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Blood pressure monitoring in a non-invasive way using regression techniques

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Abstract

Hypertension is one of the main risk factors for cardiovascular diseases (CVDs), leading cause of death all over the world. The continuous blood pressure (BP) monitoring can offer a valid tool for patient care, and using it together with other parameters, such as heart rate, breath frequency, physical activity, etc, could strongly improve prevention of CVDs.
Nowadays, invasive methods are the only reliable methods for BP continuous monitoring, despite they may cause several damage and discomfort to the patient. Instead non-invasive techniques are able to return BP values every few minutes, thus today they are not considered as optimal methods to continuously monitor BP trend.
In this thesis work, the cuff-less estimation of continuous BP through the pulse transit time (PTT) and the heart rate (HR) using regression techniques is investigated. This method achieves the non-invasive estimation of the BP with an acceptable low error, according to the AAMI/ISO/ESH guidelines and taking into account the accuracy of the control device, which returns the reference BP values.
Several novelties are introduced in this work. First of all, the use of electrocardiographic (ECG) and photopletismographic (PPG) signals acquired from healthy subjects with wearable devices: the *SHIMMER* (*Sensing Health with Intelligence, Modularity, Mobility and Experimental Reusability*). In literature, similar methods have been implemented but they exploited physiological signals extracted mostly from online databases (e.g. *MIMIC* database).
Another novelty is represented by the implementation of preprocessing of the ECG and PPG signals, and by the research and processing of the features related to them in order to continuously monitor BP in a non-invasive way, exploiting linear regression techniques. In fact, recent studies have been demonstrated that HR and PTT can be linearly combined to obtain BP values. So, the manipulation of these two parameters is the key point to non-invasively estimate reliable BP values.
Definitely, the work described here aims to give an input to the research of a method which allows the continuously monitoring of the BP in a non-invasive way that is equally dependable with respect to the current methods and that is easy for the patient to carry out. The comfort in use results in measuring the BP at different times of the day without causing discomfort

to the patient, and wherever he/she is without necessarily being in a clinical setting.
Therefore, the proposed method is also intended for the integration of this type of algorithm on wearable devices, in particular on those developed for the European *SINTEC* project.

Acknowledgements

Before proceeding with the discussion, I would like to dedicate a few lines to all those who have been close to me in this path of personal and professional growth.

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Finally, I dedicate this thesis to myself, to my sacrifices and my tenacity that have allowed me to get here.

Contents

Achronimous table

ACHRONIMOUS	MEANING
ABP	Arterial Blood Pressure
AC	Alternating Current
AM	Ante Meridiem
BMI	Body Mass Index
BP	Blood Pressure
CVDs	Cardiovascular Diseases
DBP	Diastolic Blood Pressure
DC	Direct Current
ECG	Electrocardiography/Electrocardiographic
HR	Heart Rate
IBC	Intra-Body Communication
IoT	Internet of Things
LED	Light Emitting Diode
MAE	Mean Absolute Error
MLR	Multivariate Linear Regression
PCB	Printed Circuit Board
PM	Post Meridiem
PPG	Photoplethysmography/Photoplethysmographic
PTT	Pulse Transit Time
RFR	Random Forest Regression
RR	Ridge Regression
SBP	Systolic Blood Pressure
SD	Standard Deviation
SHIMMER	Sensing Health with Intelligence, Modularity, Mobility and Experimental Reusability
SINTEC	Soft Intelligence Epidermal Communication platform
SVR	Support Vector Regression

Chapter 1

Introduction

The thesis work is based on improving the performance of the *SINTEC* medical device algorithm exploiting physiological signals recorded with the reference devices. *SINTEC-Soft intelligence epidermal communication platform* is an European project which is born in June 2019 and aims to develop an innovative technology capable of monitoring the health of the wearer [1]; in particular, the final device should be able to return the subject's heart rate, systolic (SBP) and diastolic blood pressure (DBP) during a periodic monitoring. The entire work has been carried out at the LINKS Foundation, which has been operating for about 20 years on a national and international level and it aims to promote, lead and enhance innovation processes through research projects with a strong innovative potential and which can create an impact on the production and the public sector, comparing themselves with an international context [2].
The main idea of the project is based on the use of a new technology with water-repellent features and dynamic with permeable and extensible encapsulation (e.g., intelligent patches) able to resist a vigorous action on it, sweating and water, making it ideal for an active life [3]. Its unique features allow the realization of an innovative intra-body communication (IBC) technology which offers secure broadband and low power transmission. [4].
SINTEC wants to provide to the need of developing new interconnection technologies, non-invasive and which do not interfere with the life of people who wear them. In fact, smartphones and smartwatches will give way to what is called *bodyNET*, a term which refers to a network of sensors and intelligent devices embedded in clothing, worn on our skin or implanted in our body [5].

