood pressure and Pulse Transit Time (PTT)

The arranged procedures and functions have been progressively tested.

4. **Algorithms validation:** a validation is necessary in order to understand the quality of the obtained results and to establish the level of reliability reached by the developed algorithms. This phase is carried out by means of the collaboration with San Giovanni Bosco hospital, acquiring ICU patients' signals.

Chapter 2

Background

2.1 Heart and blood pressure physiology

The heart is one of the key organs in the whole body. Thanks to its pumping action on the blood, the body tissues get a constant supply of nutrition in order to survive.

The heart is made up of four chambers: the upper atria and the lower ventricles. They work together in order to circulate blood through two circuits: the pulmonary and the systemic pathways. The first one allows for the exchange of gasses between lungs and blood: it acquires oxygen that is spread through all over the body. As blood flows from the heart, the size of the blood vessels, made of connective tissue and muscle, decreases related to the pressure inside this one. Oxygenated blood, also called as "red blood", travels via artery to smaller arteriole, then to the smallest vessels for nutrients, metabolic waste, oxygen and carbon dioxide exchange, the capillaries. As soon as the blood is deoxygenated, begins the return to heart via venules and then veins, ready for the reacquisition of oxygen through the pulmonary pathway *[4]*.

The heart pump functionality is composed by two separate phases: systole, or the contracting phase, and diastole, or the period of time in which the heart refills with blood.

In the diastole of a cardiac cycle, the ventricles are relaxed, the atrioventricular valves (mitral or bicuspid valve for the left part of the heart and tricuspid valve for the right side) are open and the blood flows from the atria in the respective ventricles (as shown in *Figure 2.1(a)*). At the end of diastole, both the atria begin to contract, properly filling the ventricles (*Figure 2.1 (b)*). Increasing the ventricular pressure, the atrioventricular valves close and the ventricles systole occurs. After a beginning phase of isovolumetric contraction, the semilunar valves (the aortic valve for the left part of the heart and pulmonary valve for the right side) open and the blood is pumped out into the arterial system (*Figure 2.1 (c)*).

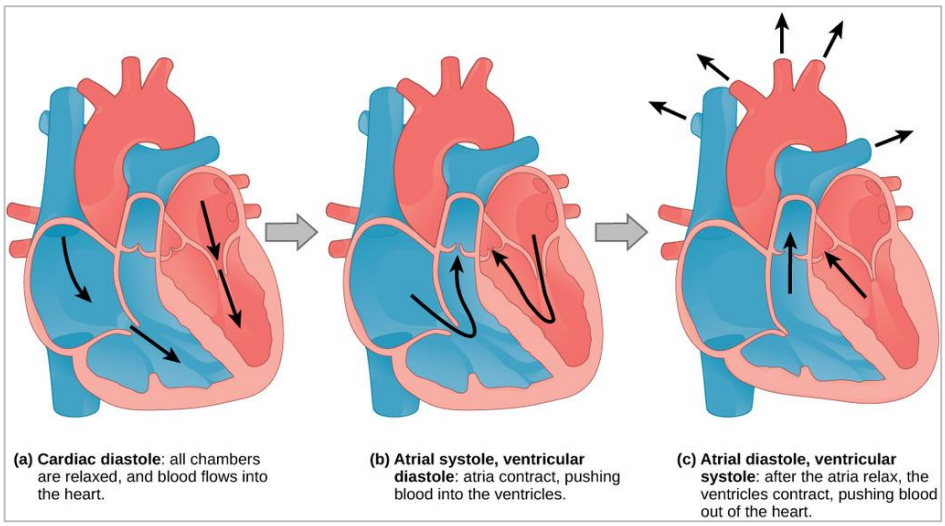

Figure 2.1 Cardiac cycle. [5]

The *Figure 2.2* shows the trends of aortic, left ventricular and left atrial pressure, whose variations allow the proper opening and closing of the valves, the ventricular blood volume and the electrocardiogram.

Blood pressure is one of the most meaningful vital signs for determining the health conditions of a person. In the clinical world, without further specifications, it refers to the arterial blood pressure, or rather the pressure exerted by blood, coming out from the heart and pushing against the walls of blood vessels *[6]*.

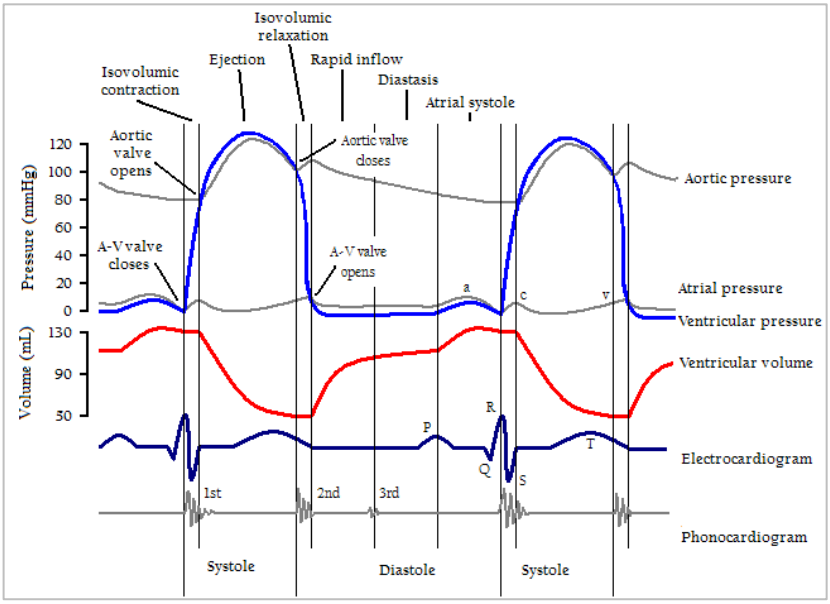

Figure 2.2 Trends of aortic pressure, left ventricular pressure and left atrial pressure, ventricular volume and electrocardiogram during the cardiac cycle. [54]

Blood pressure is usually measured in millimeters of mercury (*mmHg*). The artery walls are also made up of tiny muscles to keep their shape, despite pressure is changing minute by minute during the cardiac cycle.

The blood pressure is often reported as a ratio between the systolic blood pressure (SBP) and the diastolic blood pressure (DBP). Thus, the upper number concerns the maximum pressure exerted during the ventricular systole and the lower one concerns the minimum pressure measured when the ventricles are full of blood. According to American Heart Association (AHA), physiological values are around 120/80 *mmHg* for adults from 18 years old and older.

As shown in *Table 2.1*, values a bit higher than normal mean a state of prehypertension; while from 140 systolic or 90 diastolic, it implies a hypertension stage, divided into 3 ranges of pressure related to the risk of cardiovascular diseases. Such a risk doubles every 20 *mmHg* systolic or 10 *mmHg* diastolic for adults from 40 to 89 years old *[7]*.

It is also possible to have abnormally low pressure (readings lower than 90/60), that could hide an underlying cause to be investigated.

Table 2.1 Blood pressure categories defined by American Heart Association. [7]

Blood Pressure Category	*Systolic (mmHg)*		*Diastolic (mmHg)*
Normal	Less than 120	and	Less than 80
Prehypertension	120 - 139	or	80 – 89
High Blood Pressure (Hypertension) Stage 1	140 - 159	or	90 – 99
High Blood Pressure (Hypertension) Stage 2	160 or higher	or	100 or higher
Hypertensive Crisis	Higher than 180	or	Higher than 110

Among the high blood pressure complications, there may be damages of the vessels cells, inducing artery walls less elastic and limiting blood flow throughout the body. The constant high pressure may lead to enlargement of a section of the wall and consequently to an aneurysm, whose rupture causes a very dangerous internal bleeding.

High blood pressure levels force heart to work harder in order to properly deliver the blood throughout the body, causing an expansion of left part of the heart with a

ventricular hypertrophy. The strain of the heart in this condition increases the possibility of heart failure, heart attack or sudden cardiac death.

High blood pressure levels also affect the brain, with a discontinuous or absent supply of blood, which may lead to strokes or cognitive impairments, and the kidneys, with a risk of failure, glomerulosclerosis or aneurysm in the arteries leading to them *[8]*.

There are many recommendations that assure a heart-healthy lifestyle and avoid incurring in hypertension, a symptomless "silent killer": exercising regularly, eating a healthy and low-salt diet, minimizing alcohol and caffeine, quitting smoking and reducing stress in general.

Blood pressure normally rises with age and body size. In childhood, it has very low values, considered normal in this range of age. Moreover, it changes during the day. Indeed, it is recommended to measure blood pressure at the same time during the 24 hours, because BP reaches the lowest value when a person is asleep and it increases gradually few hours before you wake up. It continues to rise with a peak in the middle of the afternoon; then it decreases.

2.2 Conventional methods measuring blood pressure

Arterial blood pressure can be measured in two ways: invasively and noninvasively.

2.2.1 Invasive methods

Nowadays invasive blood pressure measurements, with a pressure transducer joined with patient's artery by a catheter over a needle, represents the gold standard: indeed, it is the most accurate method that allows a continuous measure. It is used mostly when there is the need of a long-term recording. A catheter, with the help of a needle, is ushered into an artery (usually radial one) and the blood flow conduces it into the vessel. Besides the intra-arterial cannula, the basic components of the pressure-transducing system (*Figure 2.3*) are a flexible hose incorporating an infusion system, a transducer, a microprocessor and a display screen.

Despite the accuracy and continuous measurement, it is a highly uncomfortable measurement method. Indeed, it is a procedure adopted only in case of hospitalized patients in intensive care units or in the operating suite, because of a need of close supervision. In fact, it might cause serious bleedings, for example in case of disconnection of the measurement equipment. Furthermore, it is more difficult than other methods and there is a real possibility of infection.

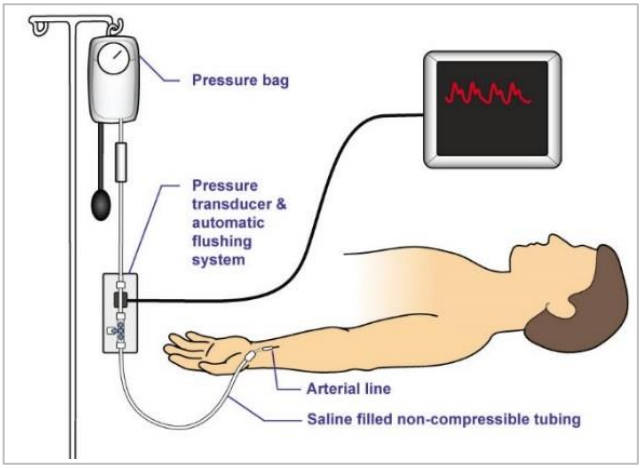

Figure 2.3 Gold standard method in measuring blood pressure.

As shown in *Figure 2.4*, the typical blood pressure waveform measured with this invasive method has different components. With a delay between last ventricular depolarization and the arrival of the signal to the pressure transducer, there is a systolic upstroke, corresponding to the ventricular ejection. Then the blood pressure reaches its maximum value (Systolic Blood Pressure - SBP). Subsequently, the ventricular contraction comes to an end and a rapid decline occurs. A dicrotic notch changes the descendent trend of the wave and coincides with the aortic valve closing; the minimum amplitude (Diastolic Blood Pressure - DBP) is the pressure exerted by the vascular tree back to the aortic valve.

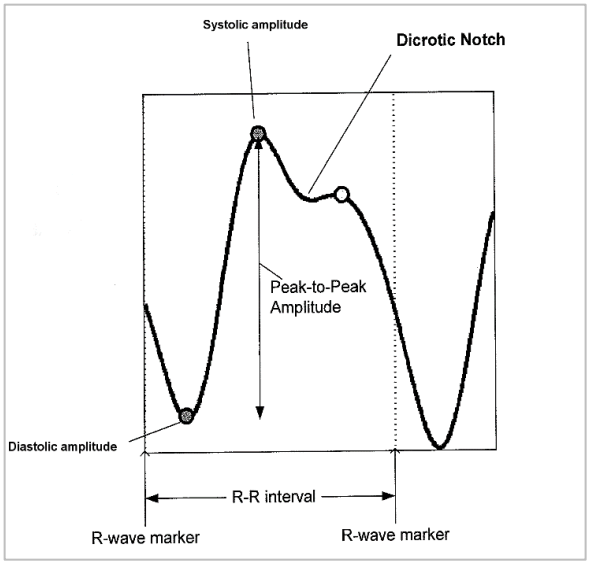

Figure 2.4 Blood pressure waveform measured with an invasive method. [9]

Mean Arterial Pressure (MAP) is a parameter equivalent to the area under the blood pressure curve, divided by the duration of the beat and averaged over several beats.

This is a general trend of blood pressure, but slightly different waveforms can be measured depending on the site of insertion *[10]*.

2.2.2 Non-invasive methods

Most common way of measuring blood pressure, practical also at home, is the occlusive approach. The instrument that occludes the artery (usually the brachial one) is the sphygmomanometer, invented by Riva Rocci in 1896. The *Figure 2.5* shows the Riva Rocci mercury based sphygmomanometer and a modern aneroid one, or rather "without fluid".

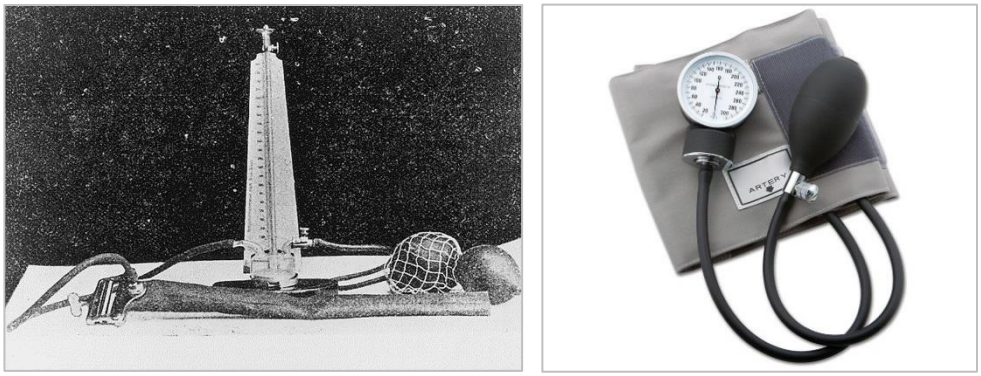

Figure 2.5 Riva Rocci sphygmomanometer at left and a modern one at right. [11]

It consists of an inflatable cuff, usually placed on the left arm at heart level and filled with air by a pump at a controlled pressure by a mercury manometer.

Reaching a pressure such that, the artery is occluded, blocking the circulation, the cuff is slowly deflated in order to restore the normal blood flow.

Analyzing phenomena that occur during this restoration, it is possible to obtain systolic and diastolic pressure values, thanks to auscultatory and oscillometric method.

This approach leads to a non-continuous measure of blood pressure, because its values cannot be collected in every heartbeat or minute by minute.

Auscultatory method

The auscultatory method is based on the sounds produced during the restoration of blood flow and the decrease of pressure imposed on artery from the cuff. The detection of the sounds can be done by means of a stethoscope placed usually between the arm and the cuff, or anyway downstream of the occlusion.

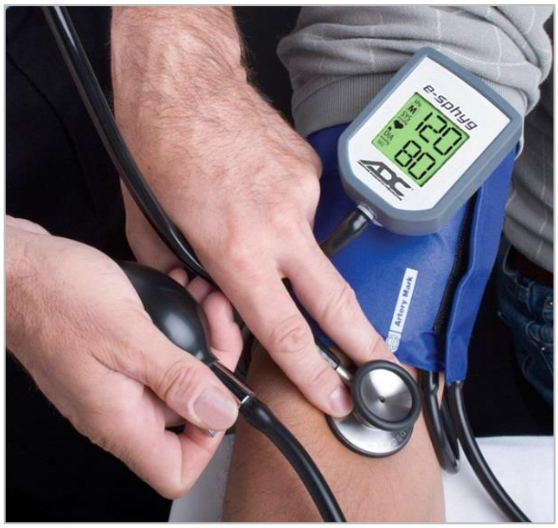

Figure 2.6 Auscultatory method for measuring blood pressure. [11]

The analyzed sounds are called Korotkoff sounds by the name of the Russian physicist Sergeivich Korotkoff who noticed them the first time and studied their correlation with blood pressure values.

Korotkoff sounds result from the vibration of the artery wall due to phenomena of blood flow turbulence in correspondence of the occlusion. In the initial condition of complete obstruction of the artery, the flow is blocked because of a cuff pressure greater than the systolic blood pressure. By opening the sphygmomanometric release valve, the pressure for which it is possible to hear the first sound corresponds to the systolic blood pressure. Subsequently, the blood continues to be turbulent because of the small section of the vessel, until reaching a normal lumen and consequently a normal blood flow, ending up its noise associated. The diastolic blood pressure corresponds to the pressure of the cuff on the instant following the last Korotkoff sound.

The accuracy and precision of this method is difficult to quantify because of the influence of the operator. The uncertainties about the instant in which Korotkoff noise is detected, auditory sensitivity of the operator and its reaction time in associating a pressure value on the manometer to the absence or presence of Korotkoff sounds play an important role in the reduction of accuracy.

In order to make the instrument independent from operator, it has been developed sphygmomanometer with automatic air pump into the cuff and a microphone to detect the Korotkoff sounds *[11]*.

Oscillometric method

E. I. Marey first demonstrated this technique in 1876. Nowadays, an instrument which follows this approach is composed of a pneumatic circuit connected to a cuff and an electronic circuit with a pressure sensor able to record the oscillations of pressure in the cuff, produced by the passage of the pressure wave in the artery (as shown in *Figure 2.7*). The measurement is performed automatically but the oscillations begin at approximately systolic pressure and continue below diastolic one.

Figure 2.7 Oscillometric method for measuring blood pressure. [55]

Therefore, these values are estimated indirectly thanks to other expedients. The pressure wave is reflected totally at the occlusion, inducing a very weak pulse pressure in the cuff, detected by the pressure sensor.

As the cuff deflates, the amplitude of the pulse increases until it reaches a maximum, corresponding to maximum variation in the section of the artery during the cardiac cycle, and then decreases permanently.

In condition of maximum of inflation pressure of the cuff, it is a measure of the mean arterial pressure. Usually values of systolic and diastolic pressure are estimated from MAP empirically. Systolic blood pressure is computed as the inflated pressure before the achievement of the MAP corresponding to an amplitude of the oscillations equal to 45 - 55% of the maximum. Diastolic blood pressure is in correspondence with amplitudes of around 74 - 82%.

This method is advantageous because there is not the need of a transducer placed on the brachial artery and it is less susceptible to outward noise (but not to low frequency mechanical vibration).

The main disadvantage is, indeed, that this system does not work well during physical activity when considerable movement artifacts are possible.

Tonometric method

Tonometric approach is a simple and cuff-less system that provides continuous measurement of arterial blood pressure, compressing a superficial artery, for example the radial one, on the underlying bone. The device consists of an array of pressure transducers placed on the skin and the sensor is used to press against the tissue with a resulting pressure less than arterial pressure (*Figure 2.8*). Therefore, the compressed artery is not totally occluded and arterial pressure waveforms are transmitted directly to the transducer. Then, computer algorithms compute the input signal and furnish continuous values of blood pressure.

It is required a calibration of the system with systolic and diastolic measurements by means of a standard arm cuff with oscillometric technique.

This approach could reproduce, with high fidelity, the intra-arterial blood pressure waveform, but its accuracy is decreased because it is highly susceptible to sensor position and wrist movements *[12]*.

Figure 2.8 Tonometric method for measuring blood pressure. [12]

Volume-clamp method

The volume-clamp approach consists of keeping constant ("clamped") the diameter of an artery under a cuff wrapped around the finger, at a certain value ("set-point"), regardless of the changes in arterial pressure during each heartbeat. As shown in *Figure 2.9*, a volume-clamp tool is composed of an infrared light-emitting diode (light source) and an infrared photodiode (light detector) and an inflatable air bladder

connected to the frontend unit via an air hose. This plethysmograph is built into a finger cuff and allows the detection of diameter changes *[13]*.

If during systole arterial diameter increased, the pressure of the finger cuff is instantly raised by a pressure servo controller system to anticipate the diameter change and in this way the device can track the BP as a beat-to-beat tracing. The blood pressure measured on a finger is considered to correspond to the aortic blood pressure in healthy patients, but for them with hypothermia, low peripheral perfusion or low-flow states this relationship fails, so it is not the most reliable method to use.

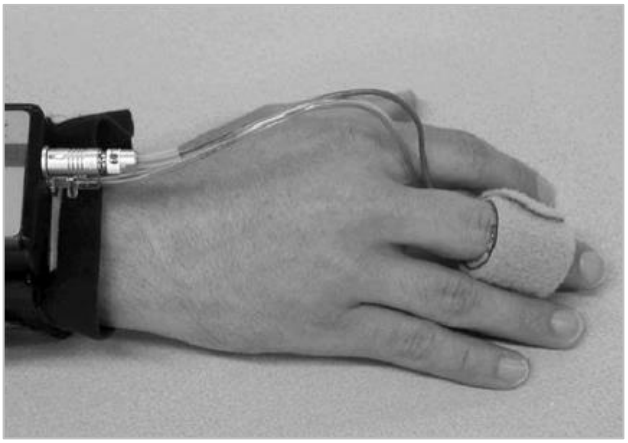

Figure 2.9 Volume-clamp method for measuring blood pressure. [12]

2.3 Blood pressure estimation using other physiological parameters

The cuff-less continuous non-invasive BP estimation is more advantageous for people to systematically monitor their blood pressure. In recent years, the blood pressure estimation using other physiological parameters has been extensively studied. This section will report and review these methods, specifically Pulse Transit Time based BP estimation and a photoplethysmographic approach are considered. Both techniques use PPG to have an indirect estimate of blood pressure, but in the first case the pulse transit time (PTT) is directly correlated with pressure and to calculate this time it is necessary to acquire beyond the PPG, also the ECG. Instead, in the second technique, it is sufficient to record only the photoplethysmographic signal that, through a step of machine learning (linear regression), allows to directly extract the BP values. Before reviewing the state of the art of these two techniques, general overviews on ECG and PPG signals are reported.

2.3.1 The Electrocardiographic signal (ECG)

During the cardiac cycle, a part of the cardiac tissue is depolarized, or in a contraction phase, and another part is polarized, or rather at rest, resulting in a charge separation and constituting an electrical dipole. The moving dipole creates fluctuating electric fields throughout the body.

An "electrocardiogram" is a measurement of electrical activity due to heart muscle depolarization and its changes over time. As shown in *Figure 2.10*, the ECG waveforms result from the electrical potential differences when during the cardiac cycle ventricles and atria depolarize and repolarize.

Although it deals with very small electrical variations, ECG electrodes attached on the surface of the skin can pick up it reliably, detecting the voltage of these electric fields. It gives rise to the electrocardiogram, a signal of voltage versus time, generally displayed in millivolts (*mV*) versus seconds.

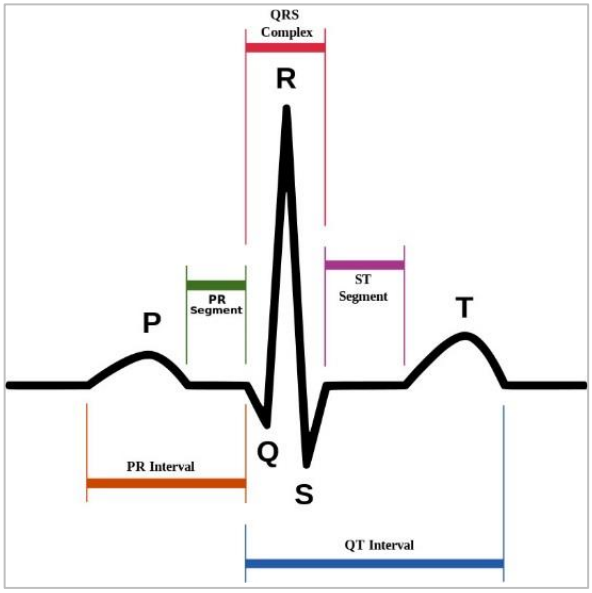

Figure 2.10 A typical Lead II ECG waveform. [14]

The *Figure 2.11* shows the beginning of a cardiac cycle in the right atrium with the firing of the sinoatrial node, which does not correspond to an ECG wave because it does not consist of enough cells to produce an electrical potential with high enough amplitude to be detected with distal electrodes. The sinoatrial node depolarization is transmitted quickly throughout right and left atria, originating the *P-wave*. It is in general approximately 80–100 milliseconds (*ms*) in duration, representing the atria depolarization and the beginning of atrial contraction.

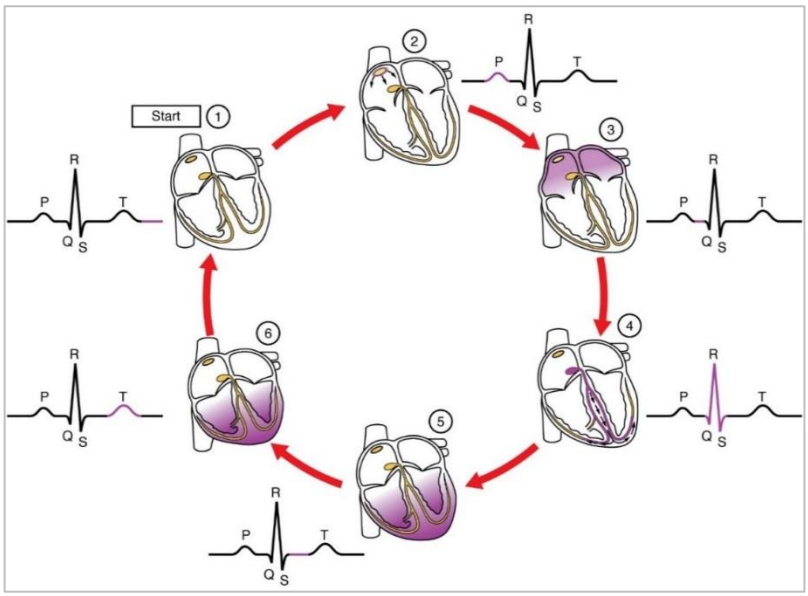

Figure 2.11 Electrical conduction in the heart.

Then the electrocardiographic signal returns to baseline while action potentials (not large enough to give rise to a wave) spread through the atrioventricular node. The detected *QRS complex*, that is around 100 *ms* in duration, corresponds to both the ventricles depolarization, which starts approximately 200 *ms* after the beginning of the *P-wave*. The *QRS complex* is composed of the *Q-wave*, the first negative deflection, the *R-wave*, the large positive deflection, and if there is a negative deflection immediately after, it is named the *S-wave*. Subsequently, the ventricles are totally depolarized and the contraction begins. At the same time, the atria end their contraction and repolarize, but the effect of the atrial repolarization is sufficiently covered by the ventricular depolarization which involves a larger amount of tissue; consequently, it is not generally distinguished in the ECG signal.

Subsequently, the ECG returns to baseline, before the end of ventricular contraction and their repolarization, originating the *T-wave*, or rather the last detected potential in the cardiac cycle.

Placement of electrodes

Typically, ECG electrodes are wet sensors, used together with a conductive gel to get greater conductivity in the skin-electrode interface.

The several positions of electrodes placement differ in the morphology of the resulting ECG signal. Generally, an ECG may be obtained with electrodes placed in different locations or with several configurations. Nowadays, the commonly-held lead positions are three: bipolar limb leads, unipolar augmented limb leads and precordial leads.