1.1 Non-invasive smart technologies in clinical field

Smart wearables are the next step in the evolution of *Internet of Things (IoT)*. *SINTEC* project's first goal aims to demonstrate the advantages of this new technology in the clinical and sportive fields [6]. This work goes deep just with the first one.
To do this, a PCB technology with an extensible substrate and liquid alloy is being tested with the integration of complex embedded systems within the substrate in order to apply it in different complex situations of the daily life [7]. Furthermore, in the communication between sensors and hub, a new Fat-IBC data transfer system is being developed, which aims to overcome Bluetooth communication issues [8]. The unique features of this technology will enable a revolution in IBC that will ensure secure communications with high bandwidth and low power [9]. This system will make it possible to acquire inputs with many nodes, corresponding to the sensors distributed on the body, using the adipose layer of the integument as a vehicle for the signal [10].
The first part of the work is focused on evaluating the performance of the reference devices: the explored sensors will be electrodes for electrophysiological signals (bioimpedance) for ECG and optical sensors (LED and photodiode) for PPG [11][12]. The results of these analyses will drive the architecture of the final system which is constantly updated. The algorithm for the extraction of physiological parameters, such as HR, PTT, SBP and DBP has been integrated and tested. The results obtained from the validation will provide feedback for the optimization of the final device. LINKS Foundation main focus for the *SINTEC* project is its applicability in a clinical and hospital environment. Nowadays, just invasive methods are reliable for continuous BP monitoring; they consist in the intrusion of invasive arterial catheters (Fig. 1.1) which presents potential risks for patients, such as infection and several vascular damage [13]. The possibility of having a continuous and reliable non-invasive BP monitoring represents a great advantage in terms of prevention and reduction of the risk associated with CVDs for which hypertension represents the main risk factor [14].

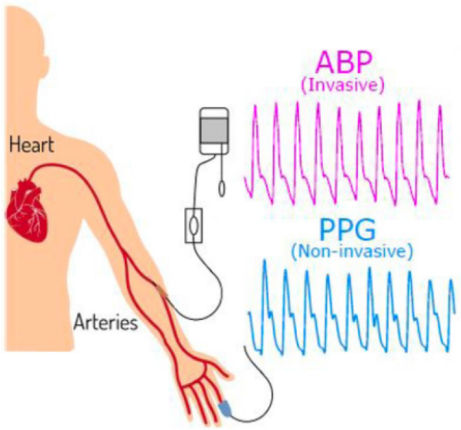

Figure 1.1: Comparison between invasive arterial blood pressure (ABP) and non-invasive PPG.

1.2 Hypertension and associated monitoring methods

Hypertension is called the "silent killer" because of the difficulty of diagnosis before the symptoms are evident and have already caused irreversible damages [15]. Previous studies suggested that hypertension accounts for nearly 13% of annual cardiovascular disease death; the raised blood pressure may cause a severe damage to the vascular system, including the damage to arterial wall, and may even damage the target organs like kidney and brain [16].
The early detection of hypertension has a significant meaning in the prevention of CVD death but it is critical for blood pressure monitoring devices to be accurate. Particular variability in the accuracy of BP devices compared with intra-arterial BP has been demonstrated in the cuff blood pressure range from prehypertension to grade I hypertension (SBP 120–159 to DBP 80–99 mmHg) [17]. The mercury sphygmomanometer is the main measuring cuff BP devices and remains largely unchanged, but there are some evidences underlining that cuff BP may not be a good representation of the true intra-arterial BP values [18]. While cuff blood pressure is measured at a peripheral artery, the aim is to estimate the pressure experienced by the central organs supplied by the aorta as the best marker of risk from hypertension [17]. Other BP measurement methods are represented by ambulatory BP monitoring [19], which has a high sensitivity for predicting cardiovascular clinical outcomes, or automated in-clinic (unobserved) blood pressure [20]. However, if the devices in the hands of doctors are substantially inaccurate, the risk in prediction of the clinical outcome is always present. Ultimately, there is the necessity of more accurate ways to measure

blood pressure, which must lead to greater agreement between international hypertension guidelines, improved diagnostic confidence, improved clinical decisions, and better patient clinical outcomes [17].
In order to achieve the early diagnosis and decrease the mortality of hypertension, it is important to find a non-invasive monitoring method which is safe and equally reliable as the invasive one. Developing a device with these features could provide a valid contribution to the prevention and monitoring of cardiovascular diseases.
With these assumptions, *SINTEC* aims to have a revolutionary impact on the patients' lives with CVDs. It is hoped that the number of people who track their blood pressure will increase by providing them a convenient and reliable means of monitoring [21]. This could prevent the onset or degeneration of CVDs which nowadays are still the leading cause of mortality all over the world.

1.3 Progress beyond the reference technology

Demonstrations in clinical performance applications will show several advantages over current reference devices. The main ones should be in comfort and in the not much movement of the sensor over the skin surface [22]. Its major impact will not be in replacing other wearable devices but rather in providing new capabilities: wearables are considered to give an huge impact on society with a new intelligent support which aims to improve life, e.g., nomadic healthcare and telemedical technology [23].
The major potential impacts are:

- PCB manufacturability: the *SINTEC* project will inspire those electronics production companies to the necessary investments in technology for both stretchable insulator materials, as well as for liquid conductive materials [24];

- Healthcare: aging and/or poor health people increase the demand for constant monitoring, and limited existing medical resources and expensive conventional medical treatments are unable to satisfy these requirements [25]. Therefore, it will become necessary to replace the conventional healthcare system with a new, efficient and economic one. Wearable medical sensor technology will give a significant contribution in tackling these challenges [26].

1.4 ECG and PPG for BP monitoring

As previously said, the final device should return DBP and SBP values. The first (also called minimum pressure) is the value of the blood pressure when

the heart of an individual relaxes; in other words, it is the value that BP assumes when the heart rests between an heartbeat and the next one [27]. On the other hand, SBP (or maximum pressure) is the BP value when an individual's heart contracts, therefore the BP value at each heartbeat [27]. In order to measure the physiological parameters of interest in a non-invasive way, it is necessary to record ECG and PPG signals: this allows the extraction of the two features (PTT and HR) to be included in the regression equations shown in Eq. (1.1), and finally obtain the SBP and DBP values.

$$\begin{cases} SBP = \alpha_0 + \alpha PTT + \beta HR \\ DBP = \beta_0 + \gamma PTT + \delta HR \end{cases} \tag{1.1}$$

1.4.1 ECG

The ECG signal is obtained in a non-invasive way, and visually represents electrical and chemical cardiac muscle fibres activity during the cardiac cycle. An important role is played by QRS complex, a series of intense upward and downward deflections due to ventricular depolarization and it consists of three waves, namely Q, R and S (Fig. 1.2)[28]; in particular, once the time interval Δt between two consecutive R-peaks (reflecting left ventricle depolarization activity) is found, it is possible to calculate the HR (Fig. 1.3), which formula is the following:

$$HR = \frac{1}{\Delta t} \tag{1.2}$$

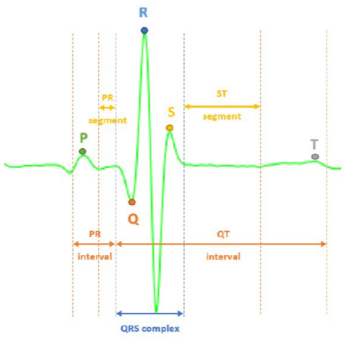

Figure 1.2: ECG waveform.

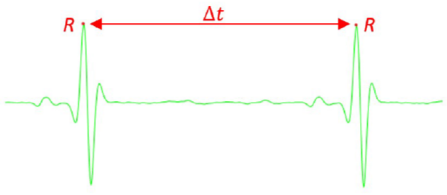

Figure 1.3: Time interval between two consecutive R-peaks.

1.4.2 PPG

PPG instead is a simple and low-cost optical technique used to detect blood volume changes in the microvascular bed of tissue at the skin surface level [29]. PPG waveform comprises a pulsatile ('AC') physiological waveform attributed to cardiac synchronous changes in the blood volume with each heartbeat, and is superimposed on a slowly varying ('DC') baseline with various lower frequency components attributed to respiration, sympathetic nervous system activity and thermoregulation (Fig. 1.4)[29]. Thanks to this waveform, it is possible to calculate PTT as the time interval between an ECG R-peak and the nearest S-peak of the PPG signal (Fig. 1.5).