In the first configuration of electrodes, imaging the torso of the body as an equilateral triangle, known as "Einthoven's Triangle", where each vertex corresponds to an electrode placement. The ECG traces are measured among such electrodes as follows:

- **Lead I:** left arm (LA) versus right arm (RA) electrode biopotential;

$$V_{LA} - V_{RA} = V_I \tag{2.1}$$

- **Lead II:** left leg (LL) versus right arm (RA) electrode biopotential;

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

- **Lead III:** left leg (LL) versus left arm (LA) electrode biopotential.

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

Figure 2.12 indicates the polarity of each lead measurement, according to the universal convention. The positions of the electrodes placed on the vertices of the triangle can be the wrists and left ankle, as well as the shoulders and lower torso *[16]*.

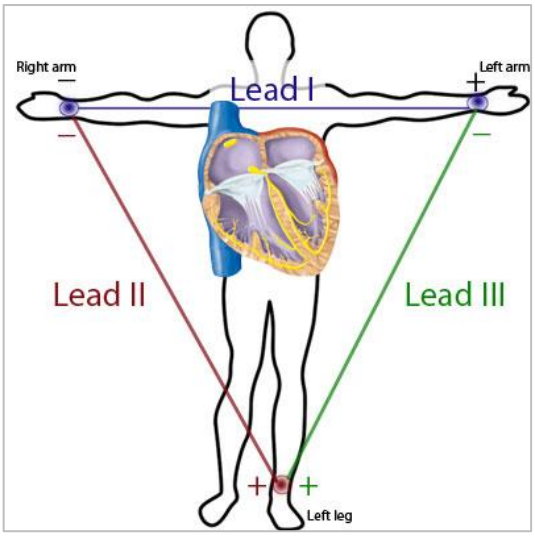

Figure 2.12 Bipolar limb leads. [15]

The unipolar augmented limb leads are shown in *Figure 2.13.* The electrical potential is acquired between one limb electrode and a virtual electrode created connecting together the remaining two limb sites (neutral reference lead). In this way the positive lead of the ECG is represented by the single limb lead, whereas the negative one is virtually located in proximity of the heart and it is represented by the neutral reference lead. Thus, there are three unipolar derivations in the limbs, each of them called:

- **Lead aVL (Augmented Vector Left):** left-arm limb lead versus neutral reference lead electrical potential;

- **Lead aVR (Augmented Vector Right):** right-arm limb lead versus neutral reference lead biopotential;
- **Lead aVF (Augmented Vector Foot):** left-leg limb lead versus neutral reference lead biopotential *[16]*.

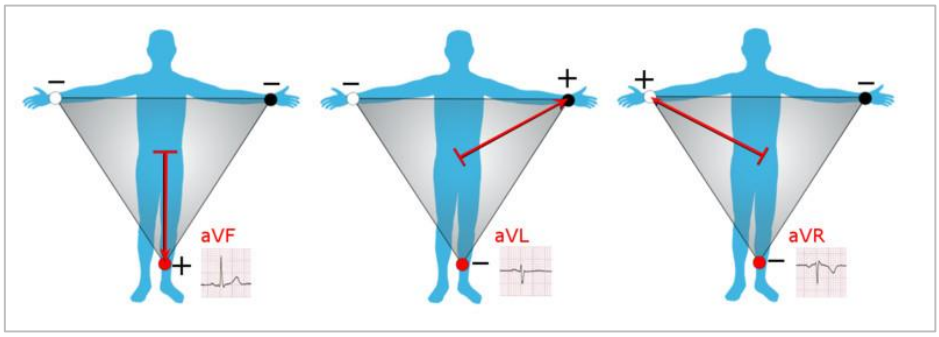

Figure 2.13 Unipolar augmented limb leads. [56]

Even the precordial or chest leads are unipolar, measuring electrical activity in the traverse plane instead of the frontal plane. The neutral reference lead is virtually created by connecting all the three limb leads, similarly to the unipolar limb leads. On the other hand, the positive or "exploring" electrodes are placed around the chest with the following configuration (*Figure 2.14*):

- **V1:** right sternal 4th intercostal space;
- **V2:** left sternal 4th intercostal space;
- **V3:** halfway between V2 and V4;
- **V4:** mid-clavicular line 5th intercostal space;
- **V5:** anterior axillary line 5th intercostal space;
- **V6:** mid-axillary line 5th intercostal space.

Precordial leads, thanks to their proximity to the cardiac muscle, allow to identify and localize the possible heart damage with more accuracy than the other electrodes configuration *[16]*.

Generally, electricity moves through the heart following an imaginary diagonal line from the right shoulder to the left lower abdomen. Therefore, different leads may lead to different ECG morphologies *[17]*.

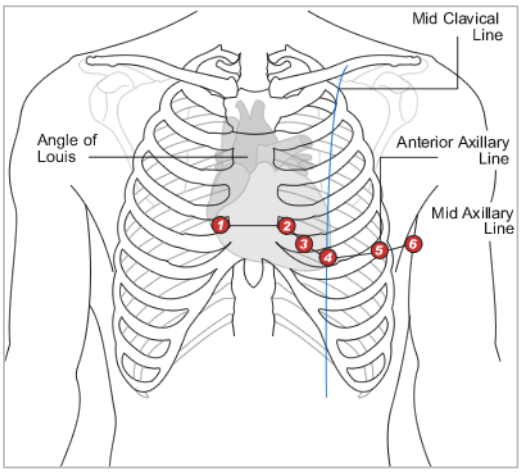

Figure 2.14 Precordial leads. [17]

2.3.2 The Photoplethysmographic signal (PPG)

The use of photoelectric plethysmography, as all the optical techniques, in biomedical monitoring and diagnosis is becoming progressively widespread, first of all because of the non-invasive nature of optically derived measurements *[18]*.

The word "plethysmograph" derives from the union of two ancient Greek words: "plethysmos" which means increase and "graph" which means writing. It is also called Digital Volume Pulse (DVP) *[19]*.

It is a device useful to identify and report the changes in blood volume or flow, which occur throughout the whole body during each cardiac cycle. PPG is acquired by means of an optical measurement technique that does not need direct contact with the skin surface. Indeed, it employs an invisible infrared light sent into the tissue by a photodiode (at a wavelength of around 900 *nm*) and the amount of the backscattered light collected by a photodetector (typically a phototransistor) is linked to the variation of the blood volume. An increase in blood volume points to a decrease of backscattered collected light intensity and vice versa.

Different substances, including pigments in the skin, bone, arterial and venous blood, can absorb light travelling through biological tissue. In 1938 Hertzman found a relationship between the blood volume and the intensity of backscattered light. The convenience, simplicity and cost effectiveness of this technology could offer significant benefits to healthcare.

As shown in *Figure 2.15*, the wave contour of PPG signal, whose distortions represent the effects of blood movement in the vessel, is simple but it is difficult to detect changes in the phase of the inflections. Then, PPG signal first and second derivative were introduced to facilitate the interpretation of the original PPG waves.

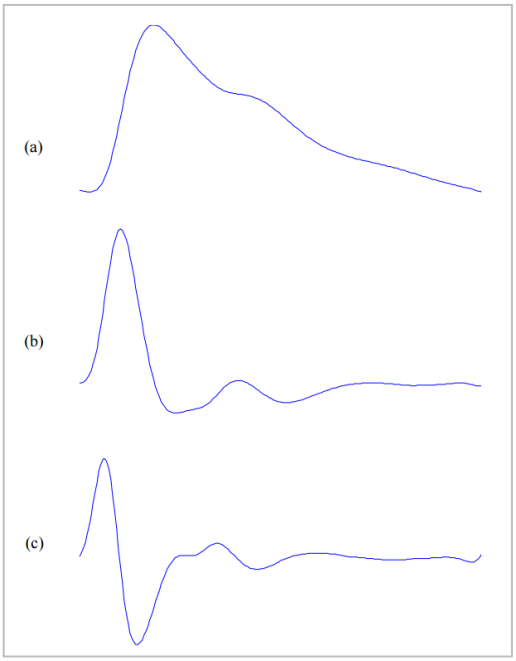

Figure 2.15 (a) PPG signal (b) First derivative (c) Second derivative. [19]

A photoplethysmographic waveform (*Figure 2.16*) is made of slowly alternating DC (direct current) and pulsatile AC (alternating current) components.

The direct current component is related to the tissue structure and the average blood volume of both arterial and venous blood. It represents the detected optical signal (transmitted or reflected) from the tissue. Moreover, this contribute depends slightly on respiration.

The AC component results from the blood volume changes that occur between systole and diastole. Representing the vascular pulsations with each cardiac cycle, the main frequency of this contribute changes with the heart rate *[20]*.

A PPG pulse can be divided qualitatively into two phases: the rising edge of the pulse is called anacrotic phase that concerns with the systole, whereas the catacrotic phase is the falling edge of the pulse and concerns with diastole and wave reflections from the periphery. Most of times, in subjects with healthy compliant arteries, there is a dicrotic notch in the catacrotic phase *[19]*.

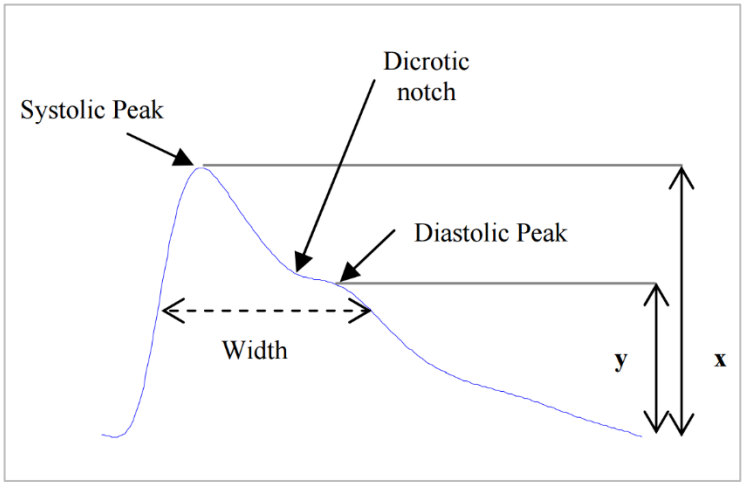

Figure 2.16 A typical waveform of the PPG and its characteristic parameters. [19]

The PPG waveform presents the following features, well described in literature:

- **Systolic amplitude:** in *Figure 2.16* it is represented by x and indicates the pulsatile changes in blood volume around the measurement location.
- **Pulse width:** usually measured as the pulse width at the half height of the systolic peak, it is linked to the systemic vascular resistance.
- **Pulse area:** it is calculated as the subtended area of the photopletismographic waveform.
- **Peak to peak interval:** it is the interval between two consecutive systolic peaks in the PPG signal (*Figure 2.17*). It is closely linked to the R-R interval in an electrocardiographic signal because both of them correspond to a complete cardiac cycle.
- **Pulse interval:** in the same cardiac cycle, the interval between the beginning and the end of the photopletismographic curve in the same cardiac cycle is named the pulse interval (*Figure 2.17*).
- **Augmentation index:** it is defined as the ratio of the height of the diastolic peak y and the systolic peak x in the pulse. (*Figure 2.16*)

$$AI = \frac{y}{x} \tag{2.4}$$

- **T1:** it is the interval of time between the systolic and diastolic peaks. The definition of T1 depends on the photopletismographic waveform since its contour depends on subjects. In absence of a second peak in the PPG curve,

this time interval is calculated between the systolic peak and the point of inflection in replacement of the diastolic peak.

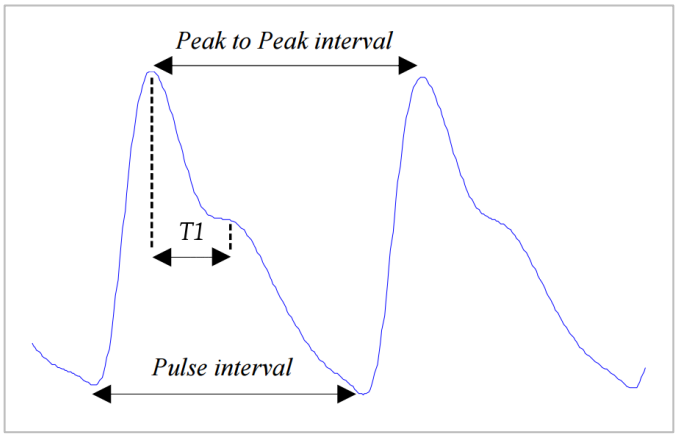

Figure 2.17 Two consecutive PPG waves. [19]

2.4 State of the art: BP estimation using signal processing techniques

In this section, some studies and works about PTT-based and PPG-based blood pressure estimation are reported.

2.4.1 The Pulse Transit Time based method

Arterial system is the network of blood vessels that is responsible for carrying the oxygenated blood from the heart to the peripheral organs and tissues. This system is composed by vessels of different kind and presenting different mechanical characteristics. Some vessels like aorta are very elastic other, especially those located in the limbs, are more muscular. The artery elasticity is a distinctive aspect directly related to the capacity of the vessel to increase its volume in response to the blood pressure rise.

Considering the aim and the peculiarities of the vascular system it is possible to monitor its activity by means of an external pressure transducer located on well know specific sites. On the neck area it is possible to detect the carotid artery activity, close to the groin it is possible to check the femoral artery pulse and on the wrist is present the radial artery pulse. Generally, the detectable pulse related to heart beat is known as Sphygmic Wave, Wave Pulse, or Arterial Pulse. Observing the evolution of such an

externally acquired pulse it is possible to recognize a shape similar to the pressure trend acquired by an invasive intraarterial catheter.

Pulse Transit Time (PTT) is generally defined as the time taken by a pulse wave to travel between two cardiovascular sites. It is commonly considered as an indicator of arterial stiffness and can be adopted as an indirect mean to estimate blood pressure.

PTT can be measured as the time difference from a characteristic point of the PPG signal to the R wave peak of the electrocardiogram in the same cardiac cycle. It represents the blood pulse propagation period from the heart to a peripheral site. As shown in *Figure 2.18*, different choices can be done as PTT ending point: the foot, the peak or the point of maximum slope of the PPG signal.

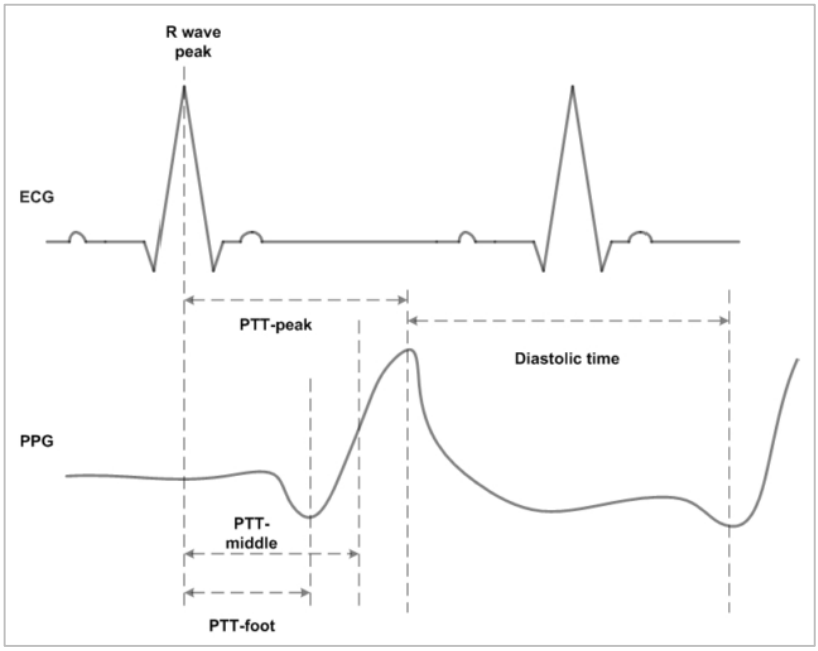

Figure 2.18 The descriptions of different PTT intervals: PTT peak, PTT middle and PTT foot. [21]

In literature, since 1976, when Gribbin et al. first inserted PTT in the area of blood pressure estimation, researchers have examined the performance and the reliability of this method. In 1979, Obrist suggested PTT as an index of blood pressure. Few years later, in 1983, Lane analyzed the correlations among PTT and SBP, DBP, and MAP through experiments and found the dependence on individuals. Many researchers have characterized such correlations with different expressions between BP and PTT. Two relationships among the most efficacious ones, widely used and extended, are Moens-Korteweg's *[22]* and Bramwell-Hill's *[23]*. Fundamentally, these researchers recognized the correlation between the elasticity of an artery and the velocity of the volume pulses that propagate through it. When blood pressure increases, the arterial

compliance is reduced, the pulse wave velocity is higher and PTT goes down. Consequently, the Pulse Transit Time based method is to apply the relationship to estimate blood pressure.

Moens and Korteweg defined the pulse wave velocity (PWV) considering the contribution of several parameters: the height of vessel wall t, the elasticity of the arterial wall, the density of blood ρ and the interior diameter of the vessel d. The final expression of the deducted function is *[22]*:

$$PWV = \sqrt{\frac{tE}{d\rho}} \tag{2.5}$$

where E is the Young's modulus related to the elasticity of the vessel wall and generally it is not a constant. More in detail, the Young's modulus E can be expresses as $E = E_0 e^{\alpha P}$ *[22],* where E_0 is the Young's modulus at zero pressure, α is a constant quantity specific for the considered vessel, normally in there range from $0.016 mmHg^{-1}$ to $0.018 mmHg^{-1}$, P is the blood pressure and e is the base of natural logarithm (2.71828). Then the expression is:

$$PWV = \sqrt{\frac{tE_0 e^{\alpha P}}{d\rho}} \tag{2.6}$$

The pressure wave velocity can also be expressed as:

$$PWV = \frac{L}{PTT} \tag{2.7}$$

where L is the distance between the pulses acquisition sites and PTT is the pulse transit time. Therefore, it is possible to equal the two expressions of PWV:

$$\frac{L}{PTT} = \sqrt{\frac{tE_0 e^{\alpha P}}{d\rho}} \tag{2.8}$$

According to this, the relationship between the blood pressure and PTT is inversely proportional as well as individual-dependent. Hence, the linear regression has been applied in estimating the blood pressure: indeed, the model coefficients are first determined on experimental data and then used for blood pressure estimation *[22]*.

In 1981, Geddes et al. tried to measure DBP and pulse arrival time to investigate the relationship using 10 anesthetized dogs. They pointed out that PTT was highly related to diastolic time, detecting it in different sites along the vessel *[24]*. Marie et al. addressed the Pulse Transit Time and BP correlation during dynamic and static exercise *[25]*. In 1988 Okada investigated about some factors (age, SBP, DBP, phospholipid) that might be correlated to pulse wave propagation velocity. In his work the used transmission time was obtained from fingertip to toe tip *[26]*. In 1996 Franchi et al. studied ECG, the peripheral PPG and the intra-aortic pressure. They obtained the

relationship between BP and two delays: from aortic pulse to ear lobe pulse and from ECG R-wave to the aortic pulse *[27]*.

In the decade from 2000 to 2010, the estimation of blood pressure using the Pulse Transit Time has been widely experimented. In 2002, Nitzan et al. made a comparison between the time difference from ECG R-wave to the arrival time at the toe and the time delay between the finger and the toe. Both of them are related to pulse wave velocity and showed a good correlation with SBP (coefficients of -0.670 and -0.515 respectively) *[23]*. In 2004 Fung et al. investigated on the relationship between Pulse Transit Time and blood pressure, using two additional variables: the kinetic energy of the wave and the gravitational potential energy *[28]*. In the same year, Lass et al. suggested the possibility of estimating SBP using PTT beat to beat during a dynamical activity *[29]*. The auscultatory method was used to measure blood pressure at the end of each recording minute and a continuous measurement device was also applied to record the beat to beat BP during the test. In 2005 Park et al. analyzed the possible use, besides of PTT, of other physical parameters, as arm length and weight, to obtain SBP estimation *[30]*. In 2009 the main work of Yoon et al. was to identify which characteristics extracted from PPG and ECG were more reliable to evaluate DBP and SBP *[31]*. The results indicate that the correlation between SBP and the Pulse Transit Time, calculated as the interval between ECG R-wave and the point of maximum slope on PPG signal, was considerable; and diastolic time from PPG presented good correlation to DBP. Moreover, both for SBP and for DBP, individual regression method was more reliable.

Heart rate was introduced to estimate BP combined with pulse arrival time by Cattivelli and Garudadri in 2009 *[32]*. The results led to declare a better performance in comparison with the method only using pulse arrival time for the estimation of blood pressure.

The aim of the experiments in "The role of pulse transit time as an index of arterial stiffness during exercise" *[33]*, by Kounalakis and Geladas, addressed steady state exercise to verify if PTT can estimate SBP. The results were positive, and they indicate that PTT was somewhat linked to cardiac output, blood pressure and arterial stiffness changes during exercise, but not directly used to estimate BP if applied alone. In the study, twelve male subjects cycled for 70 minutes in three different conditions, with a continuous measure of BP, PPG, ECG, cardiac output and respiratory frequency. The results pointed out a correlation between the changes of PTT and SBP, with a coefficient of -0.65; however, the data analysis reported that Pulse Transit Time variability only could be ascribed to SBP only on the 29% of the cases. Foo and Wilson *[34]* re-examined the clinical applications of PTT-based method and his pros and cons. Eventually, such applications could be in respiratory sleep and cardiovascular areas, and this method had potential to use for small infants during critical care. The PTT method provides the beat to beat readings, unlike the conventional non-invasive BP

measurements, that, additionally, face the issues of selecting the proper cuff size and position to have higher accuracy.

More recently, Zhang from Chinese University of Hong Kong and Muehlsteff from Philips Research Europe, respectively, have studied this PTT-based method. Their results will be described in the following paragraphs.

Since 2005, the group of Zhang collected continuous BP, PPG and ECG signals from 11 volunteers with healthy body state, showing how pulse transit time can be used to calculate roughly blood pressure *[35]*. In another related work *[36]*, they discovered that the PTT-based method could be applied in wearable devices. In 2006, experiments were conducted during dynamic exercises and they compared the results with the measurements by a non-invasive blood pressure monitoring device. They noticed that there was only occasional discrepancy during the recovery period after exercise *[37]*. Subsequently they introduced a model trying to solve individualized calibration problem, as this method is dependent on individuals *[38]*.

Because the experiments were executed before indicating that estimated PTT was influenced by the contact force between the fingertip and the PPG sensor, they proposed a theoretical modeling covering also the pressure applied to the sensors in 2007. Examining the provided results, it was evident that increasing the pressure on the sensor, PTT went up. So they suggested to control carefully the sensor applied on the fingertip during the experiments to ensure reliable PTT values *[39]*.

In 2008 they indicated also another element to which pay attention: the effect of pre-ejection period on the blood pressure estimation. They systematically noticed the inclusion of pre-ejection period in Pulse Transit Time for BP estimation *[40]*. Since BP was differently related to PTT in time, accurate beat to beat blood pressure estimation required a frequent calibration. They used least-squares regression to estimate BP in the first test and in a repeatability test performed 6 months later, using the regression coefficients of the first test *[41]*. The results pointed out that, during the recovery period after exercises, BP went up and PTT went down, and SBP was related to PTT. Nevertheless, regression coefficients acquired during the first test didn't allow an accurate blood pressure estimation on the other test.

This topic has also been explored by Philips Research Laboratories Europe. In 2006, they investigated the influence of pre-ejection period on pulse arrival time more than PTT *[42]*. In a work of 2007 *[43],* they showed the correlation of SBP with pulse arrival time, as a combination of PTT and pre-ejection period. In 2008, they explored an application of PTT-based method: a wearable body sensor network, with a wireless data transmission described in *[44].* They collected information on physical activity and posture of persons on which were conducted experiments, studying their influence on the PTT measurement *[45]*.

As PTT has been accepted as an indicator of BP estimation, another application has been explored: the health monitor systems. Heard et al. tested the DxTek monitor in 2000. They used the continuous and non-invasive PTT-based blood pressure estimation, ensuring an accuracy comparable to oscillometric devices *[46]*.

In 2006 the Wearable Intelligent Sensor and System for e-Health was developed, monitoring the continuous health condition and displaying it, additionally, treatment and alarming can be adopted and configured *[47]*. Part of the system is composed by a wearable health-shirt. In their test experiments, continuous vital signals, including PPG, ECG, SBP and DBP, were recorded for 15 minutes, as the combination of 5 minutes of pre-exercise, 5 minutes of riding on a bicycle and 5 minutes at rest. Analyzing the results, it is evident that the error of the estimated BP was quite high. The smart vest, a wearable multi-parameter remote physiological monitoring system, was developed to monitor body temperature, ECG, PPG, heart rate and, applying PTT-based method, SBP and DBP *[48]*.

Recently PTT-based blood pressure estimation method has gained deal of attention. Indeed, it gives reasonable good results, but so far there are no devices on the market that use this approach, whether portable or not. All the reported works at most have led to some prototype devices or some patents, despite all positive conclusions declared. There are still fields of study that have to be examined in depth and that influence results, like for example the signal processing procedure that would be studied to improve the accuracy of the method.

2.4.2 The photoplethysmogram signal based method

Blood pressure predictions based on pulse transit time requires PPG together with a simultaneous ECG acquisition, with the consequent need of electrodes placed on the addressed subject. In order to accomplish a simpler measurement, some attempts were made to estimate blood pressure directly from a simple PPG signal.

In order to estimate BP, the photoplethysmographic signal could be investigated considering also a spectral analysis. Teng and Zhang chose four features of PPG signals: width of 2/3 pulse amplitude, width of 1/2 pulse amplitude, systolic upstroke time and diastolic time *[49]*. In the analysis of PPG signals, obtained from 15 young healthy subjects, they used continuous wavelet transform (CWT) to address the issues related to the uncertainties linked to sphygmic wave foot position recognition, fundamental to have a reliable feature identification. Linear regression line in the form of $y = ax + b$ was adopted for SBP and DBP respectively using the data of some trainings. Then some other trials on the same subject were used to estimate BP. The results pointed out a high correlation of the systolic upstroke time, diastolic time and the photoplethysmographic signals with BP. In general, they noted a better efficiency

in the estimation of DBP, with the mean differences using systolic time and diastolic time, respectively, but performance in the SBP estimation was not satisfactory *[49]*.

Yan and Zhang proposed a new characteristic, normalized harmonic area (NHA), acquired from the photoplethysmographic signal in the frequency domain and claiming an high correlation with blood pressure *[50]*. They used the discrete period transform algorithm, particularly useful in the treatment of low frequency signals (such as PPG), to estimate the amplitude spectral analysis of each beat. The experiments were conducted on 28 healthy persons, aged 24-30 years, proving that NHA allow smaller error than both PTT and diastolic time in BP estimation with an improved correlation. The mean differences and standard deviations between the BP estimated from NHA and the reference BP obtained from a standard sphygmomanometer are 0.37 ± 4.3 *mmHg* and 0.47 ± 4.8 *mmHg* for SBP and DBP, respectively *[50]*. For blood pressure estimation it was employed a linear regression curve, obtained in a calibration phase from the same subjects, then adopted on the following test phase. However, the physiological mechanisms of the relation are not yet fully explored.

In a work from Seoul National University of Technology in 2006 *[31]*, only systolic upstroke time and diastolic time were used as parameters to predict SBP and DBP.

The experiment was carried out with five subjects on five different days. Also in this case, a linear regression analysis was set up for the data set of each subject (individual calibration). The estimation of blood pressure was done with the "leave-one-out" method, using four days for calibration and one day as test. Results showed that diastolic time was a better choice for DBP prediction (correlation coefficient of -0.764) whereas SBP had the same correlation coefficient (-0.605) with respect to the systolic upstroke time and the diastolic time but the first parameter was favorite to estimate SBP.

A remarkable example of a system able to evaluate the systolic and diastolic BP trends only approaching the PPG signals was discussed in *[51]*. PPG signals were captured using mobile devices and these signals were used for feature extraction, computing 14 features, starting from systolic peak, valley point and dicrotic notch points, in addition to the subject's height, weight and age. These extracted features were modeled through a linear regression model and by the adoption specific Support Vector Machine (SVM). Those two mathematical descriptions were used to evaluate not the exact blood pressure values but BP bin levels. The test phase was implemented over PPG signal from a mobile device as well as with a standard data set from an internet database. Linear regression better fits on low noise signals from standard data set instead SVM performs better, and with preferable results, on noisy signals acquired by mobile phone.

Another approach where specific PPG features were analysed and linked with the arterial blood pressure, was that of Samria et al. *[52]*. In this study, in addition to

Systolic Upstroke Time (SUT) and Diastolic Time (DT) parameters extracted also in other works, it was also considered a new feature that is the time interval between the systolic and diastolic peak (called T1). A statistical description of diastolic and systolic blood pressure linked to SUT, DT and T1 was given, also in this case, by linear regression line. Signals were measured on 22 subjects from different age groups (18-25 years and 26-50 years). On subjects between 26 and 50 years, the correlation between DBP and the T1 was very high (achieving a value of -0.923 as correlation coefficient), while the correlation between SBP and diastolic time was still good with a correlation coefficient of -0.869. Subjects from the 18-25 age group reported the highest correlation between DBP and diastolic time, with a correlation coefficient of -0.811 but in this age group not proper correlation was found for systolic blood pressure.

The same considerations made for the state of the art analysis of PTT method, can also be made in this case. All examined works provide more or less satisfactory results in terms of correlation between blood pressure and photoplethysmographic signal but none of these shows really a comparison between the pressure values estimated through the algorithm and the blood pressure ground truth, detected through a clinical device. In this way it is not possible to have an effective feedback on the accuracy of the inferred pressure. It should also be highlighted that experiments were often carried out in patients under strictly controlled conditions that do not reflect the measurement conditions of a portable device that could be based on this method.

2.5 Overview of the employed tools

For the realization of this work, the resources used were:

- the Matlab computing environment, which allowed to develop and verify algorithms;
- the PhysioNet web signals archive, from which some processed signals were obtained in order to check algorithms behavior;
- the GE Healthcare S/5 clinical monitoring equipment, thanks to which was possible to collect data and signals from different patients in hospital.

2.5.1 Matlab

Matlab is a high-level interactive framework for numerical computation, visualization, and programming. Using this tool as development environment, it is

possible to easily analyze data and perform signal processing. It is possible to generate, measure, transform, filter, and visualize signals. Furthermore, the language, tools, and built-in math functions enable to validate algorithms and application routine rapidly with immediate visual feedback through plots.

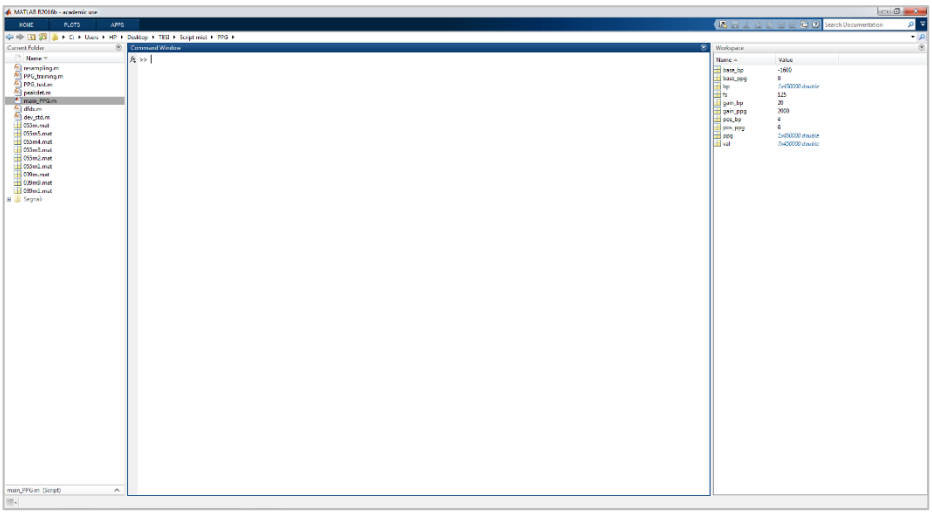

Figure 2.19 The Matlab work environment, with the central command window.

2.5.2 PhysioNet

PhysioNet is a web-based database which contain digital recorded physiologic signals, very useful for the biomedical research. Signals are freely accessible through the proper archive on the website, which is called PhysioBank (*Figure 2.20*). PhysioBank's collections are organized into more than 50 databases, each containing a number of records, and each record containing information collected from a single subject. Archives include several kinds of biomedical signals and parameters covering both healthy subjects and patients with a plurality of health conditions.

In the input panel of PhysioBank it is possible to choose a database from the list, the record and the signal (waveform) of interest. Then the output section allows to choose the length of the record, the starting time and data format of the samples. Once the data to examine are specified, from the toolbox menu it is possible to select the desired tool, like for example plot waveforms graphically or export signals in Matlab format.

In this work, the chosen database, where the signals of interest are taken, is the MIMIC database (Multi-parameter Intelligent Monitoring for Intensive Care). It includes over 90 patient records, with a length up to 48 hours of continuous data collected from patient monitors in the medical, surgical, and cardiac intensive care units (ICU) of Boston's Beth Israel Hospital, between 1992 and 1999.

Patients recorded were selected from those showing hemodynamic variability during the considered recording period. The gathered physiologic signals contain ECG and blood pressure signals, heart and respiration rates and other parameters like for example photoplethysmographic signals. Blood pressure is recorded using a radial intraarterial catheter, in this way an accurate and continuous monitoring is possible.

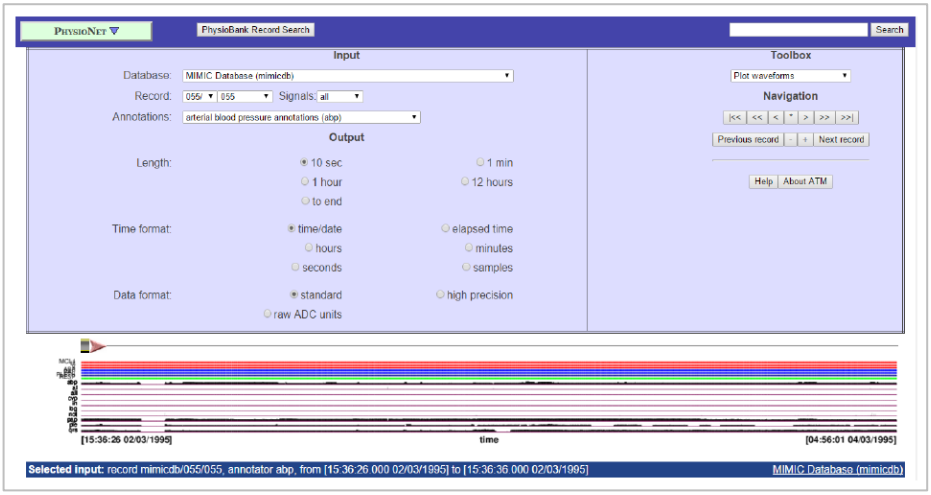

Figure 2.20 PhysioBank toolbox interface, from where it is possible to explore the archive, choosing the database, the patient, the type of signal and then export the selected data. (http://www.physionet.org/)

2.5.3 GE Healthcare S/5

The GE Healthcare S/5 iCentral allows a hospital wide connectivity, monitoring up to 32 patients with a view of patient vital sign measurements made at the bedside, supported by a wide spectrum of clinical information (*Figure 2.21*).

Data is grouped to organ specific cardiac, circulation, ventilation and brain views. It stores up to 72 hours of waveforms and numerical trends.

The GE Healthcare Network manages the network link between the GE Healthcare bedside monitors and other networked devices in the monitor network, transferring information between all the devices and iCentrals (in particular up to 1024 monitors, 32 iCentrals and 32 iCentral clients). It allows a connected device to manage and process information received from all the equipment available on the network

Furthermore, it coordinates also the transfer of information between the GE Healthcare Network and Hospital Information Systems (HIS).

Figure 2.21 GE Healthcare S/5 iCentral, networked with the monitors bedside and all the other devices in the monitor network. On the right screen, an example of monitoring of 8 patients with their vital sign measurements made at the bedside. On the left screen, a viewing of one patient more in detail.

GE Healthcare S/5 Collect is the software used to interface on the network of patients' data and whose use allows to record and acquire high-resolution physiological signals.

It is a LabVIEW application designed for recording acquired data from various GE Healthcare monitoring solutions to a PC for analysis. It allows to collect trend, waveform and alarm data from minutes to days directly from a monitor connected in the network. Through the GE Healthcare S/5 Central user interface is then possible to real-time check parameters and signals of a specific patient and store data for an off line analysis.

In online mode, the collected data can be saved in .drc files (Datex Record Interface format) for further analysis in offline mode.

In offline mode, it allows converting physiological data files archived by the GE Healthcare S/5 Central into .drc format, and back.

Chapter 3

Strategy Adopted

A wide literature research allowed to identify several methods able to estimate blood pressure values from just a photoplethysmographic signal or from the pulse transit time, that is using both photoplethysmography and electrocardiogram. Being a topic where study and research are still in progress, and also because results in literature are not really exhaustive and they are not shown in a clearly way, it is currently difficult to say which is the better and more reliable approach. Indeed, each of these strategies denotes critical and positive aspects in various situations and for different patients.

3.1 Problem statement

As a first stage of the thesis work, several critical aspects of the application have been identified and analyzed in order to understand what is the optimal approach and what could be the minimal requirements necessary to reach a good outcome.

Problems identified from a general and initial overview are:

- Considering the many available methods reported in literature and focused on the cuff-less and non-invasive blood pressure estimation, it is indispensable to identify and validate an appropriate technique characterized by strong robustness and reliability. None of the investigated papers have shown clearly the results of their works, comparing the values of their estimations with the measured BP values, therefore it is necessary to test the different approaches, adapting the methods to our experimental designs.
- Blood pressure variations are a very slow event in non-pathological subjects in normal conditions, in fact several tens of minutes are necessary to show significant changes. This leads to a processing of a large amount of data, a lot of BP recording hours need to be analyzed to have relevant results. Therefore, to validate an estimation algorithm, long duration recordings for the same subject have to be available.

- A quite high medium age of the analyzed patients could be a problem for an algorithm which estimates the BP, especially when addressing only the PPG signal features. This is because, as reported in literature and as shown in *Figure 3.1*, the time delay between the systolic and diastolic peaks decreases and the diastolic peak becomes less evident with age as a consequence of increased large artery stiffness *[19]*. Moreover, the depth of the dicrotic notch seems to vary with different test conditions. A subject at rest shows this point at a position and depth different from a subject after exercise; hence, the determination of the diastolic peak may change *[50]*.

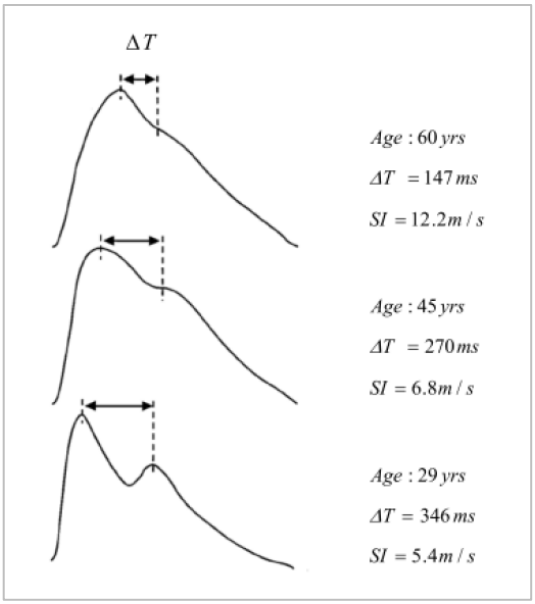

Figure 3.1 Typical PPG waveforms show the parameter T1 changes with age. [19]

- To conduct direct experiments on patients may help in preventing measurements with invalidating events and knowing something more about the limits of blood pressure estimation using physiological signals. It allows to control all the variables involved during the recordings, such as health conditions of patients during the measurements, their movements, positioning of sensors, etc.
- Acceptable mean error in blood pressure estimation, for both SBP and DBP, has to be less than 5 *mmHg*, while the mean error standard deviation must not be in excess of 8 *mmHg*. This according to the American National Standards of the Association for the Advancement of Medical Instrumentation (AAMI), an organization responsible for the safety and efficacy of medical instrumentation.
- The output of the algorithm must be systolic and diastolic blood pressure values, but it is important to define at which time interval the results have to be provided.

Having pressure estimated values on every heartbeat will turn into a redundant amount of information and the available computational time will reduce, therefore it is more useful and cost-effective to generate output in some minutes, as it could be a continuous measurement of BP by a sphygmomanometer.

3.2 Addressed solution

Considering the consumer market segment, a reasonable goal is to develop an algorithm for a wearable device the least possible invasive, therefore taking less signals as possible from the body, so it was preferred to examine the standalone photoplethysmographic signal at first. On the other hand, it was decided to develop the PTT-based technique, which is more suitable for a medical environment, requiring the additional ECG information.

The envisaged PPG feature based method consists in recording, from the body, only the photoplethysmographic signal and, computing a linear regression function, estimating the SBP and the DBP of the subject. In the linear regression approach, one of the basic time parameters of the PPG waveform is correlated with the BP values, in order to perform a linear dependence between the variables.

The first step of the study is therefore to evaluate what is the PPG feature having the highest linear correlation with the SBP and DBP recordings. In literature different features have been proposed, so at first it is necessary to choose the parameter which guarantees the best correlation. After this phase, it has been started with the definition and development of the algorithm.

It forcedly consists in two phases, one for the calibration and the second of testing, where the trained algorithm is applied to the signals and the BP estimation process really happen. The initial training phase, performed for each subject, needs a recording of BP realized using an existing accurate blood pressure meter. The BP measurement is correlated with the simultaneous PPG signal in order to define the model which is then used to estimate SBP and DBP.

The calibration phase is certainly a limit for a portable device but, firstly, this solution is a first step in this direction and, secondly, the goal of the conducted analysis is also to demonstrate that after a calibration phase, the model is able to estimate BP values for long time periods without updating the algorithm or re-computing its key parameters.

The second proposed technique is less oriented to the portability, so it is less suitable for an implementation in a wearable device, because it needs to record an ECG signal in addition to the PPG one. However, its advantages are first of all a less important

calibration phase and secondly it relies on well described biomechanics phenomenon. In fact, this method consists in the application of the Moens-Korteweg equation to the calculated pulse transit time, in order to estimate the SBP and DBP values.

As described in the previous chapters this formula links the PTT and BP trends. The PTT is calculated as the time interval between the R peak of an ECG wave and a characteristic point of the corresponding PPG wave, therefore the algorithm has to locate these features on the signals, calculate the PTT intervals and give these times in input to the Moens-Korteweg equation.

A kind of calibration is necessary also in this method, because the equation contains some physiological variables which have to be evaluated for each subject, however just two BP measurements are enough for each patient. It is therefore a simplified calibration phase with respect to the one adopted on the previous method. In fact, in the PPG feature algorithm, longer the training signal is, better could be the BP estimations.

Considering the two algorithms are based on different and independent approaches, to overcome their intrinsic limits, it is possible to think to a combined implementation. This could improve reliability and accuracy, for example in those instruments which needs a more precise BP estimation, likes medical devices.

In a first phase, the two kinds of algorithms have been applied on a set of signals coming from a publicly available online database. Among internet collections of recorded physiological signals, only the MIMIC database, on PhysioNet website, has simultaneous recordings of ECG, PPG and BP signals, necessary for this type of analysis. However, these recordings have not been conducted to the purpose of our class of experiments, therefore it has not been paid attention to the quality of signals during the measurements. Having only this database, it is impossible to compare signals waveforms with others, in order, for example, to evaluate the quality of the provided data.

Subsequently, to make a step forward towards the complete mastery of the signals, a collaboration with San Giovanni Bosco hospital have been put in place. Thanks to this collaboration, it is possible to validate and improve algorithms under a strict medical supervision, and, of primary importance, it made possible to compare the estimated results with the invasive “gold standard” BP acquisitions.

3.2.1 Trial protocol and acquisition methodology

The clinical trial at San Giovanni Bosco hospital, being in a public entity and having to ensure the privacy and the safety of patients, must be compliant to specific procedures which result from a formalisation of a protocol, approved from an ethical committee.

The protocol provides for a maximum number of 50 patients, mandatorily over 18 years old, admitted to the intensive care unit (ICU) and monitored with regard to electrocardiogram, photoplethysmography and invasive blood pressure.

The criteria for exclusion from the study were identified in:

- Terminal clinical conditions;
- Cardiovascular arrhythmias, namely ventricular fibrillation, ventricular tachycardia, supraventricular paroxysmal tachycardia and atrial fibrillation;
- Pathologies which imply disorders in the waveform morphology, preventing the proper running of the algorithms, based on the precise physiological waveform;
- Decision not to take part in the study.

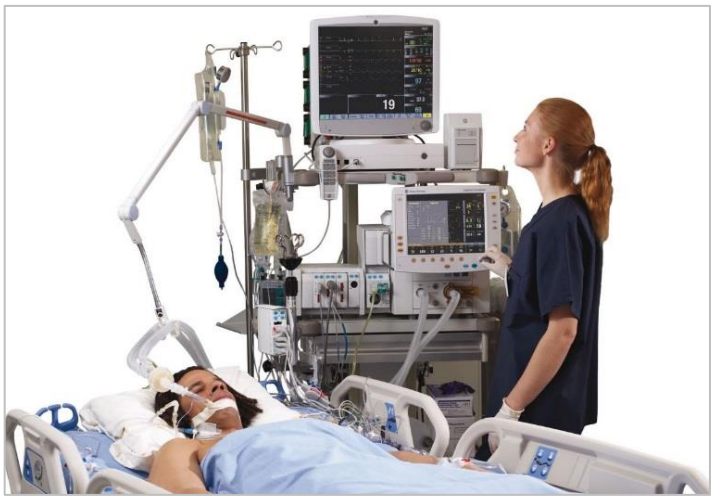

Figure 3.2 iCentral clients, networked with the GE Healthcare S/5 iCentral and whose measurements are acquired through the GE Healthcare S/5 Collect™

All the patients, who comply with the inclusion criteria of the study, are part of the trail and their personal information (surname, name, gender and birth date) are stored, together with anthropometric (weight and height) and hemodynamic clinical variables.

The relevant data for a refinement and validation of the BP estimation methodologies is the age bracket, gender, Body Mass Index (BMI), ongoing therapy and possible known pathologies and, from a medical point of view, the possibility of altering the acquisition of the signals of interest. And then, the ECG signal, the PPG signal and the intravascular blood pressure signal have to be analyzed and processed directly.

At the S. Giovanni Bosco, in the ICU the patients have their bedside monitors (*Figure 3.2*) and they are connected to a central point, the GE Healthcare S/5 iCentral, for viewing

and monitoring up to 32 patients with a view of vital sign measurements made at the bedside.

The signals under investigation are acquired through a software, purchased by STMicroelectronics, GE Healthcare S/5 Collect (whose main window in online mode is shown in *Figure 3.3*), which allows entering the network of patients' data, the GE Healthcare Network.

Figure 3.3 GE Healthcare S/5 Collect™, software used to obtain the patients' data.

Chapter 4

Basic Algorithms Development

4.1 PPG feature based method

The first developed algorithm for the estimation of blood pressure values is based on the analysis of some characteristic PPG signal features.

The flowchart of the proposed method is shown in *Figure 4.1*. There are two phases in the algorithm: a first step where it is trained and a second one of testing. Initially, in the training phase, the PPG features are extracted from the signal waveform. After that, a model of the system is created through a linear regression analysis, using various known measurements of BP and the PPG features as input. In the testing phase this model is then employed to estimate SBP and DBP values from the feature of the newly captured PPG signal.

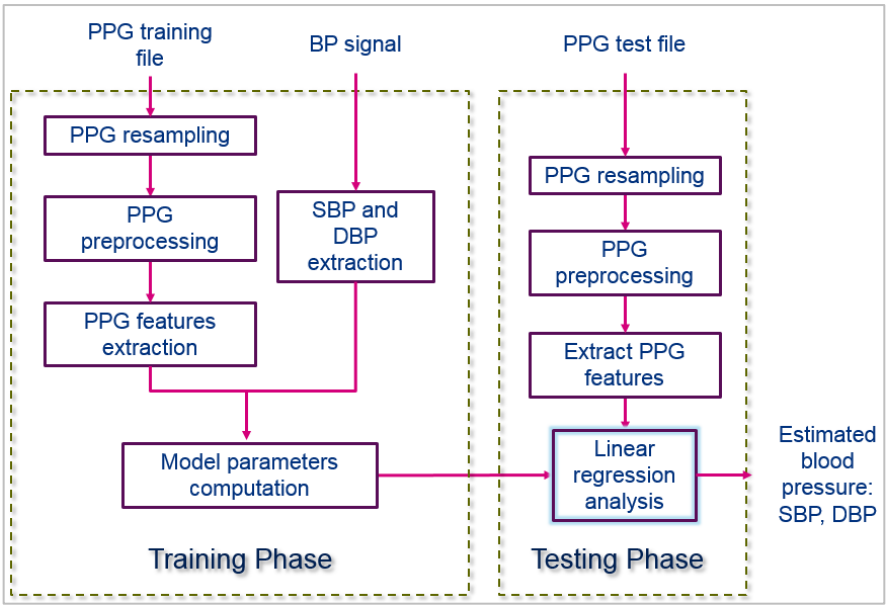

Figure 4.1 Flowchart of PPG feature-based approach for BP estimation.

The entire process has been performed for each patient dataset, therefore a preliminary individual calibration is necessary to estimate blood pressure only using the photoplethysmographic signal.

The time periods and the number of patients have been chosen according to the duration of PhysioNet recordings and to the acceptability of the signals waveforms. At the beginning, indeed, all records of the MIMIC database have been examined, plotting the signals directly on PhysioNet website, but most of recordings are very noisy or their PPG signals do not show diastolic peaks. Therefore, among the whole patient datasets, only those who ensure greater control on all the variables and with a reasonable signal quality have been chosen.

4.1.1 PPG feature selection

In order to find an optimal signal feature for estimating systolic and diastolic blood pressure, four parameters of PPG wave have been analyzed. Three of them are namely systolic upstroke time (SUT), diastolic time (DT) and time delay between the systolic and diastolic peak (T1), as shown in *Figure 4.2*.

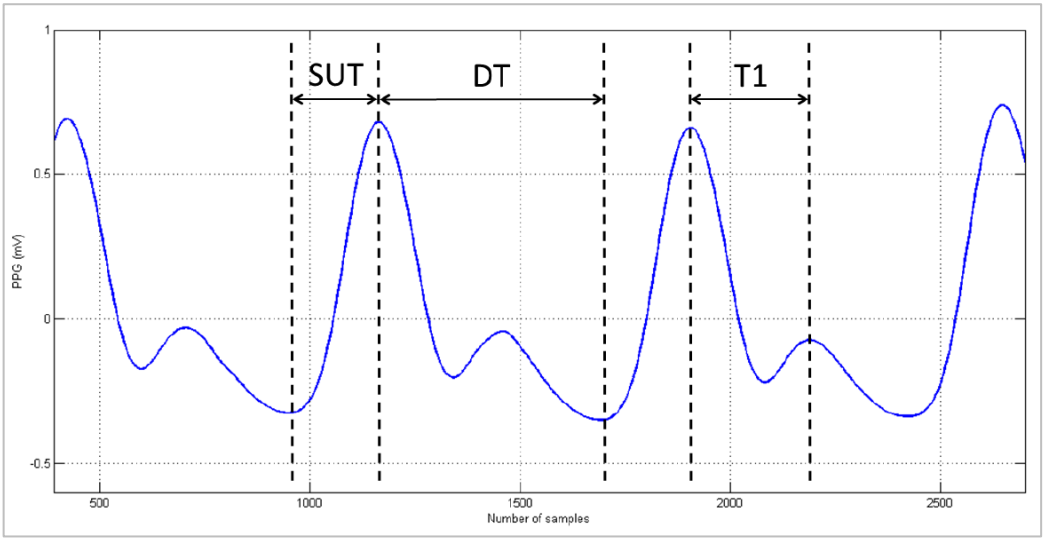

Figure 4.2 PPG waveform and its extracted features: systolic upstroke time (SUT), diastolic time (DT) and time difference between systolic and diastolic peaks (T1).

Features evaluation has been performed with a regression analysis, in fact given a variable *y* and several variables *X1, ..., Xp* that may be related to *y*, linear regression analysis can be applied to quantify the strength of the relationship between *y* and the *Xj*, to assess which *Xj* may have no relationship with *y* at all.

This analysis has been applied to some signals and the mean correlation coefficients between each PPG parameter and the blood pressure have been compared, as shown in *Figure 4.3*. Just considering the correlation of the features with systolic blood pressure, only the T1 feature is related to SBP in a linear way, with a satisfying correlation coefficient.

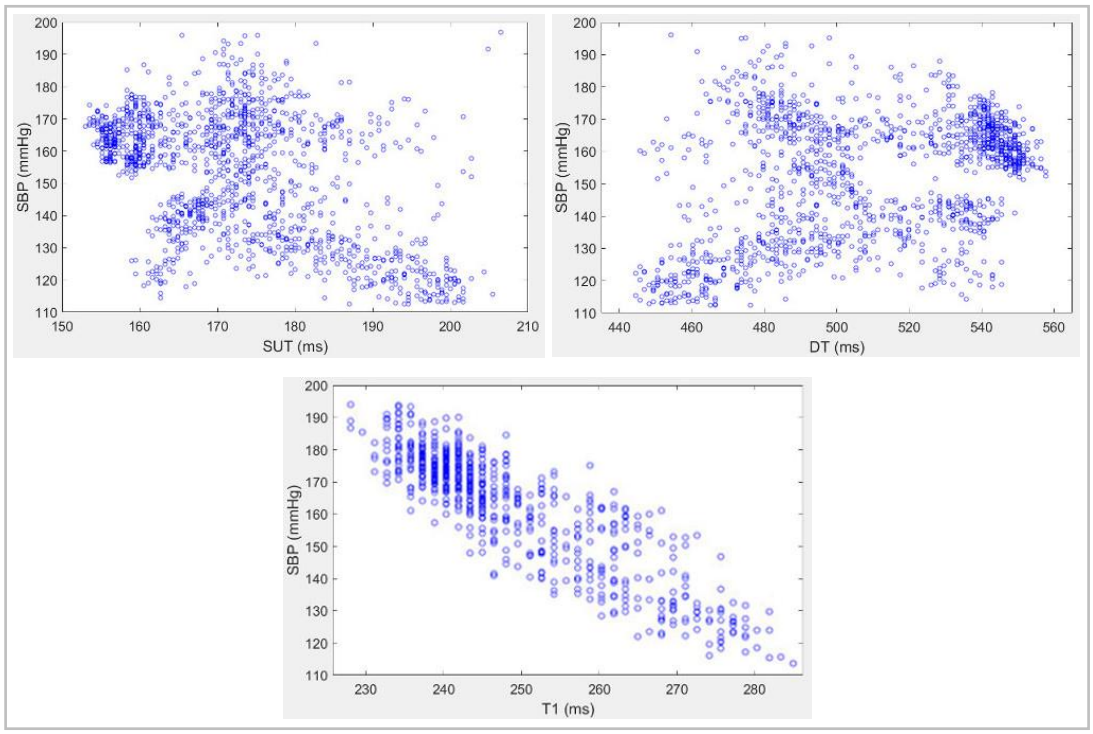

Figure 4.3 Scatter plots between the systolic upstroke time (SUT), diastolic time (DT), time delay between the systolic and diastolic peak (T1) and systolic blood pressure (SBP).

Another feature, found in literature as useful indicator of arterial blood pressure *[50]*, is the Normalized Harmonic Area (NHA). This analysis is based on the assumption that the position and depth variations of the dicrotic notch might indicate changes in blood pressure. The NHA is extracted evaluating the changes of distribution of harmonic components of the photoplethysmographic waveforms (of each beat) in the period domain, or rather using the DPT (Discrete Period Transform) to improve the resolution for low frequency signals.

The Normalized Harmonic Area is defined as:

$$NHA = \frac{\sum_{n=0}^{k2} DPT(t_n)}{\sum_{n=0}^{k1} DPT(t_n)}, \qquad n = 1,2,\dots,N \tag{5.1}$$

namely the normalized shadow area in *Figure 4.4*, where DPT is the amplitude of the spectrum component at the period t and t_{k1} and t_{k2} are the periods (the inverse of the frequencies) corresponding to the first and second peak of the harmonic components (labelled as P1 and P2 in the left plot in *Figure 4.4*).

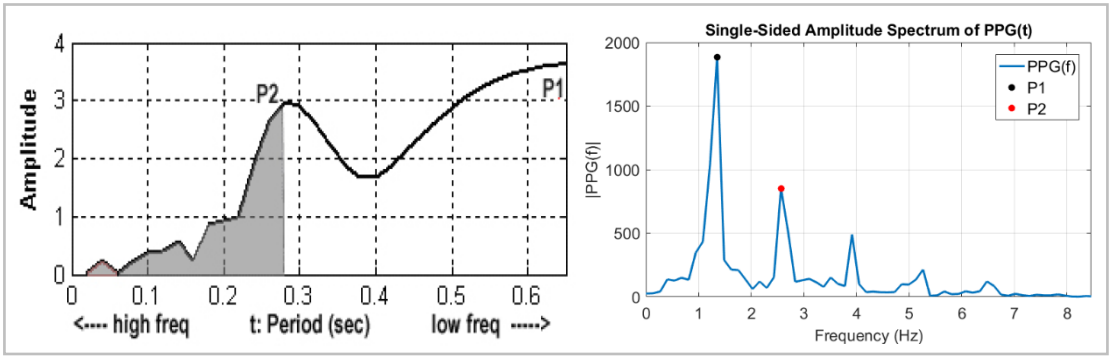

Figure 4.4 In the DPT spectrum (left plot) and in the FFT spectrum (right plot) the first and second harmonic components peaks (P1 and P2) are highlighted.

However, for a first and quick investigation, on this thesis work the conventional FFT algorithm has been employed and, once recognized the corresponding peaks of the harmonic components, the NHA has been calculated on the single-sided amplitude spectrum (an example in the right plot in *Figure 4.4*), taking into consideration the horizontal axis reversal.

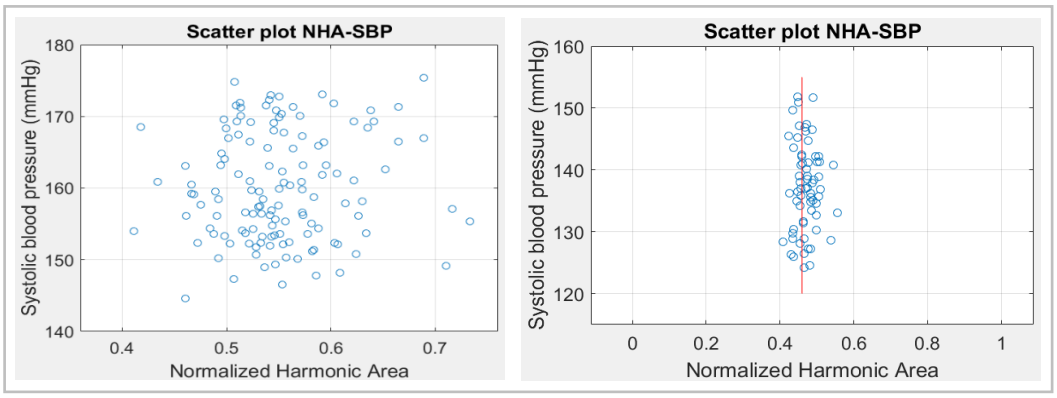

Figure 4.5 Two examples of scatter plots showing the relationship between the Normalized Harmonic Area and the correspondent systolic blood pressure.

This feature evaluation has been performed with a regression analysis and applied to some PhysioNet signals, looking for an apparent linear relationship between the NHA and the SBP/DBP. Using a scatter plot to show the correlation of the feature with the blood pressure, the output has not been satisfactory, reporting a points cloud (the left plot in *Figure 4.5*) or a relationship really close to a vertical line (the right plot in *Figure 4.5*). They simply indicate that in the first case the correlation between the blood pressure and

the Normalized Harmonic Area is undefined and in the second case that the SBP doesn't affect the feature at all.

Nevertheless, analyzing the FFT spectrum (the right plot in *Figure 4.4*), there is a very clear correlation with the patient heart rate (HR): the harmonic components peaks hold their position on the frequency axis in correspondence of the HR and its harmonics (in *Figure 4.4* the abscissa of the peaks, starting from the highest P1, are 1.35 *Hz*, 2.6 *Hz*, 3.9 *Hz* and so on). For this feature investigation it has thereby been appropriate looking for an independence of the blood pressure from the heart rate, to prevent ambiguous situations. A good example to point out a mistake to avoid is a PhysioNet signal trace from the *Subject 055*, reported in *Figure 4.6*: it would seem that the SBP is clearly linear related to the NHA, but the correlation is not direct between BP and the feature of interest; it is only due to the heart rate trend similar to the systolic blood pressure one. Circumstances like this one are very frequent in literature, because often in trials the arterial blood pressure variations are induced by physical activity, but this influences the heart rate too.

Consequently, among all the features evaluated, T1 has been selected as the best parameter to predict blood pressure values.

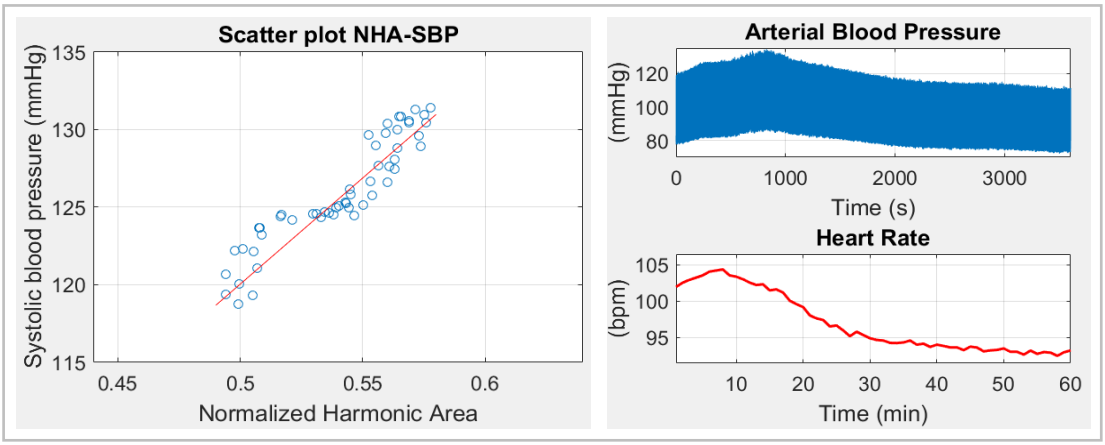

Figure 4.6 In the left scatter plot is represented the relationship between the Normalized Harmonic Area and the systolic blood pressure. The straight line which is closer to this relationship is set out in red. On the right the trends of blood pressure and heart rate are shown to highlight the similarity.

4.1.2 Training phase

PPG signal resampling and preprocessing

In order to filter out the noise, a 5th order Butterworth bandpass filter of upper cutoff frequency 7 *Hz* and of lower cutoff frequency 0.3 *Hz*, has been chosen and applied to the PPG signal. It is an infinite impulse response (IIR) filter which is characterized by a flat amplitude response in the passband and rolls off towards zero in the stopband.

In this way both high frequencies noise components that influence the signal and low frequencies artifacts, like baseline wandering (*Figure 4.7*), caused by breathing or motion artifacts, are removed and PPG is ready to be processed.

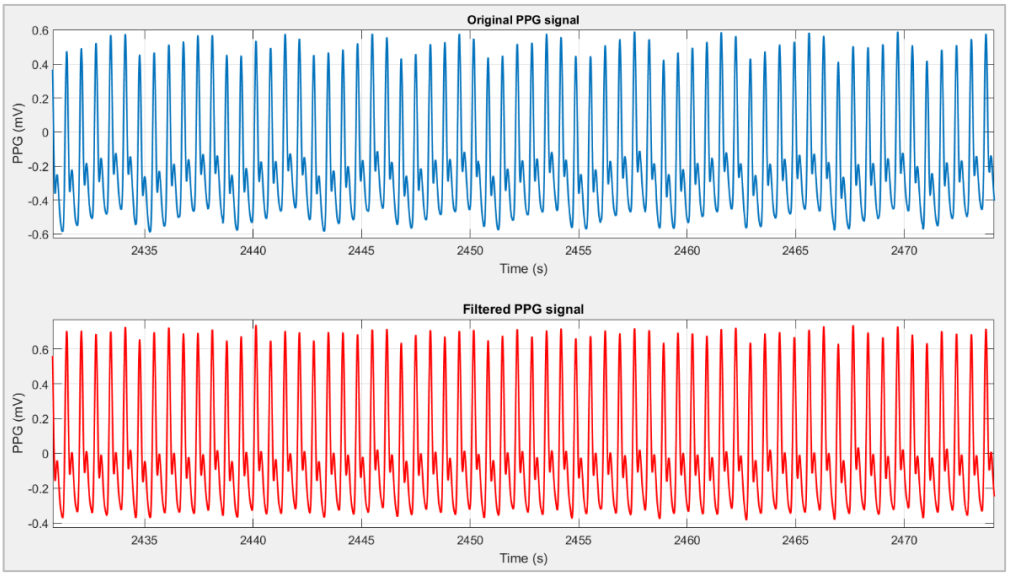

Figure 4.7 On the top plot the baseline wandering may be observed in original PPG signal. On the bottom plot there is the same PPG signal after Butterworth bandpass filtering.

The detection of the position of characteristic points (systolic and diastolic peaks) on PPG signal, significantly influences the calculation of the T1 distance, and consequently the estimation of the blood pressure values. Because of this, it is necessary that this identification is the most accurate possible. The order of magnitude of the T1 time is of milliseconds while the PPG sampling frequency is 125 *Hz*, therefore its sampling interval is 8 *ms*. It is clear in this case that even a few samples error has a significant impact on the T1 extraction.

To reduce the effect of possible errors in peak detection, it was decided to perform a sample rate conversion of the PPG signal, re-sampling the signal at a higher rate. It has been chosen an upsampling factor of 10, increasing the sampling frequency from 125 *Hz* to 1250 *Hz*, and consequently the sampling interval became 0.8 *ms*. In this way an error of few samples in the identification of the PPG characteristic peaks, will be less significant in the calculation of the time T1.

In Matlab environment, this signal upsampling is performed through a *spline* interpolation (an example is shown in *Figure 4.8*). In this interpolation method, the interpolated value for a specific point is based on a cubic interpolation of the available values before and after the considered point.

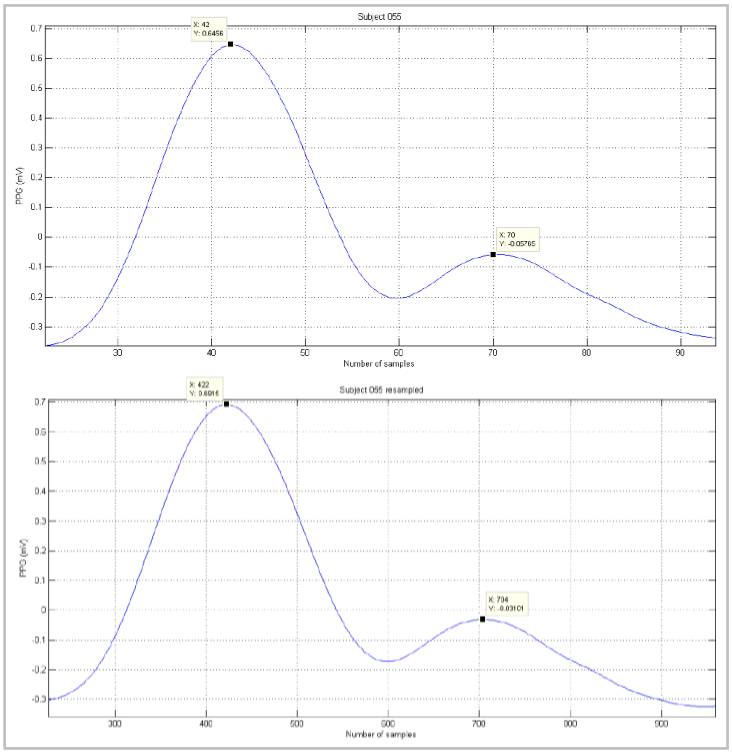

Figure 4.8 Upsampling in this PPG wave leads to a change of 1.6 ms in the time T1 (from T1= 224ms to T1=225.6ms)

PPG feature extraction

After the signal preprocessing phase, where the PPG is filtered and resampled, it is possible to start the individuation of its characteristic parameters: the systolic peak and the diastolic peak. As shown in *Figure 4.9*, the systolic and diastolic peaks are two

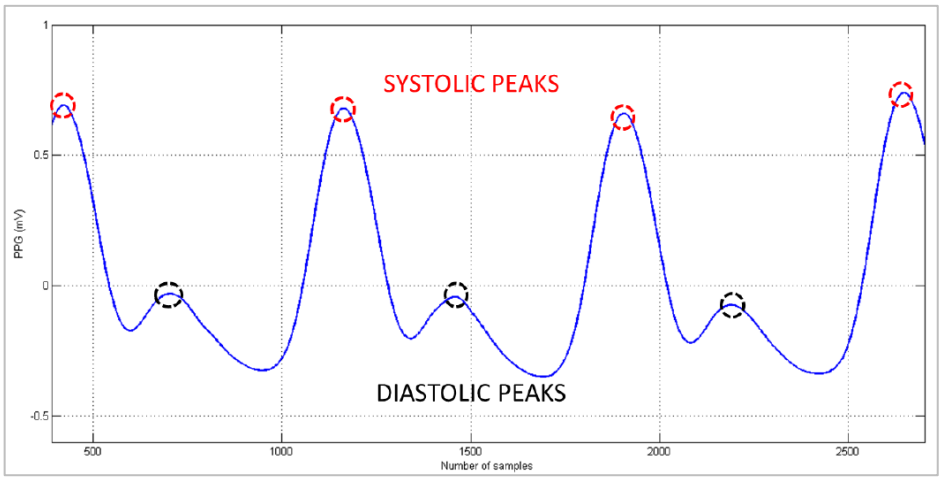

Figure 4.9 PPG waveform with highlighted systolic and diastolic peaks that have to be located.

maxima of the signal, in each PPG wave the systolic peak is the absolute maximum whereas the diastolic peak is the relative one.

Taking into consideration these aspects, the algorithm starts searching all the maximum points in the signal. This is implemented calculating and evaluating the difference quotient for each point of the signal. In this way all maxima are located as shown in *Figure 4.10*.

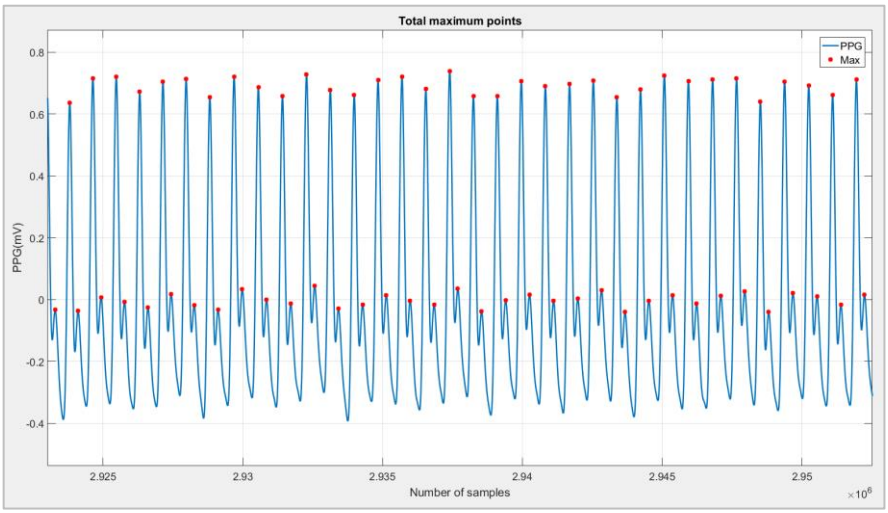

Figure 4.10 Maximum points located by the algorithm on a portion of the PPG signal.

The simplicity of the detection algorithm ensures that maxima have also been identified in very noisy areas of the signal or in correspondence of non-physiological waves.

Basing on the analyzed signals of the MIMIC database, it is possible to consider physiological PPG waves ranging between -0.5 mV and 1 mV. Consequently, a first step of maxima filtering is the exclusion of those identified fairly out of this range, taking into account that in the portions of the signal around there may be other maximum points wrongly identified because of motion artifacts. Therefore, the maxima in a window of half a second before and after every deleted maximum point are stored but not deleted, because being unaware of the kind of the peaks may lead to a wrong T1 calculation later. This first maxima filtering step is shown in *Figure 4.11*.

At this stage of the algorithm, maxima can be divided in systolic and diastolic peaks. This is accomplished in a subroutine which calculates, in every minute of the PPG signal, the mean amplitude of maximum points and then classifies as systolic peaks those greater than this threshold value and as diastolic peaks the remaining points. In *Figure 4.12* the classification in systolic and diastolic peaks of first minute is displayed.

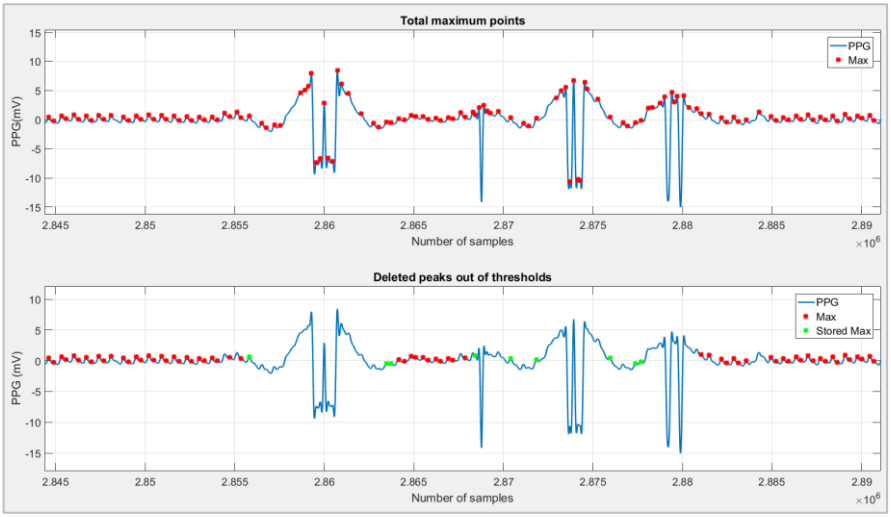

Figure 4.11 The two plots show the same PPG portion. In the upper side it is possible to see that the algorithm identifies also noisy maximum points on PPG. In the lower graph these points are rejected after filtering. In green points later deleted in one of the following filtering steps.

Once the points have been classified, it is necessary to analyze whether they have been identified correctly, in fact the algorithm does not present filter functions which avoid wrong recognition of points on the signal, beyond to eliminate points fairly out of physiological range. Therefore, it is appropriate to introduce functions which increase the specificity of the algorithm, removing selected systolic and diastolic peaks which do not correspond to characteristic points on the PPG signal.

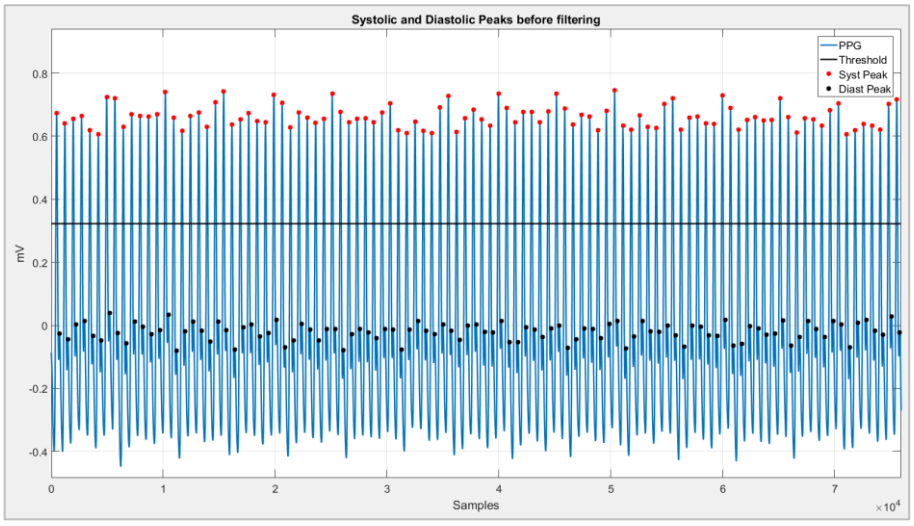

Figure 4.12 In the figure 1 min = 75000 samples of PPG signal is reported. The threshold that classifies maxima in systolic and diastolic peaks, in this minute, is 0.3227mV.

To perform this task, systolic and diastolic peaks are filtered based on their amplitude. For both the points, an upper and a lower limit are defined and those which exceed these limits are no more considered in the classification. These limits are calculated in every minute using the peaks mean value and their standard deviation (SD), which is a measure that is used to quantify the amount of variation or dispersion of a set of data values from the average. Separately for the systolic peaks and the diastolic peak, the points are rejected if their amplitudes are out of the mean value plus or minus 1.2 for their standard deviations (*Figure 4.13*).

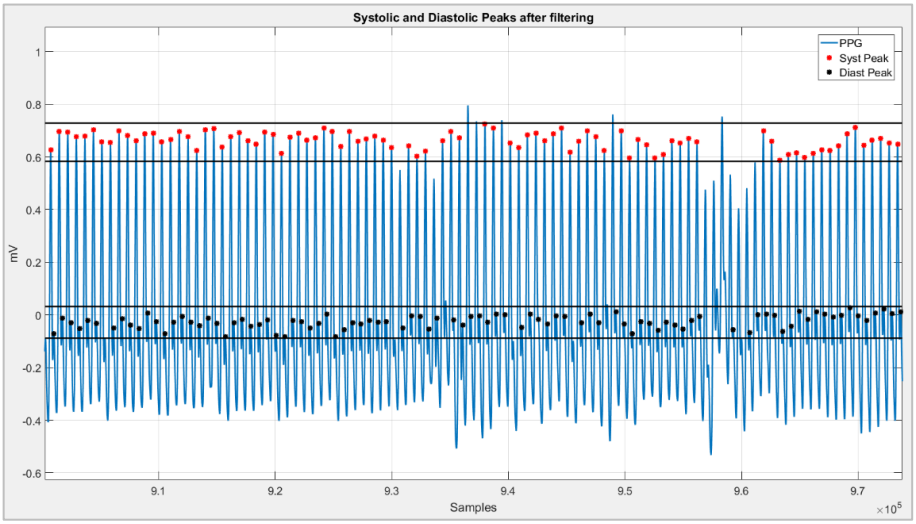

Figure 4.13 The two areas of acceptability for systolic and diastolic peaks, respectively, are highlighted. It is also possible to observe that some systolic and diastolic peaks have been filtered out.

After filtering the identified points, to avoid errors in the calculation of the time T1, it was decided to examine the sequence between the systolic and diastolic peaks, in fact, for each peak identified, it has to be present in the same wave the peak corresponding to the other feature. Therefore waves (points) where both peaks were not identified, were rejected.

Once got all the information on every wave, the stored maximum points in noisy areas of first filtering step (green points in *Figure 4.11*) have to be deleted if present in the final identified peaks, excluding also the other corresponding peak of the same wave. Thereby the first filtering step in *Figure 4.11* is an aware removal of peaks, not leading to wrong extracted T1 intervals.

T1 calculation

In this phase of the algorithm, the PPG feature chosen, the time *T*1, can be calculated because all filtered systolic and diastolic peaks are available (*Figure 4.14*).

Analyzing these time intervals, it is observed that sometimes their values are not physiological because they are too much brief or too long. This problem is due to the fact that applied filtering was only considering signal amplitudes and it was not taking into account time intervals. Therefore, in this step, to remove wrong times T1, it is necessary to apply some routines that analyze and classify time distances between systolic peaks and diastolic peaks.

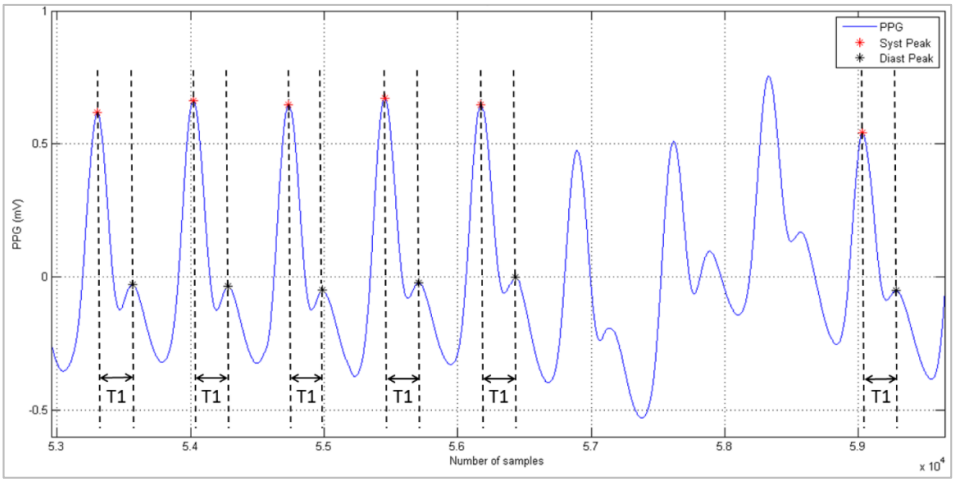

Figure 4.14 Systolic and diastolic peaks remained after filtering in a portion of PPG signal, on those regions T1 delay can be safely computed.

It has been decided to perform a preliminary filter that rejects all times T1 longer than 964 *ms*. This time is chosen because it reverts to an equivalent heart rate of about 30 *bpm* which is a non-physiological human heartbeat rate. Therefore, applying this kind of filtering, it will not impact true physiological PPG waves.

The second developed function analyzes T1 in each minute of the signal. In every minute the average of the time delays between systolic and diastolic peaks is extracted and is then compared with each T1. If the considered time delay is greater than the average plus its 20%, it is filtered out.

Finally, considering the final aim of the system, the trends of systolic and diastolic blood pressure values are the relevant information that the system has to show in output. These trends change within minutes, they are quite "low" signals, so it is unnecessary to perform an algorithm that analyzes signals information on every heartbeat. Therefore, for these reasons it was decided to average, on each minute, the T1 intervals, in this way there is only one T1 mean value for every 60 *s* of input signal.

So, the output of this function is an array of filtered average values (compute on each minute) of *T*1 intervals where all the noise related events have been removed (shown in *Figure 4.15*). The array of *T*1 delays is the first input of the linear regression analysis, the second is the corresponding array of blood pressure measurements. In the next paragraph

is shown the algorithm related to the analysis of the BP signal and the extraction of SBP and DBP raw values.

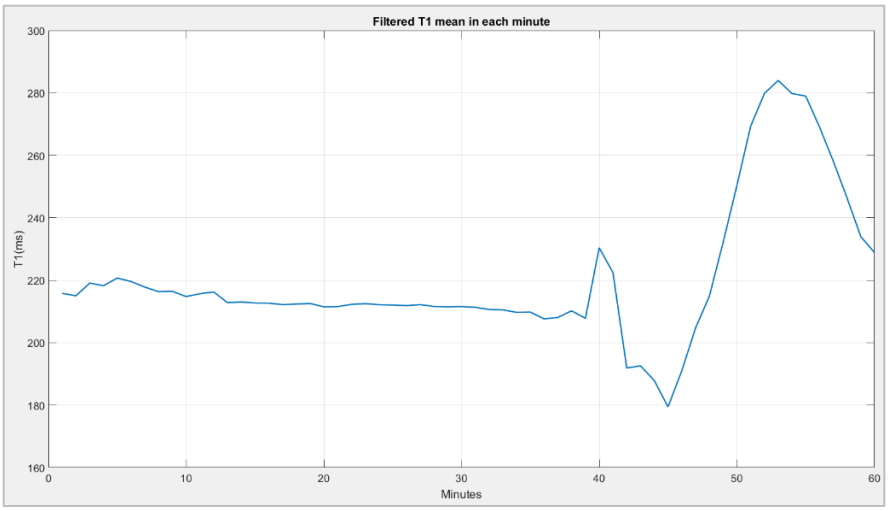

Figure 4.15 T1 intervals mean in each minute

BP analysis

In the training phase of the machine learning approach it is necessary to record systolic and diastolic blood pressure values, in order to correlate them with the selected PPG characteristic feature. Therefore, maximum and minimum pressure values have to be extracted from a continuous signal.

The blood pressure signal, unlike the PPG, is not preprocessed, because firstly the available signal is not too much affected by motion artifacts or high frequency noise, then applying a filter, BP amplitudes will be modified, changing systolic and diastolic measurements. For these reasons the signal is handled as it is.

This algorithm section starts locating all maximum and all minimum points in the pressure signal, in order to collect the systolic and diastolic amplitudes. Each BP wave is composed of two maxima and two minima, the first maximum corresponds to SBP whereas the second minimum is the DBP, as it is possible to see in *Figure 4.16*. Therefore, in a second step, it is necessary to classify all the individuated signal extrema, rejecting those which are not related to SBP or DBP.

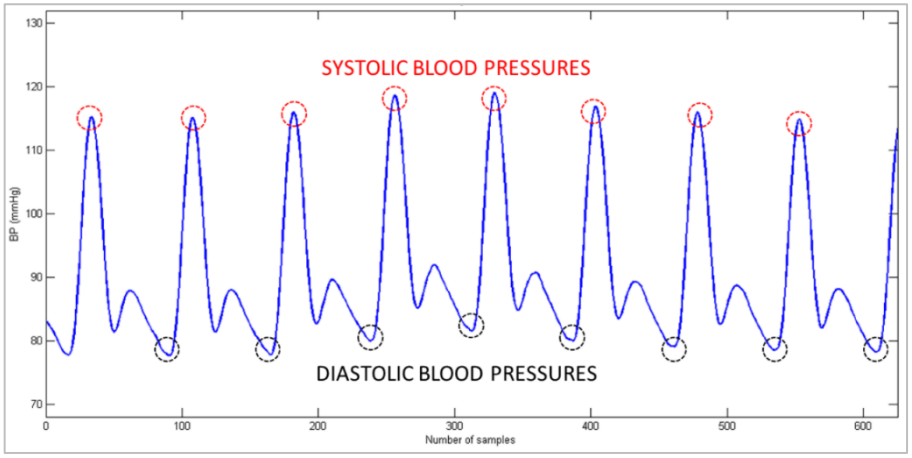

Figure 4.16 5 s of blood pressure signal with systolic and diastolic values highlighted.

The detection of peaks and depressions in the signal is implemented by a routine that analyzing all the points, considers a maximum or a minimum peak if it has the maximal or the minimal value, and was preceded by a value lower or greater by a chosen delta parameter. The value of delta was established after some tests considering different input BP signals. By choosing the appropriate value for δ, it is possible to realize a sort of filtering on the extracted minimum and maximum peaks. The result of this step is shown in *Figure 4.17*.

As stated previously, in the second part of the algorithm the systolic and diastolic peaks are selected from all the maximum and minimum points identified by the routine. This is carried out in a similar manner for both the SBP and the DBP: the blood pressure signal is divided in periods of 1 minute and all the maxima and all the minima included in each time frame are averaged. In this way for each minute there is a mean value both for

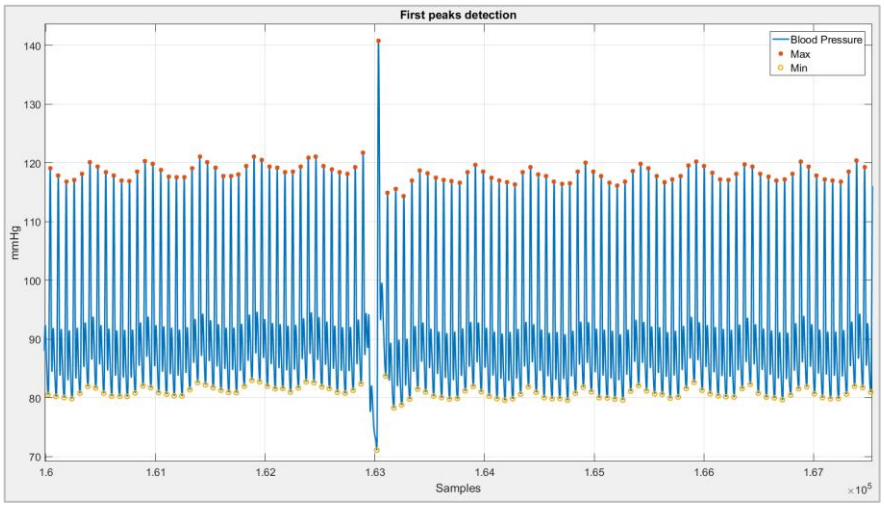

Figure 4.17 Maximum and minimum points located on a minute of BP signal

maximum and minimum points. Therefore, a peak point is a systolic peak if its amplitude is lower than the average in that minute plus 10 *mmHg* and greater than the average minus 10 *mmHg*. Similarly, a minimum point is DBP if it is included between the mean value of minima plus 10 *mmHg* and the mean value minus 10 *mmHg*. It is possible to see a graphical representation of the selection step in *Figure 4.18*.

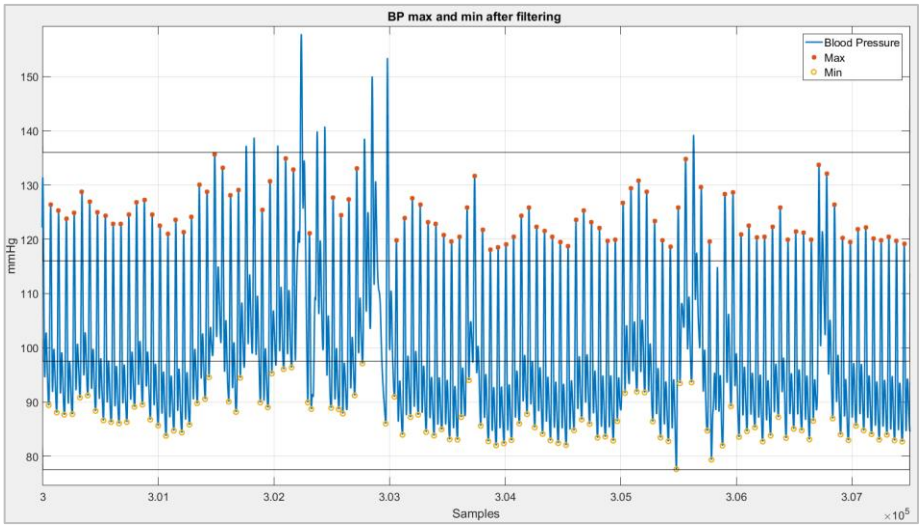

Figure 4.18 In this minute of BP signal is possible to see the selection of maxima and minima, accepted if ranging in their amplitudes mean value in the minute plus or minus 10 mmHg (limits marked with black lines).

After this stage, systolic and diastolic blood pressure values for each heartbeat are the collected data. However, as said in the previous chapter, the relevant information to show is the trends of SBP and DBP, therefore it is necessary to average the systolic and diastolic pressure values in the same time periods of 1 min, chosen for T1 intervals extraction. In this way on every minute of recording it is possible to correlate one value of the PPG feature T1 to one of SBP and one of SBP (*Figure 4.19*).

Analyzing more data, it was realized that in many cases the photoplethysmographic signal was totally absent or so much noisy that it was impossible to extract a T1 time in a minute of signal while in the same minute the blood pressure waves were clean and reliable. This causes a disparity between data from PPG and those from BP, therefore they cannot match as inputs for the regression analysis.

To avoid these situations, the algorithm identifies the time frames of 1 min where there is not information about T1, i.e. there are not acceptable systolic and diastolic peaks to calculate the time feature, and it discards the SBP and DBP extracted in the same time periods. In this way the delays T1 are in one to one relationship with the systolic and the diastolic pressures.

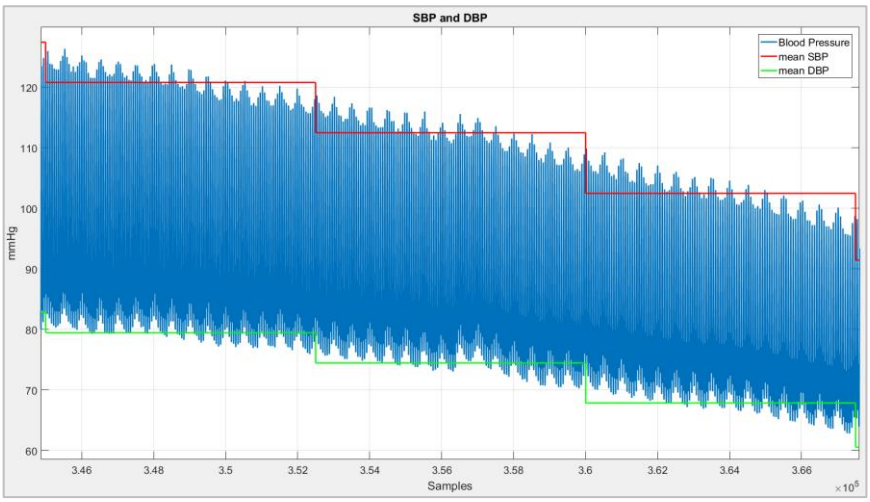

Figure 4.19 The figure shows 3 minutes of blood pressure signal. In red and green are reported the mean values of SBP and DBP in each minute.

Once completed this section of the algorithm, also the blood pressure signal has been analyzed and its fundamental information has been inferred. Therefore, the training phase of the algorithm can end with the linear regression analysis, which takes as inputs the times T1 and the pressures SBP and DBP.

Linear regression analysis

On last step of training phase, a calibration curve for SBP and DBP, respectively, is set up by linear regression. This curve is necessary in order to estimate systolic and diastolic pressure values in the testing phase, giving in input to the model only the PPG feature.

Regression analysis is made for the individual data set of each subject, therefore an individual calibration is performed. Linear regression is an approach for modeling the relationship between a scalar dependent variable y and one or more independent, or predictor, variables $x_1, \ldots, x_n$. Relationships are modeled using linear predictor functions whose unknown model parameters are estimated from the data. The most common way to fit linear regression models is based on the adoption of the least squares approach *[49]*.

The case of one only independent variable is called simple linear regression and it uses the relation:

$$y = ax + b \tag{4.2}$$

where a is the slope (or regression coefficient) and b is the y-intercept. If there is an input set of n observed values of x and y given by (x_1, y_1), (x_2, y_2), ..., (x_n, y_n), using the simple linear regression relation, these values form a system of linear equations.

Representing these equations in matrix form:

$$\begin{bmatrix} y_1 \\ y_2 \\ \vdots \\ y_n \end{bmatrix} = \begin{bmatrix} 1 & x_1 \\ 1 & x_2 \\ \vdots & \vdots \\ 1 & x_n \end{bmatrix} \cdot \begin{bmatrix} a \\ b \end{bmatrix} \tag{4.3}$$

Simple linear regression identifies the straight line which better fits the provided input points. This line is selected adopting a least squares residual approach, in other words the sum of squared vertical distance between the line and the input points has to be as small as possible. The slope of the fitted line is equal to the correlation between *y* and *x* corrected by the ratio of standard deviations of these variables. The estimation error for a specific point is represented by its value minus the estimated value. An indication of the goodness of the association between the two variables can be represented by the correlation coefficient, which is represented by a value in the range from -1 to 1.

In the implemented algorithm, for each patient, data obtained from one hour of recording are used to set up a calibration curve for SBP and DBP respectively:

$$SBP_{train\{1,\dots,n\}} = a_{SBP} \cdot T1_{train\{1,\dots,n\}} + b_{SBP} \tag{4.4}$$

$$DBP_{train\{1,\dots,n\}} = a_{DBP} \cdot T1_{train\{1,\dots,n\}} + b_{DBP} \tag{4.5}$$

where n refers to the number of minutes, if signals are enough clean to extract parameters from all time periods of 1 min. The distributions of diastolic and systolic blood pressures in relation to the parameter T1, and their related regression lines, are illustrated in graphical form in *Figure 4.20*.

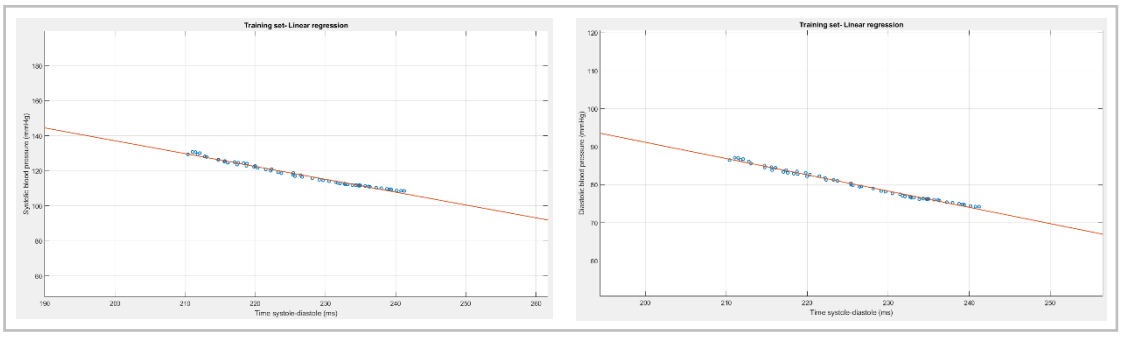

Figure 4.20 Both figures show the distribution of systolic (left) and diastolic (right) blood pressure in relation to the parameter T1 and their regression lines for one hour of signals.

In Matlab environment this analysis is performed using two functions: *polyfit* and *polyval*. The first function returns the coefficients for the polynomial of degree equal to 1 (simple linear regression), that is a best fit (in least-squares sense) for the data.

The second one returns the value of the polynomial, evaluated at each element of *x* (in this case *T*1). Therefore, the training phase gives as outputs the parameters of the regression lines (a_{SBP}, a_{DBP}, b_{SBP}, b_{DBP}), that in the testing phase will be employed to estimate the systolic and diastolic blood pressure values.

4.1.3 Test Phase

After defining, during the training phase, a model of the BP-PPG system, the proposed method considers to evaluate whether the discovered relationships hold over a test data set. More formally, in this phase a test set is used to assess the robustness and usefulness of the predictive relationship.

Since an individual machine learning approach is implemented, i.e. a model of the system is defined for each patient, as test data set is taken a set of some hours of recordings, successive to the hour of recording on which the model was trained.

Therefore, the algorithm uses the linear regression model defined during the training phase to predict the systolic and diastolic blood pressure values, providing in input to the system only the differences between the systolic and diastolic peaks (T1) of the PPG signal.

During the test phase the workflow followed to process the PPG signal and to extract its basic parameters is the same implemented in the training phase. Then, the set of T1 values calculated for each minute of the signal is used as input to the linear regression model obtained from the training:

$$SBP_{est\{1,\dots,n\}} = a_{SBP} \cdot T1_{test\{1,\dots,n\}} + b_{SBP} \tag{4.6}$$

$$DBP_{est\{1,\dots,n\}} = a_{DBP} \cdot T1_{test\{1,\dots,n\}} + b_{DBP} \tag{4.7}$$

where SBP_{est} and DBP_{est} are vectors of estimated blood pressure values; a_{SBP}, a_{DBP}, b_{SBP} and b_{DBP} are the parameters obtained from the training phase; $T1_{test}$ is the test vector representing the time interval between the systolic and diastolic peaks. The number of samples n depends on the hours of the signals used to test and on the quality of the PPG waves.

The blood pressure signal during the testing process is used only to compare the real measured values of SBP and DBP with the estimated systolic and diastolic pressures. Therefore, also in this phase it is necessary to extract the SBP and DBP from the BP signal in order to have one averaged value of SBP and one of DBP in each minute. The steps followed are the same of those in the training phase.

Finally, for the purpose of assessing the effectiveness of the proposed algorithm, the trends of measured and estimated, systolic and diastolic blood pressures have been plotted together, in this way they could be compared and evaluated.

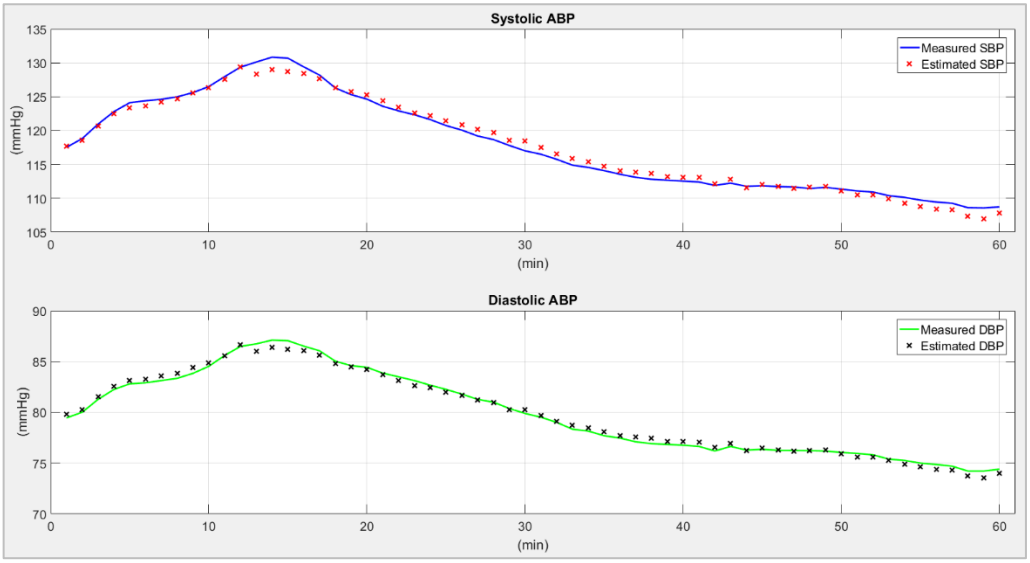

Figure 4.21 The figure shows one hour of systolic (upper) and diastolic (lower) blood pressure values, each of them from instrumentation measurements and from algorithm estimation.

These graphs are reported and described in detail in the following paragraph.

4.1.4 Results review

In this paragraph are reported the Matlab results obtained from the previous illustrated algorithm of blood pressure estimation. As previously mentioned, all studied signals come from the internet MIMIC database and *Subject 055* is described in detail in this section. The recording time periods of both signals are shown in *Table 4.1*, discerning the acquisition period chosen as training set from the other periods chosen as test set for the algorithm.

Table 4.1 Recordings time periods for Subject 055.

Training set	from 16:36:26 to 17:36:26, 2 March 1995
Test set 1	from 17:36:26 to 18:36:26, 2 March 1995
Test set 2	from 19:36:26 to 20:36:26, 2 March 1995
Test set 3	from 23:36:26 to 00:36:26, 2-3 March 1995

Extracting the delays T1 from the PPG and the SBP-DBP values from the BP signal, the results of the linear regression analysis are shown in *Figure 4.20*. It is easy to see that in these two cases the relationship between the delay T1 and the pressures (systolic and diastolic) is linear with an inverse proportionality in both. The correlation coefficient is

$r_{SBP} = -0.9932$ for the SBP whereas for the DBP it is $r_{DBP} = -0.9958$. Values are very high, therefore they show a very high correlation between the variables for this dataset.

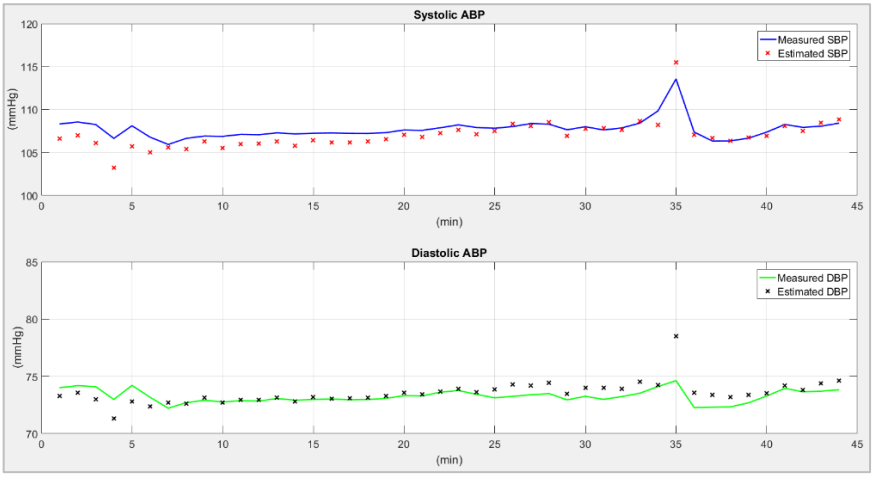

Figure 4.22 Test set 1 - Trends of SBP and DBP, measured and estimated, 1 hour later the time of the training signals.

The outputs of the regression analysis are the coefficients for the polynomials that are the best fit for the data and which are then used to estimate the blood pressure values. The two obtained polynomials, for SBP and DBP, are in this case:

$$SBP = -0.7330 \cdot T1 + 283.7676 \quad (4.8)$$

$$DBP = -0.4280 \cdot T1 + 176.7619 \quad (4.9)$$

Therefore, the previous polynomials allow to estimate SBP and DBP for the *Subject 055*.

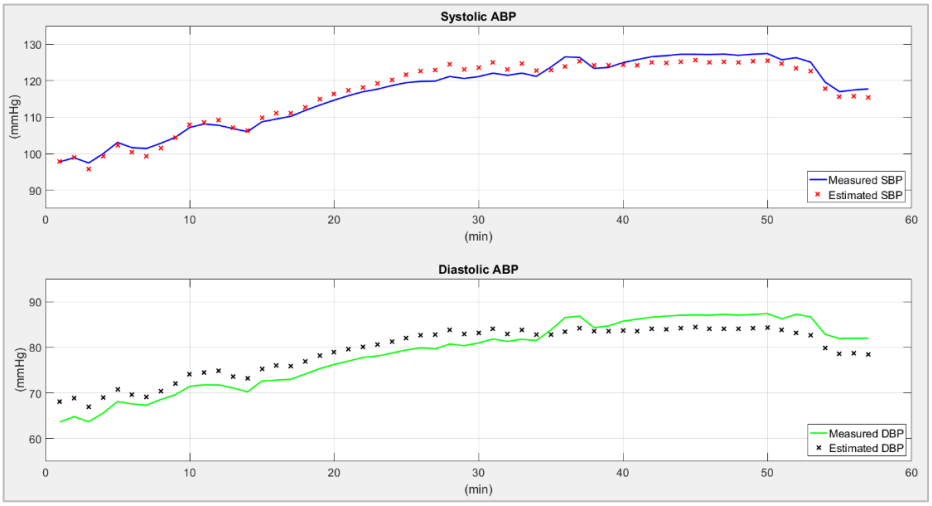

Figure 4.23 Test set 2 - Trends of SBP and DBP, measured and estimated, 3 hours later the time of the training signals

As it is possible to see from the graphs (from *Figure 4.22* to *Figure 4.24*), in these time periods the algorithm well succeeds to estimate blood pressure values only from the PPG signal. The solid lines (measured BP) and dotted ones (estimated BP) are always very similar and this shows an equivalence between the measured and estimated pressure values.

Mostly the algorithm is able to "follow" the variations in pressure trends like for example the sudden increase of BP in *Figure 4.22* or its slow drop after the minute 45 in *Figure 4.24*.

It is important to highlight that the BP estimation is correctly performed even 7 hours later the time frame used to calibrate the algorithm (see *Figure 4.24*). This shows that there is the possibility to have SBP and DBP values over long-time periods, only measuring the PPG signal.

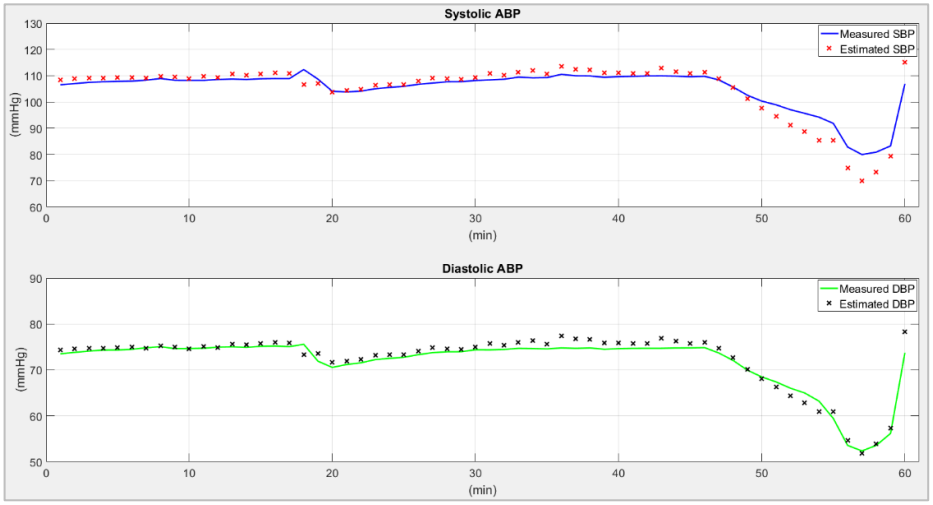

Figure 4.24 Test set 3 - Trends of SBP and DBP, measured and estimated, 7 hours later the time of the training signals

Analyzing in a statistical way the results of the algorithm, the *Table 4.2* gives the mean differences between estimated and the measured blood pressure, and corresponding mean standard deviations for SBP and DBP, respectively.

These data confirm even more the goodness of the estimate for this patient and for these time periods. Given the limits of the American National Standards of the Association for the Advancement of Medical Instrumentation (AAMI) (absolute value of error mean less than 5 *mmHg* and the error standard deviation less than 8 *mmHg*), these estimations results are fully compliant, also considering that the PPG feature based method is primarily oriented towards a consumer device, not a medical one, therefore requirements are less strict.

Table 4.2 Averages and standard deviations of the differences among the BP estimation and the measured BP, using T1 for different PPG signals considered as test sets, for the Subject 055 (numbers in the form of Mean Value ± SD)

Test set	*SBP (mmHg)*	*DBP (mmHg)*
1	0.8670 ± 0.9008	0.6018 ± 0.8453
2	1.5615 ± 1.7695	2.6963 ± 2.7709
3	2.5286 ± 3.5017	1.0643 ± 1.1341

4.2 Pulse Transit Time based method

As described in the previous paragraph, the estimation of BP only using a PPG signal is not always possible. The diastolic peak on PPG waves which allows to calculate the time delay T1, correlated then with BP values, is not detectable in the PPG signals of every subject, especially in those of old people *[19]*. Therefore during this thesis work, it has been addressed also a different, non-invasive and continuous approach for the SBP and DBP estimation: the pulse transit time based method, whose flowchart is shown in *Figure 4.25*.

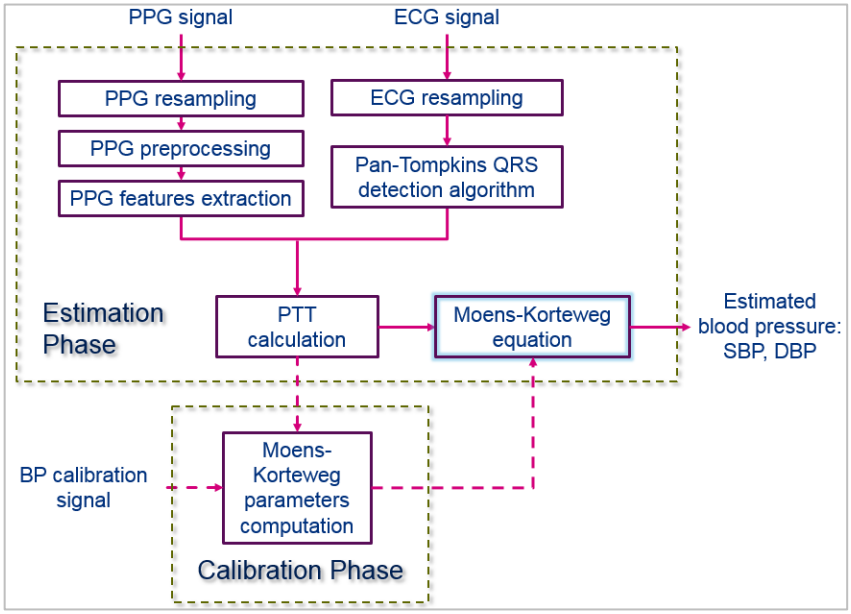

Figure 4.25 Flowchart of PTT approach for BP estimation.

It is a more onerous method if compared to the previous ones, in fact to calculate the PTT used to estimate the pressure values, are necessary both the PPG and the ECG signal.

In that sense also the portability of a hypothetical device that will implement the algorithm will be reduced. However, on the other hand, it is a method that can be applied on all types of patients because the pulse transit time is calculated between the R peak of ECG and a characteristic point on PPG signal which is not impacted by subject age.

The physical relationship which connects the PTT with the BP values is the Moens-Korteweg equation, already described in *Chapter 2*. Basing on physical laws, this relationship allows to calculate SBP and DBP, but it contains some subjective parameters which have to be defined before to be able to evaluate the equation. Therefore, also in this technique a preliminary and individual calibration is required, so at least two known BP measurements are necessary.

Also with this approach, the algorithm development and first evaluation have been carried out on signals taken from the PhysioNet MIMIC Database. However, it is important to remark that with this method it was possible to reconsider some patients rejected by the previous technique because on their PPG waves the diastolic peak was not detectable.

As explained in the *paragraph 2.4.1*, in literature there are several definitions for the Pulse Transit Time. In this thesis work, four different implementations have been considered: the PTT peak, the PTT middle and two different PTT foot approaches. All these three parameters represent a time interval between the ECG R-Peak and a characteristic point on the photoplethysmographic signal evaluated on the same cardiac cycle. What changes among PTT peak, PTT foot and PTT middle is the characteristic feature considered on the PPG signal which can be respectively: the maximum peak, the foot or the point of maximum first derivative of the sphygmic wave.

In the following paragraphs are detailed the extraction steps adopted for each of the considered PTT intervals and the resulting blood pressure estimation.

4.2.1 Algorithm description

ECG signal preprocessing and R peaks detection

The algorithm starts analyzing the electrocardiographic signal in order to locate R-peaks on the waves, those peaks are then used as starting point for the pulse transit time intervals.

The QRS complex is the most striking waveform within the ECG, since it establishes the heartbeats event localization. QRS complex or R peak detection provides the fundamentals for almost all automated ECG analysis algorithms *[53]*.

As mentioned in *Chapter 2*, with R wave detection it is intended the correct identification of the instant when depolarization of the ventricles occurs in the heart. This

physiological event has the largest amplitude than the rest of the waves forming the signal and it has a very short lifespan (about 60-100 *ms*).

Whenever a heartbeat takes place, acquisition system electrodes record the electrical pattern due to the ventricles depolarization. This event, as for all the biological signals, can be very difficult to recognize. This is because ECG signal is affected by physiological randomness, variability and several kinds of noise as muscle noise, artifacts due to electrode motion, power-line interference, baseline wander, and T waves with high-frequency characteristics similar to QRS complexes.

In this thesis it has been chosen to implement the Pan-Tompkins QRS detection algorithm, one of the most important and reliable methods for R-peak detection. The Pan-Tompkins method already considers a noise reduction phase, so no further ECG signal filtering steps are required.

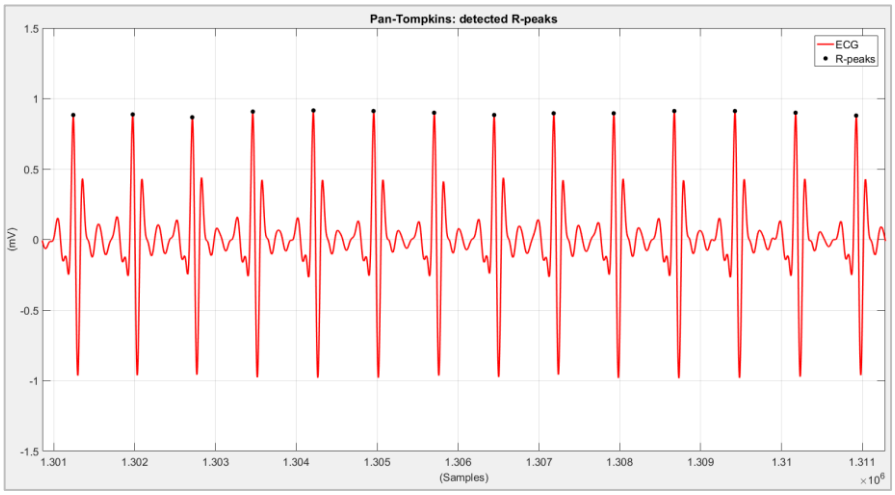

Figure 4.26 The figure shows the output of Pan-Tompkins QRS detection algorithm: indeed, in black, are reported the R-peaks on ECG signal

In the ECG preprocessing stage, only a resampling routine has been implemented. As in the PPG feature-based method, it has been chosen an upsampling factor of 10, increasing the sampling frequency from 125 Hz to 1250 Hz. In this way an error of few samples in the identification of the R-peaks is less significant in the calculation of the Pulse Transit Time. The ECG signal is then ready to pass through the Pan-Tompkins algorithm and the detected R-peaks in output are shown in *Figure 4.26*.

PPG signal preprocessing and feature extraction

After the detection of R-peaks in the ECG signal, it is necessary to analyze the PPG in order to detect the PTT interval ending points.

Before to start to analyze the PPG, a filtering and resampling process is carried out by a 5th order Butterworth bandpass filter with an upper cutoff frequency of 7 *Hz* and a lower

cutoff frequency of 0.3 *Hz,* while the resampling phase will increase the sampling frequency from 125 *Hz* to 1250 *Hz*.

Therefore, a routine that locates the PPG characteristic points is developed. It is very important to accurately identify those peaks because a wrong identification leads to a wrong PTT calculation and finally to a wrong BP estimation. To accomplish this task, a threshold algorithm working on limited portion of the signal (windows) is implemented.

Among the algorithms based on different definitions of PTT, the only changing step is the extraction of the characteristic point on PPG waveform. As previously said, the PTT peak (*Figure 4.27*) requires the PPG peak (systolic peak) to be detected on every cardiac cycle.

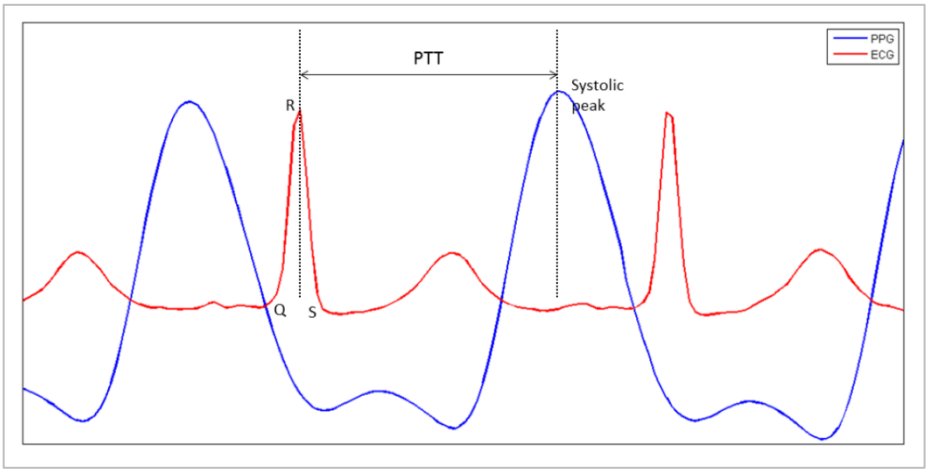

Figure 4.27 Definition of PTT peak: distance between the R-peak of ECG signal and systolic peak of PPG signal.

Since the PTT peak interval starts from the R peak of an ECG wave and it ends on the peak of the PPG wave of the same heartbeat, therefore all systolic peaks are inevitably located between two consecutive R peaks. Considering this, the algorithm analyzes each portion of the PPG signal between two subsequent R peaks, searching the location of its maximum point. To improve the research and to avoid the detection of wrong systolic peaks, it is defined a blanking time of 200 *ms* which follows each R peak and where the PPG peak detection is avoided (*Figure 4.28*). This time interval is sufficient to prevent the algorithm to detect noisy PPG systolic peak during the blanking time. On the other hand, the defined blanking period prevents to correctly detect peaks with a heart rate in excess of 210 *bpm*, which indicates a non-physiological condition or at least a very high tachycardia.

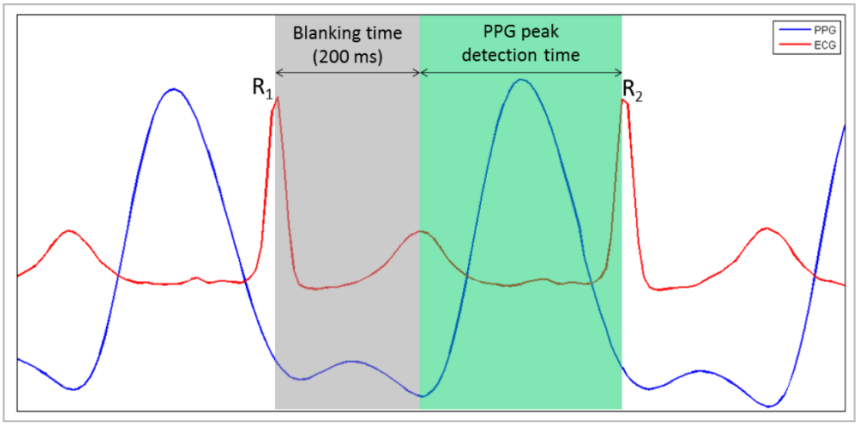

Figure 4.28 In the amount of time between two R-peaks it is defined a blanking time of 200 ms where the PPG peak detection is prevented.

Hence, to perform the PPG peaks detection, for each R-peak located over the ECG signal, three R-R windows are defined as shown in greater detail in *Figure 4.29*:

- The first window ($Window_{-1}$ in *Figure 4.29*) involves the time interval between the R peak before the one considered in this cycle and the current R peak, excluding the blanking time.
- The second window ($Window_{curr)}$ considers the current heartbeat but it starts from the current R peak plus the blanking period and it ends with the R peak of the successive heartbeat.
- The third window ($Window_{+1}$) is comprised between the R peak of the heartbeat following the current one and the R peak of the second ECG wave after the current, disregarding the blanking period.

Once defined the time windows, in each of them it is calculated the mean value of the comprised PPG signal, so three average values of the PPG signal are generated (PPG_{avg-1}, $PPG_{avgcurr}$ and PPG_{avg+1} in *Figure 4.29*).

Then, these three values are averaged in order to obtain only one mean value of PPG which will be considered the threshold value characterizing the current cardiac cycle (PPG_{avgi}). Summarizing, for each heartbeat detected, it is calculated a corresponding PPG mean value, obtained considering three windows on the signal (the current, the previous and the following one) and this mean value is then used as a threshold for the detection of PPG peaks, as described later.

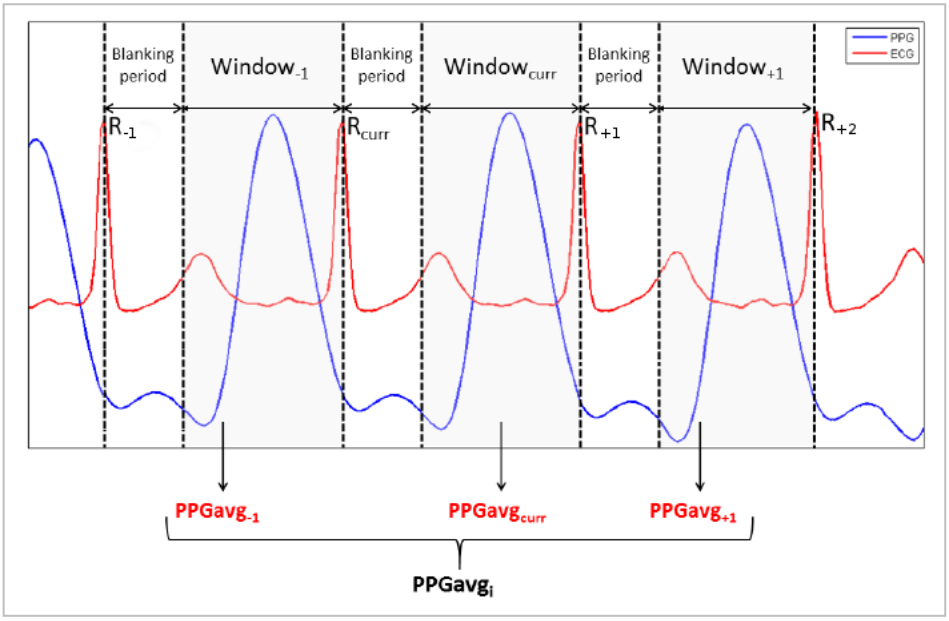

Figure 4.29 A portion of PPG and ECG signals analyzed in an algorithm cycle: highlighted the three windows considered.

To locate PPG systolic peaks, a maxima detection routine has been implemented for each $Window_{curr}$ (see *Figure 4.29*) considered. It consists of three phases:

1. PPG maximum points detection;
2. Amplitude averaging of PPG maximum points;
3. Threshold classification.

Therefore, the first phase consists in finding all PPG maximum points included between the ECG R-peak of the current heartbeat and the R-peak of the following heartbeat, without considering the blanking interval. This detection has been performed calculating the difference quotients over the portion of PPG signal and evaluating where they are positive and negative. However, in this way also noisy PPG peaks could be detected, so the algorithm needs two other sharpening steps.

In the second phase, to reject the local maxima that could be identified in the previous phase, only the maximum value among the detected maxima (on the considered window) is taken into account from now on.

Finally, to classify this global maximum point as a systolic peak for PPG, it has been compared with the threshold calculated in the previous step of the algorithm for this time window. Only if the amplitude of this maximum is greater than the threshold value, it is classified as a systolic peak and then used to calculate the PTT peak.

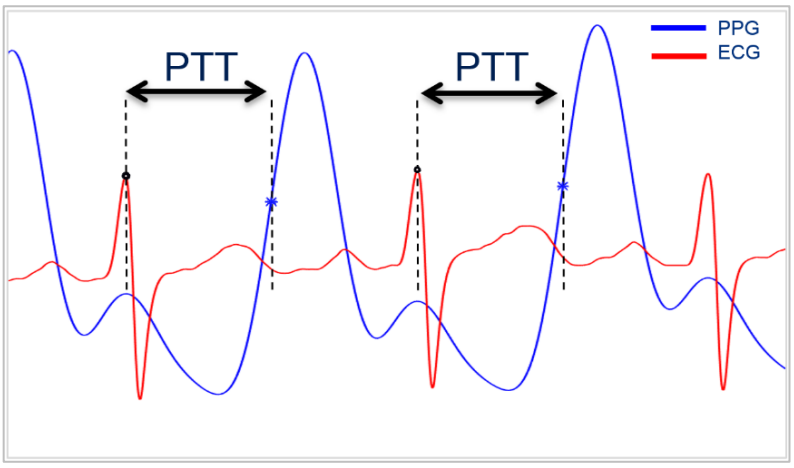

Figure 4.30 Definition of PTT middle: distance between the R-peak of ECG signal and the maximum point of the PPG signal first derivative.

Considering the PTT middle (*Figure 4.30*), the maximum of PPG signal first derivative has to be detected on every PPG wave. So, the same routine already described above, is applied on first derivative of PPG signal: the maximum point of first derivative is searched between two consecutive R-peaks (blue star markers in *Figure 4.30*).

When approaching PTT foot, a chance to act is to identify the point at which the second derivative is maximum (black circles on PPG signal in *Figure 4.31*). It is a less used approach, but the simplest one to detect the PPG foot.

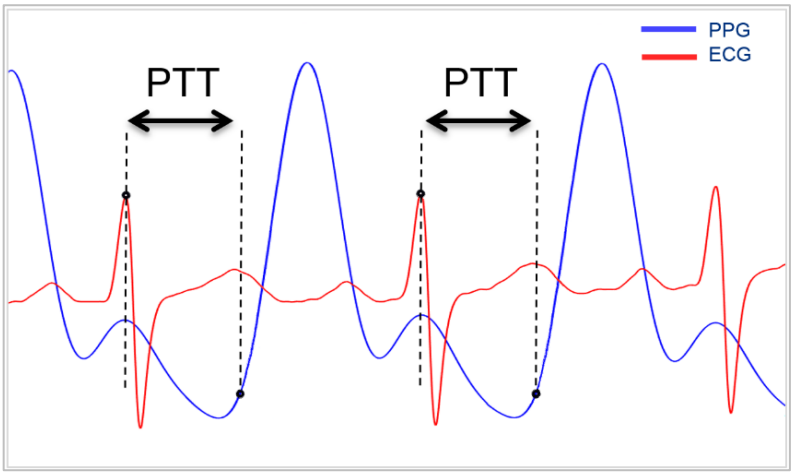

Figure 4.31 Definition of PTT foot: distance between the R-peak of ECG signal and PPG foot, detected identifying the maximum of second derivative.

An alternative of PTT foot (*Figure 4.32*) requires the extraction of the PPG foot through the intersecting tangent technique. As shown in *Figure 4.32*, once got the maximum of PPG first derivative (blue star markers), similarly to the PPT middle, a line centered on it is generated, extending itself adding points along the systolic upstroke until the

correlation coefficient between the fitted line and the PPG signal became less than 0.999. The characteristic point is the intersection of this line (magenta line in *Figure 4.32*) and a horizontal line that passes through the point of absolute minimum of the PPG waveform (cyan line). In this way the PPG feet are determined and will be used, together with ECG R-peaks to calculate the PTT foot.

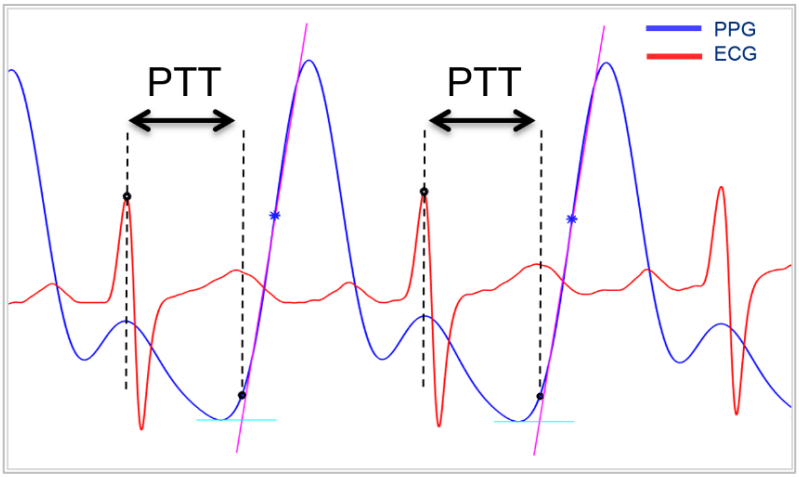

Figure 4.32 Definition of PTT foot: distance between the R-peak of ECG signal and PPG foot, detected through the intersecting tangent technique.

Considering physiological waves of the analyzed signals of the MIMIC database ranging between -0.5 mV and 1 mV, a reasonable implication is that the PPG systolic peaks should have at least positive amplitude; therefore, a second step of systolic peaks filtering is the exclusion of those identified out of 0 - 1 mV, taking into account that in the portions of the signal around there may be other peaks wrongly identified because of motion artifacts. Therefore, also in this case, a window of a second around the noisy peak is investigated, deleting all the systolic peaks inside. Analogously, the first derivative maxima of PTT middle are excluded if out of 0 – 0.5 mV and the range of identification of the PPG feet is -0.5 – 0 mV.

This feature extraction routine, regardless whether PTT peak, PTT foot or PTT middle, is cycled for each ECG R-peak, however there could be some cases where nothing can be detected between two R peaks, so it is necessary to reject the corresponding ECG peak. This is implemented updating a new vector of R waves for each detected PPG characteristic point; in this way the one-to-one correspondence between the two features is guaranteed. The result is a vector of R waves for each detected and filtered PPG points and it is possible to calculate a reasonable value for the PTT.

PTT calculation

At this stage of the algorithm, the pulse transit time is calculated through a difference between the vector of PPG characteristic points positions and the vector of R waves positions.

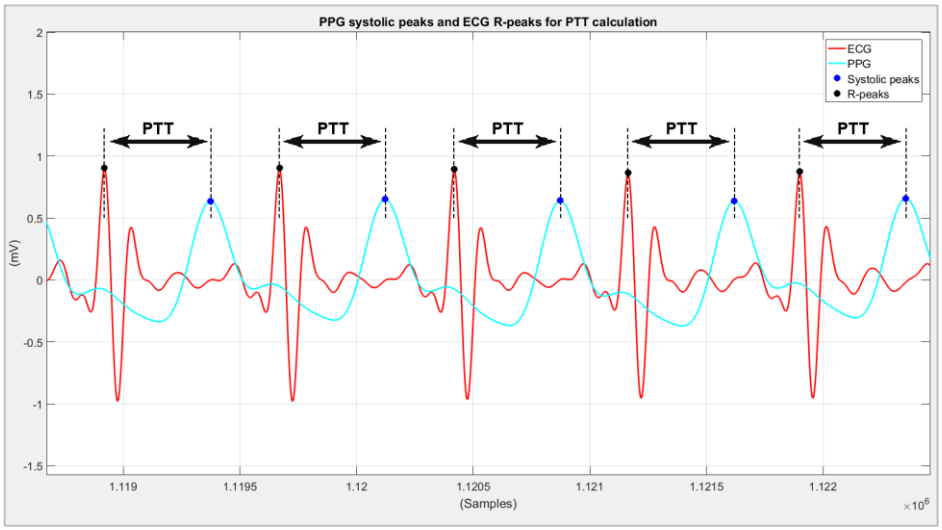

Figure 4.33 Portion of PPG and ECG signals: are highlighted the PPG systolic peaks (blue dots) and the ECG R-peaks (black dots). PTT peak will be calculated as time difference between them.

In the upper plot of *Figure 4.34* is represented a portion of the PTT peak calculated in each acceptable heartbeat. It is possible to see that the majority of PTT values is included between 350 and 450 *ms*, but in some cases time intervals fall outside this range. The PTT values into the black circles correspond to wrong detections of R peaks or PPG peaks that result in too high or too low time intervals. To filter the PTT signal and reject these wrong time intervals, it has been decided to apply a moving average routine and, after some tests, the final size of the sliding window is 30 samples, or rather cardiac cycles.

However, having PTT values on every heartbeat leads to a redundant amount of information about SBP/DBP estimation. As said in previous chapters, it is enough to generate an output every minute, so PTT values are averaged on a window of 60 *s*.

The output of this function is an array of filtered mean values (computed on each minute) of PTT, calculated using the PTT peak definition, which is the starting point to estimate SBP and DBP through Moens-Korteweg equation. Nevertheless a calibration phase is indispensable, so in the next paragraph is shown the algorithm related to the analysis of the BP signal and the extraction of two measurements that, together with two values from the array of PTT, will lead to Moens-Korteweg unknown parameters identification.

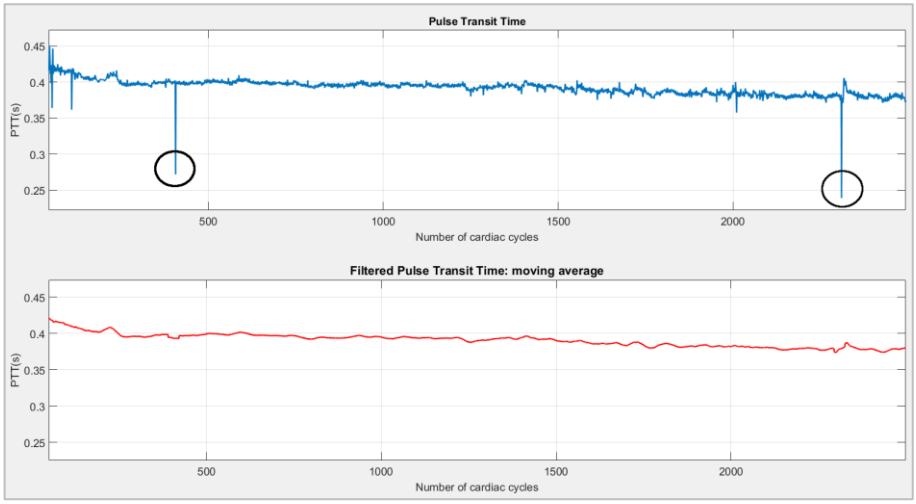

Figure 4.34 A portion of PTT peak trend, before (upper plot) and after (lower plot) a moving average routine. In the black circles noisy PTT values are highlighted.

Calibration Phase and Moens-Korteweg equation

As described in the previous chapters, starting from the Moens-Korteweg equation, it is possible to define SBP and DBP respectively, as:

$$SBP_i = \frac{1}{\alpha_{SBP}}(A_{SBP} - 2\ln(PTT_i)) \tag{4.10}$$

$$DBP_i = \frac{1}{\alpha_{DBP}}(A_{DBP} - 2\ln(PTT_i)) \tag{4.11}$$

where α is a constant that depends on the vessel and varies for SBP and DBP estimation and the other variable, which also varies for SBP and DBP, is

$$A = ln\frac{L^2\rho d}{tE_0} \tag{4.12}$$

where L is the length of the pulse wave propagation along the artery, ρ is the blood density, d is the interior diameter of the vessel, t is the thickness of vessel wall and E_0 is the Young's modulus of the zero pressure.

Therefore, with the previous equations, giving as input the extracted PTT on every acceptable minute of the acquired signals, it is possible to obtain as outputs the SBP and DBP values of the subject in the corresponding minutes. However, to solve equations it is necessary to know in addition to the PTT, also the values of α and A. These are variable parameters that change from patient to patient, but they can be considered as constants among acquisitions on the same subject.

A preliminary phase of individual calibration of the system is therefore necessary to infer the values of α and A for the systolic and diastolic pressure measurements,

respectively. So, also this method requires a BP signal where to extract real SBP and DBP values. The calibration is performed through two systems (for SBP and DBP) of two linear equations, in two variables (α and A):

$$\begin{cases} SBP_1 = \frac{1}{\alpha_{SBP}}(A_{SBP} - 2\ln(PTT_1)) \\ SBP_2 = \frac{1}{\alpha_{SBP}}(A_{SBP} - 2\,ln(PTT_2)) \end{cases} \tag{4.13}$$

for the systolic blood pressure, where 1 and 2 refers to two chosen minutes;

$$\begin{cases} DBP_1 = \frac{1}{\alpha_{DBP}}(A_{DBP} - 2\ln(PTT_1)) \\ DBP_2 = \frac{1}{\alpha_{DBP}}(A_{DBP} - 2\,ln(PTT_2)) \end{cases} \tag{4.14}$$

for the diastolic blood pressure, with not necessarily the same minutes of SBP.

SBP_1, DBP_1 and SBP_2, DBP_2 are the values extracted from the BP signal, with a BP processing identical to that performed in PPG feature-based method, founded on maximum and minimum detection, filtering and at last averaging on every minute. From the array of mean SBP and DBP, to choose the right minutes to use in the calibration phase, it has been implemented a simple Matlab routine which, evaluating the difference quotient for each point of the signal, chooses the time instants where the BP values are the highest and the lowest, respectively. In any case, these points should not be part of noisy areas of the signal.

A and α parameters are calculated as follows:

$$\begin{cases} \alpha_{SBP} = \frac{1}{SBP_2 - SBP_1} 2\,ln\frac{PTT_1}{PTT_2} \\ A_{SBP} = \frac{SBP_1}{SBP_2 - SBP_1} 2\,ln\frac{PTT_1}{PTT_2} + 2\,ln\,PTT_1 \end{cases} \tag{4.15}$$

for SBP calibration;

$$\begin{cases} \alpha_{DBP} = \frac{1}{DBP_2 - DBP_1} 2\,ln\frac{PTT_1}{PTT_2} \\ A_{DBP} = \frac{DBP_1}{DBP_2 - DBP_1} 2\,ln\frac{PTT_1}{PTT_2} + 2\,ln\,PTT_1 \end{cases} \tag{4.16}$$

for DBP calibration.

Summarizing, having the PTT array from the recording signals and applying the equations *(4.9)* and *(4.10),* it is possible to estimate the SBP and DBP minute values only from ECG and PPG signals. However, to apply the previous equations it is necessary to implement an individual calibration of the algorithm, in order to calculate the variables α and A from at least two known measurements of SBP and DBP.

4.2.2 Characteristic points comparison

All the characteristic points of the photoplethysmographic signal found in literature have been investigated looking for the time interval between them and the ECG R-peak which, used in the Moens-Korteweg equation, leads to the best blood pressure estimate.

A first upstream analysis among them has been made in terms of accuracy of the resulting PTT, before turning to the correctness of the blood pressure estimate. It is assumed that a patient with a stationary systolic and diastolic blood pressure has a corresponding PTT as steady as possible. From this perspective, taking three sections of stable blood pressure signals and deriving the PTT intervals from the corresponding photoplethysmographic and electrocardiographic signals, their standard deviations, as an index of variability of the measure, have been evaluated since they should approach zero. In *Table 4.3* the values of standard deviation are reported, along with the number of cardiac cycles for which it was possible to extract both the ECG R-peak and the PPG characteristic point. For simplicity, the two different methods to extract PTT foot are indicated as PTTfoot1 and PTTfoot2, referring to that involving the intersecting tangent technique and the maximum of second derivative respectively.

Table 4.3 Pulse Transit Time standard deviations (in s) and number of cardiac cycles considered in three different sections of acquisition signals with stationary blood pressure

Patient 055 (27 min)	*PTTpeak*	*PTTmiddle*	*PTTfoot1*	*PTTfoot2*
Standard Deviation	0.0018	0.0018	0.0026	0.0368
Cardiac Cycles	2423	2425	2385	2425

Patient 224 (53 min)	*PTTpeak*	*PTTmiddle*	*PTTfoot1*	*PTTfoot2*
Standard Deviation	0.002	0.0016	0.0016	0.0234
Cardiac Cycles	3888	3894	3894	3894

Patient 237 (13 min)	*PTTpeak*	*PTTmiddle*	*PTTfoot1*	*PTTfoot2*
Standard Deviation	0.0082	0.0088	0.0089	0.1740
Cardiac Cycles	894	961	975	975

Already at this level, after the PTT accuracy analysis, the PTTfoot2, which uses the maximum of second derivative as characteristic point on the PPG signal, has been excluded, because reports a standard deviation an order of magnitude larger than the other kinds of Pulse Transit Time. For this reason, second derivative based PTT feature has not been further considered for the blood pressure estimation.

4.2.3 Results review

The previous described algorithm of blood pressure estimation, with its variants depending on the chosen characteristic point on the PPG signal, is applied on one hour of acquisition from the *Subject 055* (*from 16:36:26 to 17:36:26, 2 March 1995*) of PhysioNet MIMIC database.

The graphs below (from *Figure 4.35* to *Figure 4.37*) show the blood pressure estimation, resulting from the PTT approach, in comparison with the "gold standard" invasive pressure. A graph is reported for each investigated PTT on the same hour of acquisition: in addition to the systolic and diastolic pressure charts, it is illustrated also the trend of the Pulse Transit Time. It is important to highlight that in all three figures the found PTT has a trend highly symmetric to blood pressure and this fact is a prerogative to be able to correctly apply the Moens-Korteweg equation and estimate the blood pressure.

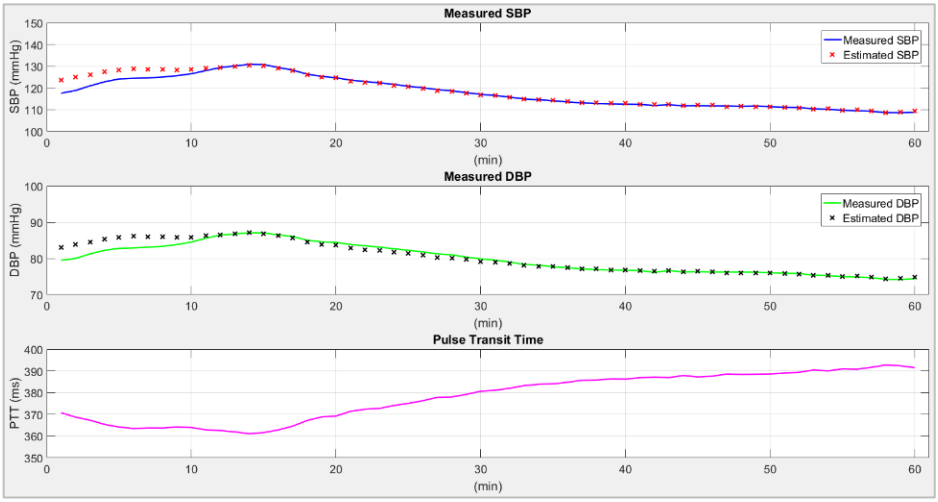

Figure 4.35 PTT peak - Trends of SBP and DBP, measured and estimated, and the PTT peak extracted during the hour of acquisition on subject 055.

Moreover, it should be noted that the values of Pulse Transit Time decrease as you move from PTT peak (*Figure 4.35* with values around 370 *ms*) through PTT middle (*Figure 4.36* with values around 300 *ms*) to PTT foot (*Figure 4.37* with values around 240 *ms*), as it should be due to the prior detection of the characteristic point on the photoplethysmographic waveform.

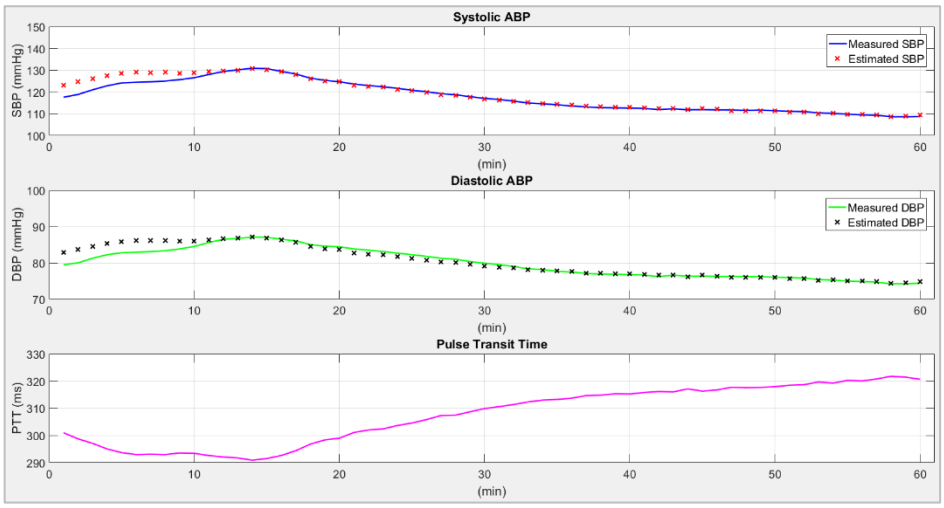

Figure 4.36 PTT middle - Trends of SBP and DBP, measured and estimated, and the PTT middle extracted during the hour of acquisition on subject 055.

Mostly, the Pulse Transit Time based algorithm well succeeded to estimate blood pressure: it is able to retrieve all the variations present in the measured pressure trends, with a slight initial deviation. In all the cases the solid lines (measured BP) and dotted ones (estimated BP) are always very similar, but a quantitative analysis can be addressed in order to discriminate between them. In *Table 4.4* the mean differences and their standard deviations between measured and estimated blood pressure are reported for a comparison among the addressed PTT end point: peak, middle or foot.

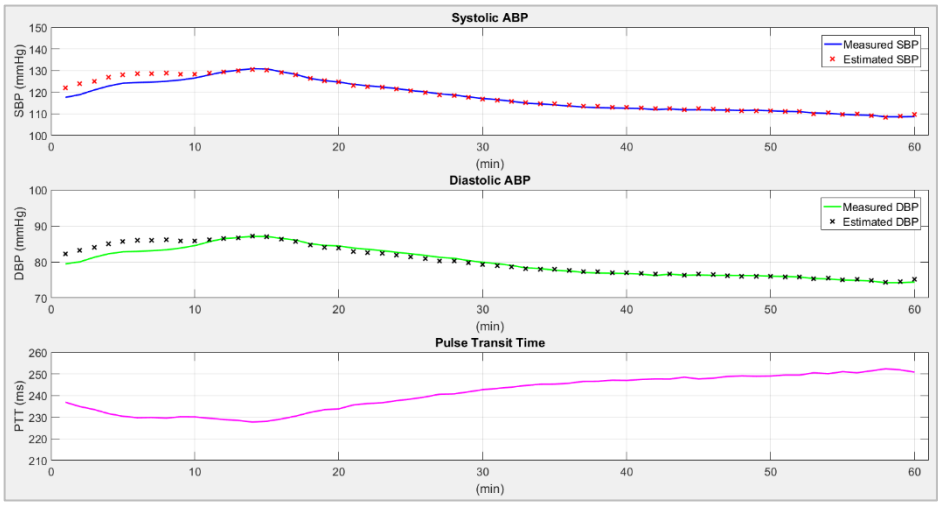

Figure 4.37 PTT foot - Trends of SBP and DBP, measured and estimated, and the PTT foot extracted during the hour of acquisition on subject 055.

Table 4.4 Averages and standard deviations of the differences among the BP estimation and the measured BP, using Pulse Transit Time for the Subject 055 (numbers are in the form of Mean Value ± SD)

PTT approach	*SBP (mmHg)*	*DBP (mmHg)*
PTT peak	0.91697 ± 1.7108	0.77692 ± 1.2732
PTT middle	0.97975 ± 1.7326	0.81013 ± 1.2805
PTT foot	0.87488 ± 1.4835	0.73981 ± 1.1483

Making a comparison among the three remaining PTT intervals (PTT peak, PTT middle and PTT foot), not only in terms of accuracy of the PTT, as debated in the previous paragraph, but also of the pressure estimation that results, there are very small differences that don't lead to a preference of an approach more than another.

From a medical point of view, if the starting point which indicates the beginning of the Pulse Transit Time is the ECG R-peak, on the PPG signal the feature to choose is likewise one that marks the beginning of the pressure wave, or rather the exact arrival of the wave started with the R-peak. Consequently, the PTT foot would appear to be the best choice, but due to the fact that statistical results achieved so far are quite similar, all the addressed features, only excluding the one based on second derivative, will be considered on the clinical trial.

4.3 Methods comparison

After a first phase of the study, with validation of the algorithms on PhysioNet signals, as has already become evident, both the method based on PPG signal standalone and the method based on the Pulse Transit Time lead to a pressure estimate not so distant from the real one, therefore they are equally considered fairly acceptable. The comparison among the two approaches shows that technical observations and the final application target should be considered. The first discussed method, or rather the PPG-based one, looks very promising in the consumer business, given the need only for the photoplethysmographic signal in order to achieve the desired result. On the other hand, the algorithm which uses the Pulse Transit Time, requiring also the electrocardiographic signal, is more suitable for medical services. This one can be useful in several applications: it would allow to take under control patients not only in operating rooms and ICUs, the only ones where the blood pressure is currently measured in the invasive way, but in any hospital room and moreover it would enable the telemonitoring for a medical supervision comfortably from home.

As debated in the following chapter, a critical issue in the PPG-based algorithm, addressed during the clinical trial at San Giovanni Bosco hospital, is the presence, and the consequent detection, of a diastolic peak, allowing the calculation of time interval which leads to the blood pressure estimation. This represents a key point in the comparison among the two methods, especially when considering the consumer application target.

Chapter 5

Algorithms Refinement

A further step has been carried out in collaboration with San Giovanni Bosco hospital in Turin, acquiring electrocardiogram, photoplethysmogram and invasive blood pressure signal from ICU patients, by means of the GE Healthcare S/5 Collect software. The captured signals are representative of real situations, belonging to ICU patients whose health conditions are very critical, notwithstanding the exclusion from the study of hypercritical pathologies as described in *paragraph 3.2.1*. The variety of acquired signals has led to further considerations and driven the development and improvement of the adopted algorithms.

5.1 Pulse Transit Time based method

5.1.1 Algorithm enhancement and noise reduction

With reference to the algorithm flowchart described in the previous chapter (*Figure 4.25*), the main steps of the PTT approach remain the same, but a gradual software improvement has been achieved as the first signals from San Giovanni Bosco hospital have been acquired. In an early stage, it has been decided to be more aggressive in the noise reduction, aiming for quality over quantity, and any modification has been made towards the algorithm robustness enhancement.

From the ECG signal point of view, Pan-Tompkins routine performs the R-peaks detection, but an upstream filtering has been inserted with the help of an ECG signal trace. Applying the QRS detection algorithm on signals with frequent movement artefacts may lead to wrong detection of R-peaks due to the adaptive threshold approach of the routine: indeed, in presence of noisy areas, it follows the noise trend and it does not proper detect the R-peaks on the following signal recovery. In order to avoid those situations, the ECG signal is considered only in tidy regions, in line with signal standard deviation values. Movement artifacts and flat lines are excluded, due to respectively too high or too low values in a signal window of 2 s, referring to the mean standard deviation of all the filtered signal. A support signal of the same length keeps trace of clean (signal at ‘1’) and noisy areas (signal at ‘0’). The *Figure 5.1* makes

it clear, showing the R-peaks detection disabled in noisy areas or flat lines, with a blanking window of some seconds at their extremes.

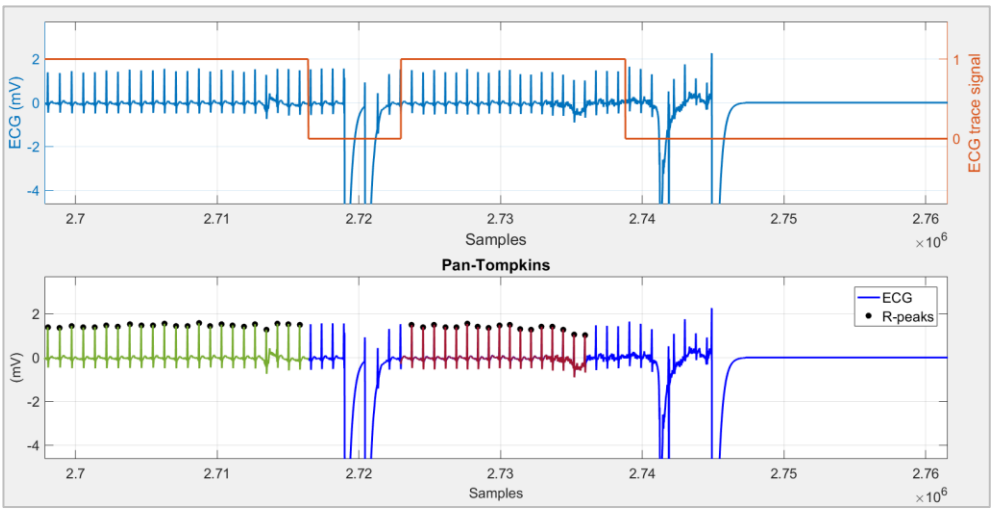

Figure 5.1 On the top the ECG signal in blue and the ECG trace signal in orange. On the bottom the Pan-Tompkins detection of R-peaks only in correspondence of enabled zones (ECG trace equal to 1)

On the other side, the PPG features are filtered too. Whereas the filtering in the algorithm based on PhysioNet signals relies on their stable dynamic, with the arrival of ICU signals from Giovanni Bosco a change in the approach has become necessary.

Just after the peaks, middle points and feet extraction, implemented in the same way as described in the previous chapter, they are filtered according to their respective mean value and standard deviation computed on the previous five minutes. This method allows to follow the potential floating dynamics, nevertheless being able to exclude incorrect features. As shown in *Figure 5.2*, the algorithm rules out all the features in the noisy part of the signal, taking an additional 2.5 *s* safe interval on both sides of the borders.

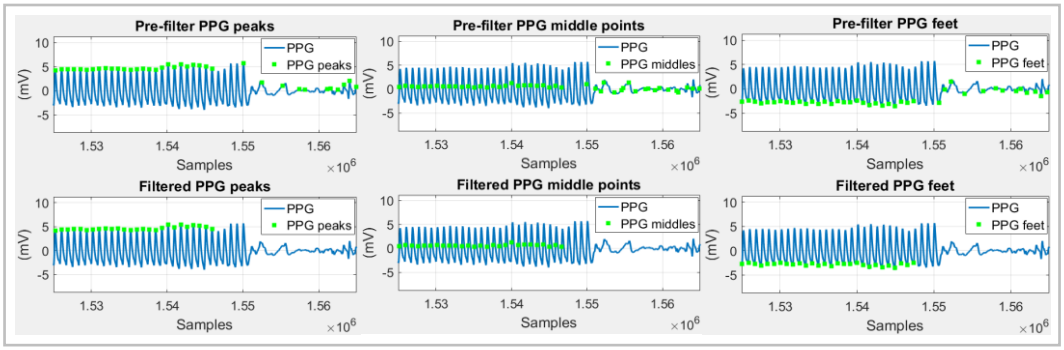

Figure 5.2 The PPG peaks, feet and maxima of first derivative (middle points) are filtered if beyond their respective mean value plus or minus 2.5 times their standard deviation value in the previous five minutes. A blanking window of 2.5 s is considered on both sides of the considered noisy regions.

Once calculated the Pulse Transit Time on every cardiac cycle as time interval between the PPG feature and the correspondent R-peak, it is filtered using the same methodology. The PPT values are filtered out if beyond the range of its mean value plus or minus its standard deviation computed in the previous five minutes (*Figure 5.3*).

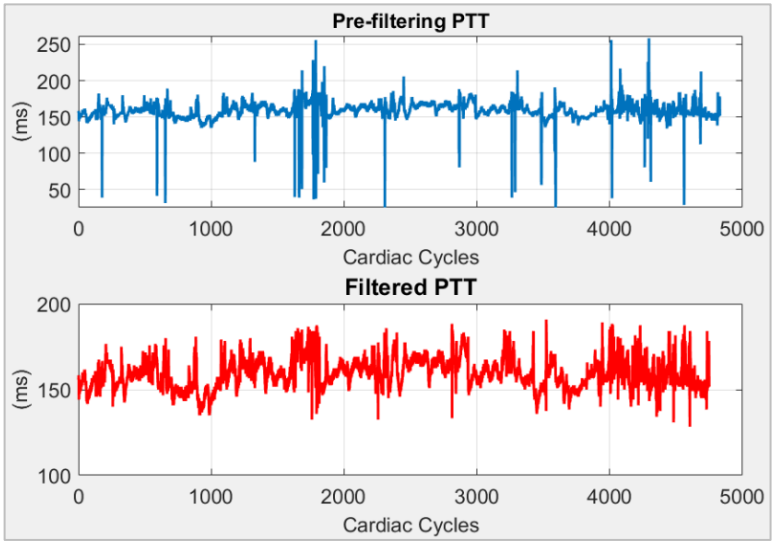

Figure 5.3 On the top the Pulse Transit Time (in this example PTT foot), computed on each cardiac cycle. On the bottom, only the filtered PTT values are displayed.

The one-minute averaging of this array of PTT is the input of the Moens-Korteweg equation; only the analysis of the BP signal and the extraction of the appropriate values for the calibration phase are left to analyze.

An improvement in BP analysis has been made with the pressure filtering, since the algorithm based on MIMIC database merely extracted the SBP/DBP from the pressure peak/nadir of the pressure curve. In the San Giovanni Bosco hospital ICU patients many alterations, that may result from the measurement environment or typical of pathological contexts, have been encountered. Examples of practical occurrences may be the kinking of the cannula or the coagulation around the nozzle.

Since varying the position of the cannulated limb, the waves gain or lose pulsatility and reliable data, noticing and filtering untrusted values become fundamental. Among the acquired signals there have been cases to be evaluated, because of abnormal stair-stepped pressure curves due to the approach of the cannula towards the arterial wall. These steps are not considered thanks to a first filtering based on the mean value and the standard deviation of the systolic and diastolic curve (*Figure 5.4* on the left). Another encountered peculiarity is the pressure variability during spontaneous breathing or mechanical ventilation. Indeed, between inspiration and expiration especially the systolic curve oscillates around its value. Therefore, it has been

implemented an additional median filter to extract the real values of SBP and DBP during these oscillations. An example of the results achievable by means of the additional filtering steps are reported on the plots of *Figure 5.4*.

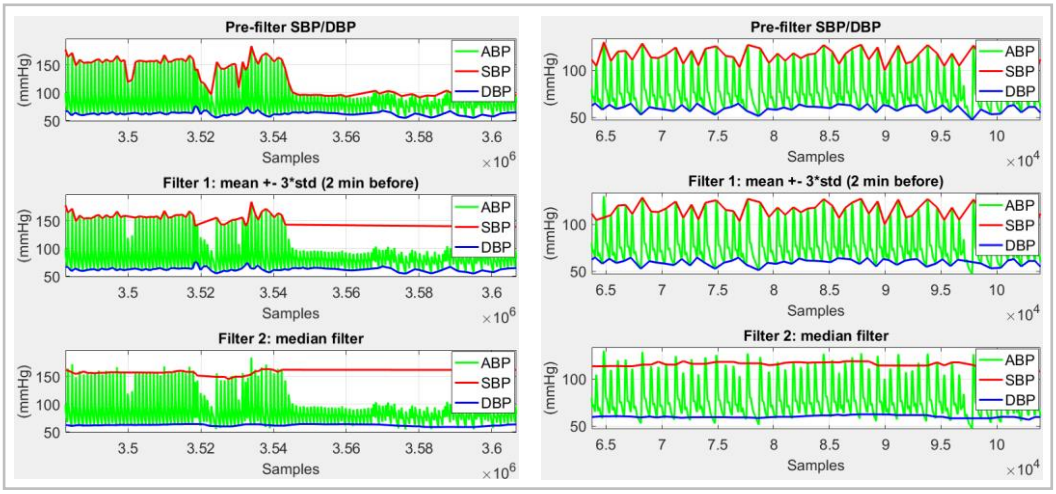

Figure 5.4 Starting from the top to the bottom, the sequence of the SBP/DBP filters is shown. On the left an example of a pressure step is displayed, showing the pressure curve which goes from 160 mmHg to the abnormal value of 100 mmHg. The first filter allows to exclude the non-physiological values. On the right, instead, the second median filter helps in finding a mean value of SBP and DBP during the breathing oscillations.

After the described filtering strategy, values of SBP and DBP are then respectively averaged over a minute and two values are selected for the calibration, together with the correspondent PTT values extracted in the same minutes.

In the algorithm described in the previous chapter, the calibration phase has been performed choosing the minutes in which the blood pressure has the highest and the lowest value. This may lead to wrong estimate due to the higher probability of noise impact on the maximum variation. An improvement has been made in this direction. During this early phase, to verify the sustainability of the concept behind the algorithm, it has been decided to apply the ideal conditions, by which the chosen minutes are the ones that allow the best blood pressure estimation. This is the only way to check the algorithm results, independently of any calibration.

5.1.2 PTT based method validation

The improved PTT algorithm has been applied on the ICU patients' signals coming from San Giovanni Bosco hospital. The graphs below (from *Figure 5.5* to *Figure 5.7*) show the *Patient 18* blood pressure estimation, resulting from the three different PTT extraction methods, in comparison with the "gold standard" invasive pressure.

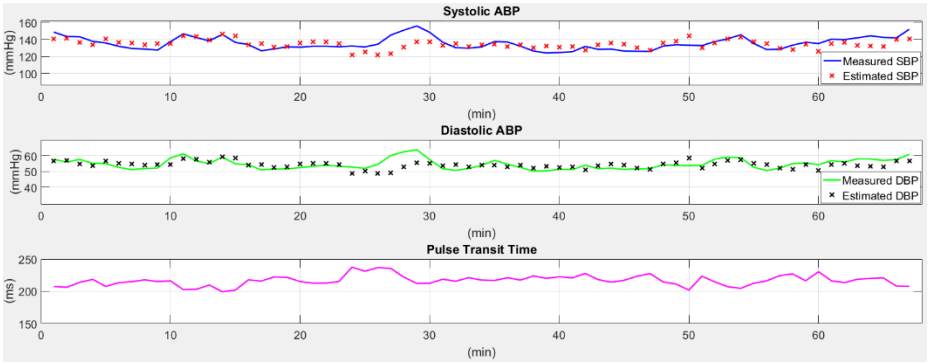

Figure 5.5 The figure shows trends of SBP and DBP, measured and estimated. On the bottom is shown the PTT foot, from which the blood pressure estimation has been made.

All the addressed approaches lead to a valuable estimate, particularly accurate especially for PTT foot and PTT middle. The trends of estimated SBP and DBP follow well enough all the actual curves variations. Only around the thirtieth minute the estimated curve increases lightly, but not enough according to the measured BP rise. On the other hand, the PTT peaks leads to a sloppier estimate.

Beyond a qualitative evaluation, as illustrated in *Table 5.1*, the mean differences between estimated and measured BP and their standard deviations show the best PPG characteristic point is the foot, followed by the middle.

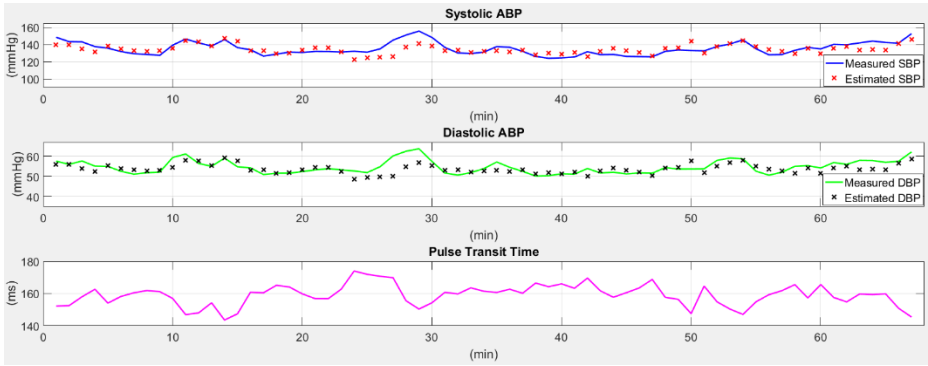

Figure 5.6 The figure shows trends of SBP and DBP. On the bottom is shown the PTT middle, from which the blood pressure estimation has been made.

Therefore, the PTT foot has been chosen as the feature that leads to an accurate BP estimation, starting from an ECG and PPG signal acquisition. As previously debated, this is also justified from a medical point of view, since the foot marks the beginning of the pressure wave as well as the R-peak is the starting point of the ventricular systole. This algorithm has been applied on all the signals coming from San Giovanni Bosco patients with an applicability percentage of 100%, since there are no constraints and niceties to observe. Among them, however, a good estimate has been observed only in the 70% of the cases, where "good" refers to a qualitative perception of the

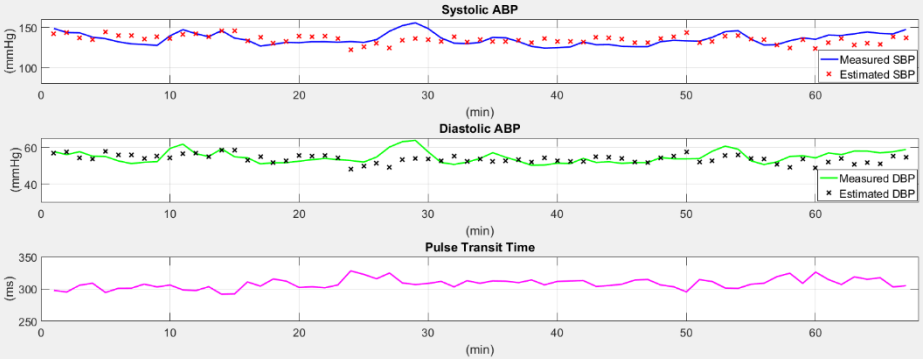

Figure 5.7 The figure shows trends of SBP and DBP. On the bottom is shown the PTT peak, from which the blood pressure estimation has been made.

ability of the algorithm output to follow the BP variations and to a quantitative rating according to the pre-established limits coming from the American Heart Association.

Table 5.1 Averages and standard deviations of the differences among the BP estimation and the measured BP, using Pulse Transit Time for Patient 18 (numbers are in the form of Mean Value ± SD)

PTT approach	*SBP (mmHg)*	*DBP (mmHg)*
PTT foot	4.75 ± 5.9776	2.1701 ± 2.7352
PTT middle	5.6519 ± 7.187	2.5426 ± 3.2318
PTT peak	6.5982 ± 8.1044	2.9842 ± 3.6792

5.1.3 PTT analysis with invasive BP

Since some discrepancies have been found, a further analysis has been conducted.

The photoplethysmographic signal leads to an information from the finger capillary level. In order to verify that the validity of Moens-Korteweg equation could be extended using an arterial information, the Pulse Transit Time has been calculated using the foot of the invasive Blood Pressure, instead of the foot of the PPG signal. The BP estimation derived from such time interval which goes from the ECG R-peak to the BP foot is shown in *Figure 5.8*.

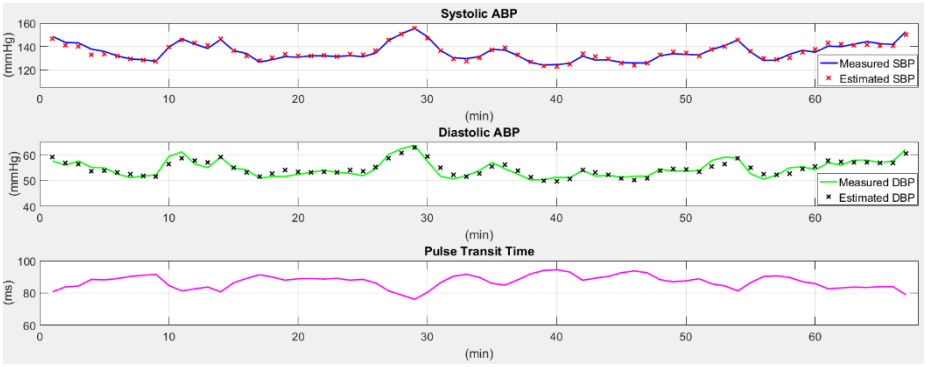

Figure 5.8 The figure shows trends of SBP and DBP, measured and estimated. On the bottom is shown the PTT using the BP foot, from which the blood pressure estimation has been made.

Just from a qualitative analysis, the BP estimation curve fits accurately with the real curve from instrumentation measurements. The Pulse Transit Time, calculated from the invasive BP, "follows" any variation and retrieves it in output with a detailed systolic and diastolic estimate, which may prove a greater validity of the basic principle.

Table 5.2 Averages and standard deviations of the differences among the BP estimation and the measured BP, using PTT foot for Patient 18 (numbers are in the form of Mean Value ± SD)

PTT approach	*SBP (mmHg)*	*DBP (mmHg)*
PTT foot	1.2878 ± 1.6383	1.1283 ± 1.3697

The reduced estimation error in *Table 5.2* represents a proof that the capillaries, from which the information is extracted with a PPG signal acquisition on the finger, have different properties from the arteries. Hence, a consideration that may implies is that an attempt to improve success percentage of this method is the PPG signal acquisition in a position on the arm closer to the BP catheter. Indeed, using this different position, the algorithm would use the arterial information which may perform better in the BP estimation. During this thesis work, it has not been possible carry out this test, due to the instrumentation supplied to the hospital. Accessing to the ICU with external tools to acquire the photoplethysmographic signal in positions different from the finger will require specific authorization not yet available.

5.2 PPG feature based method

The relevant aspect of the photoplethysmographic signal, in order to continue the study addressing only the PPG signal features, is the presence of a dicrotic notch and consequently a diastolic peak. When those features are present on the signal, it is possible to calculate the T1 interval useful to estimate the blood pressure. As previously anticipated in Chapter 3, the diastolic peak is a characteristic which tends to vanish with age. Among all the signals from San Giovanni Bosco hospital, the diastolic peak occurs in really few of them, this is because the average age of ICU patients is generally very high. Indeed, the patients who participated in our study, agreeing to send their physiological signals for research purposes, can be divided into age groups as reported in *Table 5.3*.

Table 5.3 Breakdown by age of patients, who participated in the research study

Age group (years)	*Patients*
30-39	31
40-49	5, 11, 21, 23
50-59	17
60-69	1, 3, 6, 8, 10, 16, 22, 24, 25, 26, 30
70-79	4, 7, 9, 13, 18, 19, 27, 28
80-89	2, 12, 14, 15, 20, 29

As already mentioned in *Chapter 2*, the definition of T1 depends on the PPG waveform as its contour varies with subjects and test conditions. The ending point of this time interval, by definition, is set to the point of inflection in absence of the diastolic peak. Therefore, a quick investigation has been performed with a regression analysis applied on some patients whose PPG signals did not have the diastolic peak. The results of one of them are displayed in the *Figure 5.9* and show a potential correlation between the new T1 interval and BP, since the scatter plot has a linear morphology. The straight lines which better describe these correlations are set out in red.

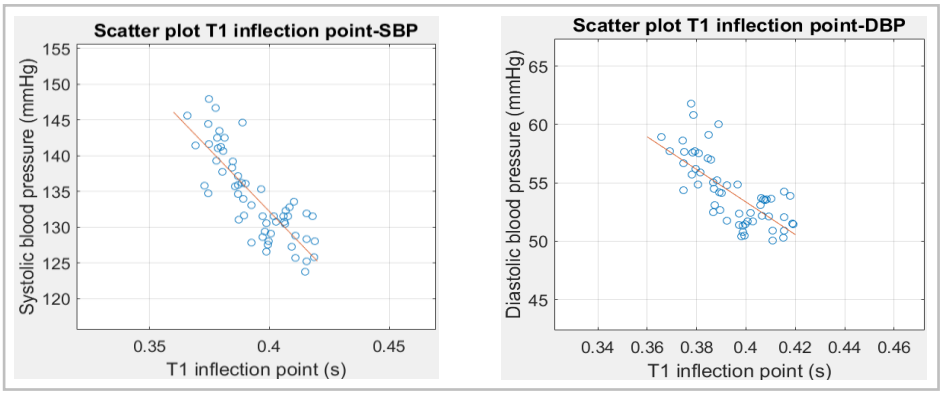

Figure 5.9 Scatter plots showing the relationships between the T1 feature, calculated as time interval between the systolic peak and the inflection point, and systolic and diastolic blood pressure (T1-SBP on the left, T1-DBP on the right).

5.2.1 Algorithm enhancement and noise reduction

The algorithm had to look for the diastolic peak as well as the inflection point, prioritising the presence of the peak when it is available, because already proven it is able to conduct to a more reliable and accurate outcome.

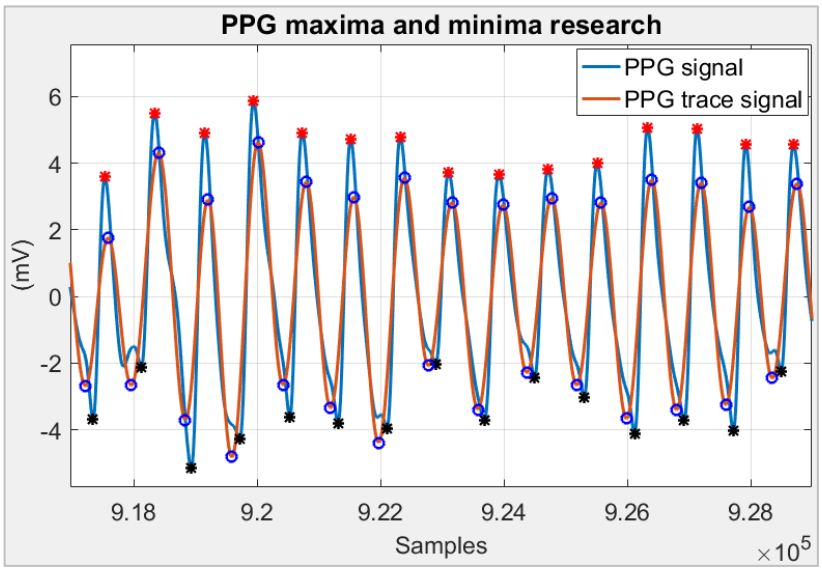

Figure 5.10 In red the PPG trace signal is displayed, with the detected maxima and minima (blue circles). In blue the PPG signal is displayed, with the correspondent maxima and minima identified in proximity of the trace signal ones (red and black star markers).

In order to synchronize the routine on the appropriate signal part for the characteristic point research and considering the different ICU patients' signals dynamics, the PPG feature extraction has been improved. A support signal, or rather the PPG signal lowpass filtered at 2 *Hz*, has been used to detect maxima and minima of the

photoplethysmographic signal. On the filtered signal the high frequency components cut and consequent noise reduction allows a more reliable identification of relative min/max points. In *Figure 5.10* is shown a portion of PPG trace signal (in red) with highlighted the maxima and minima detected. The correspondent ones in the PPG signal are identified through a window of few samples, in which the features are searched taking into account the additional shift introduced by the filter on the trace signal.

Once detected the maxima and the minima of each cardiac cycle, it is possible to look for the PPG feature between them. First of all, a peak of PPG signal is aimed and in *Figure 5.11* the red markers point out the systolic and diastolic peak of the cardiac cycles in which a peak among maxima and minima has been located. Otherwise, if the peak is not so pronounced as in the first cardiac cycles of the *Figure 5.11*, the algorithm looks for an inflection point (black marker on PPG derivative signal). In this region, for each cardiac cycle the black markers indicate the systolic peak on PPG signal and the maximum of PPG signal first derivative.

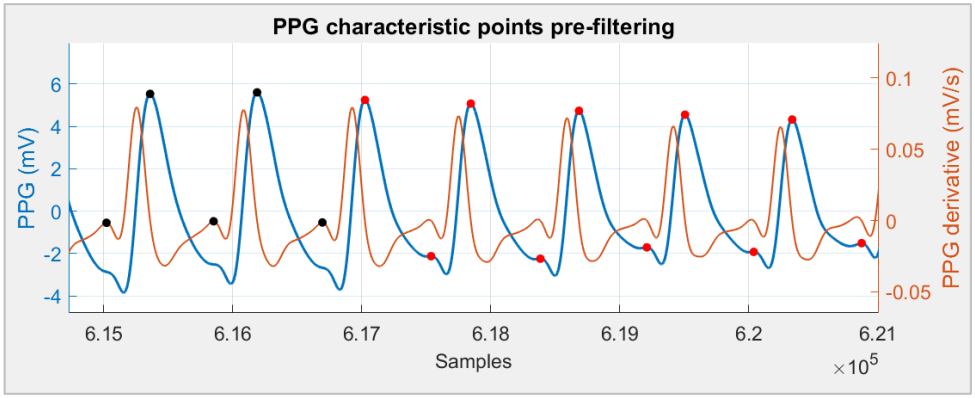

Figure 5.11 A portion of PPG signal (in blue) and its derivative (in orange) on which the feature extraction routine has found the diastolic peaks (cardiac cycles with red markers) or the inflection points (cardiac cycles with black markers) as maxima of PPG first derivative.

The two kinds of characteristic points are then filtered in amplitude using the usual method: the inflection points and the peaks are rejected if beyond the range of the respective mean value plus or minus two times their standard deviations calculated on the previous five minutes. Subsequently, the T1 time intervals are calculated, separately for the two characteristic points since the inflection point leads to a reduced value of T1 that has to be correlated with its similar ones.

The two kinds of T1 are then filtered in time using the average and the standard deviation of the previous five minutes (as shown in *Figure 5.12*) and an exclusion criterion has been selected in order to choose for which feature opt minute by minute. There may be PPG signals full of peaks, in which it is useful to exclude the inflection

points and vice versa; but there could be signals with both the features too, changing minute by minute or within a minute.

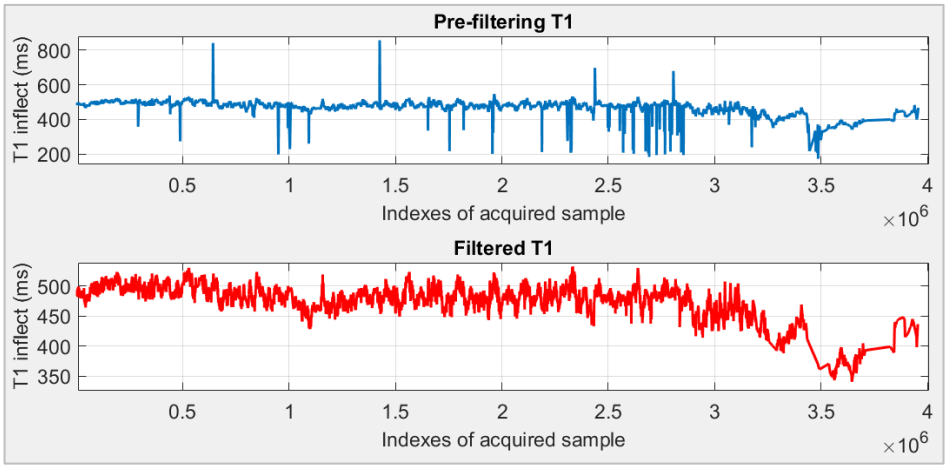

Figure 5.12 On the top the T1 time interval, calculated with the PPG inflection point on each cardiac cycle, plotted with on the x-axis the index of the acquired sample. On the bottom the same T1 array, filtered within the range of their mean value plus or minus their standard deviation in the previous five minutes.

Anyway, the two kinds of T1 time interval are averaged minute-by-minute and expecting at least 40 cardiac cycles per minute, if there are less than twenty features of a type in a minute, the corresponding T1 average is excluded. Moreover, if the final array of averaged T1 don't cover at least 30% of the total acquisition minutes, the T1 time interval of the correspondent feature is totally left out. The algorithm is able to select the most detected feature to estimate blood pressure, or both of them if sufficiently present in a similar way.

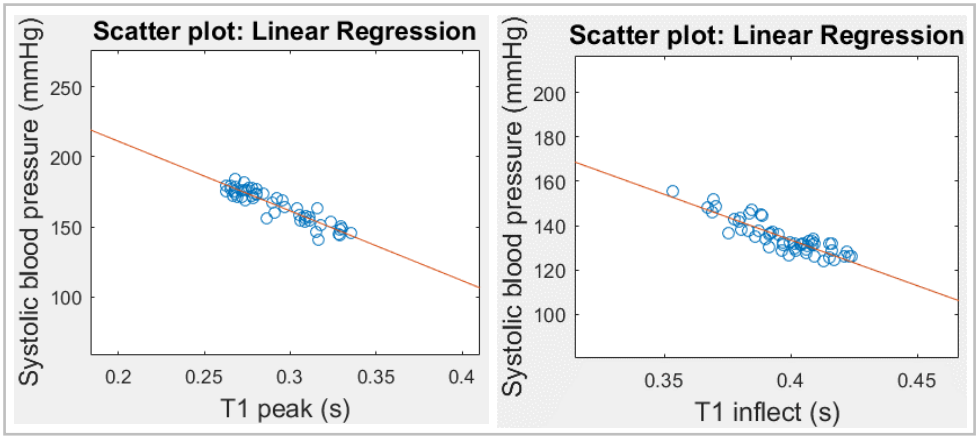

Figure 5.13 The figures show examples of relationships between T1 (on the left calculated with PPG diastolic peak and on the right with PPG inflection point) and the SBP and the closer line chosen from the algorithm is highlighted in orange.

The two arrays of T1 minute-by-minute are further given in input to the linear regression extraction model routine, together with the SBP and DBP averages calculated as in the *paragraph 5.1.1*. Finally, the slopes and intercepts of the lines which are closer to their linear relationship are deducted, as illustrated in *Figure 5.13*.

5.2.2 PPG feature based method validation

In this paragraph are reported the Matlab results obtained from the previous described, T1-based, blood pressure estimation algorithm. The slope and intercept of the line closer to the T1-BP relationships, deducted from the linear regression analysis, are then used to estimate the blood pressure on the same signal used in the training phase.

In *Figure 5.14* the T1-based estimate on *Patient 3* is illustrated, using the PPG diastolic peak as ending point of this time interval. The graphs show a good adherence between the measured and estimated BP curves. Therefore, it can be concluded that this definition of T1 leads to good results, confirming what is reported in literature.

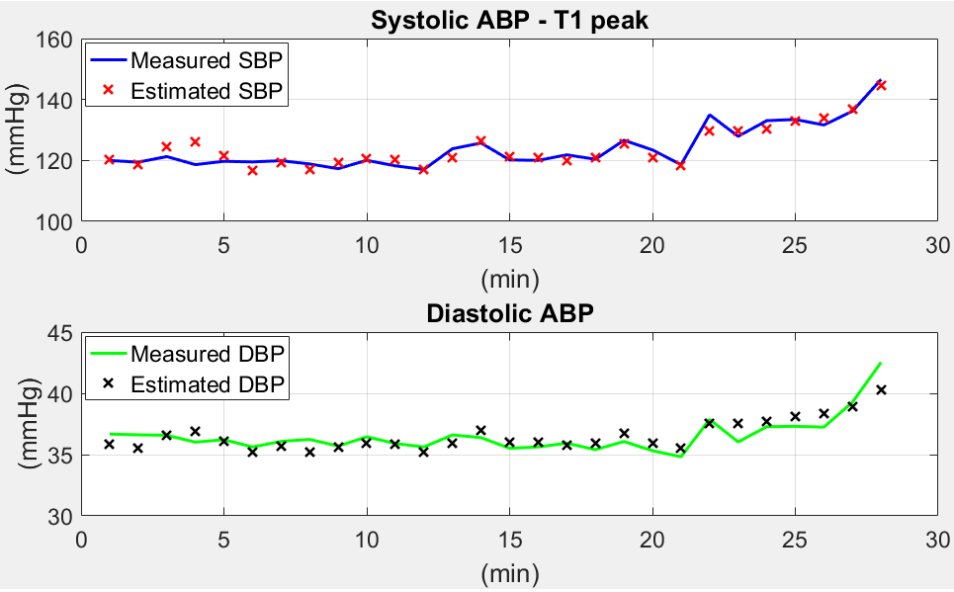

Figure 5.14 The figure shows trends of SBP and DBP, measured and estimated. The estimate is based on a T1 calculated as time interval between the systolic and the diastolic peak of the PPG signal.

On the other hand, the T1 feature based on the PPG inflection point it is not deeply addressed in literature. Despite this, the results of Patient 8 shown in *Figure 5.15* confirm it can be considered a promising method to estimate the blood pressure. It is not an accurate outcome like the others, but the estimate reveals that such T1 feature senses the BP variations, even if there is still room for improvements. These considerations are confirmed by the mean difference error in *Table 5.4*: the error of a

T1 calculated with the inflection point are the largest, but still within the pre-established limits of 5 *mmHg* ± 8 *mmHg*, compared to a T1 peak-based estimate significantly more precise.

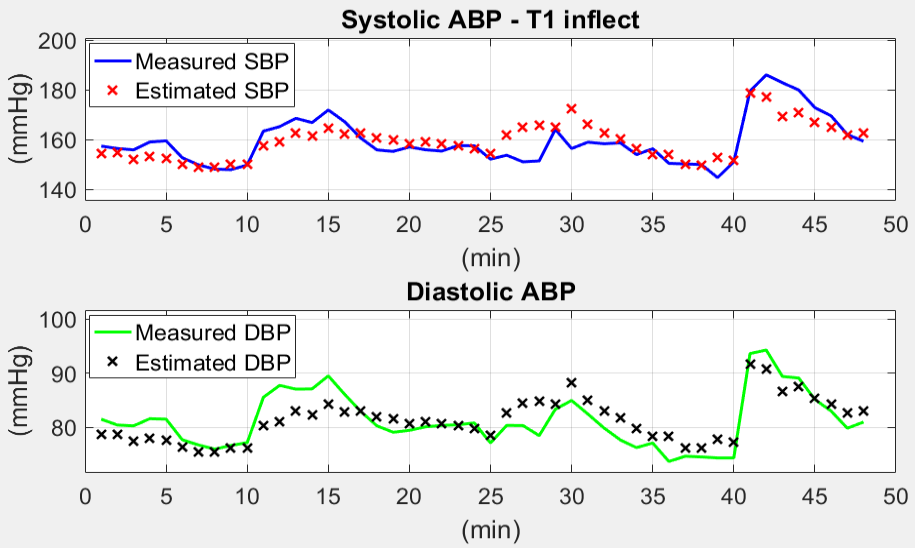

Figure 5.15 The figure shows trends of SBP and DBP, measured and estimated. The estimate is based on a T1 calculated as time interval between the systolic peak and the inflection point of the PPG signal.

Using the inflection point on *Patient 8*, whose PPG signal does not present a pronounced diastolic peak, has nevertheless allowed to achieve a BP estimation that, otherwise, it would not be possible. The percentage of the applicability of T1 peak-based algorithm on all the acquired signals from San Giovanni Bosco hospital would have been of only 27.7%. Thanks to the extension of the method on the inflection point research, in case of diastolic peak absence, has implied an increase of the applicability able to cover 100 % of the considered patients.

Table 5.4 Averages and standard deviations of the differences among the BP estimation and the measured BP, using T1 feature with diastolic peak and inflection point on Patient 3 and 8 respectively (numbers are in the form of Mean Value ± SD)

T1 definition	*SBP (mmHg)*	*DBP (mmHg)*
T1 peak	1.8328 ± 2.4656	0.62414 ± 0.7926
T1 inflect	4.4869 ± 6.0267	2.4843 ± 2.9937

Among all the acquisitions, according to the AHA limits and a qualitative perception of the ability of the algorithm output to "follow" the BP variations, a percentage of success has been estimated around 57%.

Chapter 6

Conclusion

6.1 Conclusion of the present work

This master thesis describes the development and analysis of an algorithm for the estimation of systolic and diastolic blood pressure values, by means of at least a photoplethysmographic signal. A literature review of the past studies and works regarding the PPG signal applied to the blood pressure measurement has been conducted. Two methods were selected and implemented in Matlab, adapting their characteristics to the current specifics: a technique based on PPG features and the other based on the pulse transit time. Both the implemented methods required a preprocessing phase of PPG and its analysis in order to detect some characteristic points on the signal. The PTT method required also the detection of QRS complexes on the ECG signal. After a calibration stage, the defined algorithms were tested and compared with measured BP signals.

According to the accomplishments and contributions, the following conclusions can be reached:

- The algorithms development has been performed always in a perspective of low complexity in order to allow a future implementation on wearable devices oriented embedded systems. They are purposely simple, manageable and with a limited computational capability.
- The PPG feature method in regard to the signals acquisition is more oriented towards a portable device since it works only with the PPG signal, whereas the PTT technique needs also an ECG acquisition by means of electrodes and it is more suitable for a clinical environment. However, the system calibration phase, indispensable for the PPG-feature method, could be considered a limit for the device portability.
- ICU patients health conditions are very critical and this is not a favorable condition to test an experimental algorithm primarily oriented to a consumer class device.

- The San Giovanni Bosco hospital validation has been useful in order to estimate the real accuracy and reliability of the algorithms on real subject data. In addition, the availability of a medical feedback simplified the doubts clarification and improved the problem solving.
- In the results sections, BP estimated values are shown explicitly and they are compared with the BP measured values. In all the works analyzed in the literature, SBP and DBP, estimated by the algorithms, have never shown in a such clear way and never the works results have been compared with ground truth signals. Results have been always shown in a statistical way, whereas in this thesis the direct correlation between BP estimations and measurements could be quickly evaluated.
- Regarding the algorithms results, they can be considered satisfactory, because they meet the predefined requirements. In particular BP trends are matched, the algorithm is able to "follow" the pressure variations and mean differences between estimated and measured BP are quite close to medical devices specifications.
- Both the methods in their final version can be applied to the whole acquired signals. However, the success percentage is different. The PPG feature method allows to get an acceptable BP estimate in no more than 57% of acquired signals, compared to about 70% resulting from the PTT method. Therefore, the additional ECG acquisition helps in achieving more accurate estimates.

6.2 Future work

Based on the experience and results of this thesis, improvements and changes can be done:

- A future goal is to remove or at least reduce the calibration phase for both the methods. The PTT method uses an equation based on physical laws, therefore the parameters calculated during the calibration phase, inverting the equation, could be obtained knowing some physical characteristics of patients.
- Another interesting approach is based on the possibility to combine the two algorithms in order to overcome the limits of both of them. This new combined algorithm may be addressed in medical devices which need more strict specifications with respect to consumer ones.

- A discrepancy between the arterial and capillary information has been found. An improvement may be to consider different position for the PPG acquisition, possibly closer to the invasive BP catheter.
- Once developed the algorithms, they may be integrated on a portable/wearable stand-alone system with a real time BP estimation.
- It is possible to address other machine learning approaches (neural networks and pattern recognition). They may be more effective than the regression analysis in the PPG-based method, but it has to be considered that portable devices are characterized by a limited computational capability.
- Another interesting approach is based on the Direct Pulse Transient Time acquisition using two PPG sensors. It allows to avoid ECG signal acquisition and R-peak detection.

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