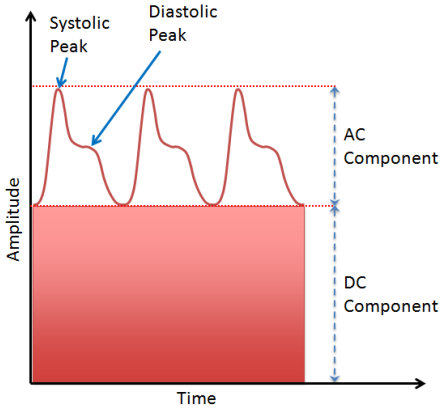

Figure 1.4: PPG waveform.

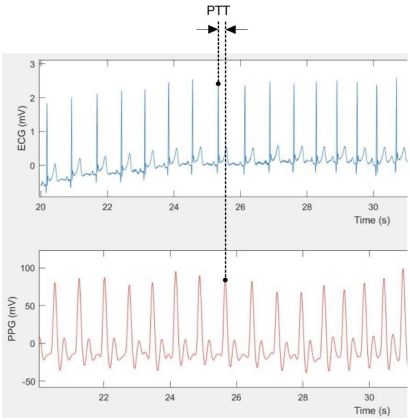

Figure 1.5: Time interval between R-peak and S-peak.

Both ECG and PPG signals have been applied in many different clinical settings, including clinical physiological monitoring (e.g., PPG in blood oxygen saturation and respiration, ECG in cardiac output, etc). Blood pressure is a very important clinical parameter to measure and in this work it is explained how to calculate it through manipulating these two physiological signals.

Chapter 2

Materials and methods

A database has been created. It includes 50 ECG and PPG recordings from six different healthy subjects, two men and four women, acquired with wearable sensors. All the subjects are between the ages of 20 and 30 and they are of normal weight. For more detailed information about the population, refer to the column relating to each subject in the tables in Appendix E. Although the number of the population may seem small, the validity of this work finds strength in the large number of measurements also taken from the same subject, since blood pressure values of the same individual are affected by variability during the day [30]. For this reason, ECG and PPG recordings of the same subject were acquired at different times of the day. Before proceeding with the acquisition of the recordings, each subject signed the appropriate informed consent with the attached information note relating to the *SINTEC* project (see Appendix A).

2.1 Devices, sensors and software

In order to record physiological signals, *SHIMMER* devices have been used (see Fig. 2.1). *SHIMMER* is a highly extensible wireless sensor platform which can be used for biomedical research applications, and its wireless and lightweight nature would be suited for applications of physiological sensing under ambulatory or home monitoring conditions [31].

Figure 2.1: Shimmer modules by which physiological signals were recorded.

2.1.1 ECG device and sensors

ECG signals have been recorded with *Shimmer3 EXG Unit SR47-4-0* module (Fig. 2.2) and Covidien ECG electrodes were used, which consist in disposable, round shape, Ag/AgCl electrodes with solid hydrogel, adhesive patches, button connection and foam support (Fig. 2.3). These ECG snap-on electrodes feature a patented pre-gelled adhesive side with non-irritating gel, especially developed to prevent allergic reactions; the foam electrode is latex free and therefore suitable for every skin type [32].
The associated block diagram in Fig. 2.4 shows a defibrillation protection, an Electromagnetic Interference (EMI) filter, a Right-Leg Drive (RLD) amplifier to counteract common-mode interference, three Programmable Gain Amplifiers (PGA) increasing the amplitude of the input signal, and an Analog to Digital Converter (ADC) to convert the input analogue signal to a digital representation using a 24-bit signed integer value for each sample.

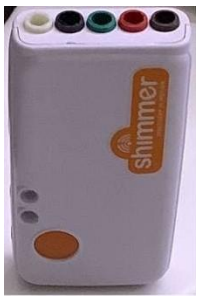

Figure 2.2: Shimmer3 EXG Unit SR47-4-0 for ECG recordings.

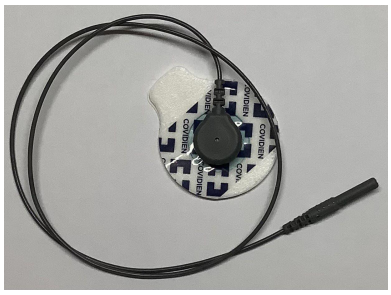

Figure 2.3: Covidien ECG electrode and Shimmer snap lead.

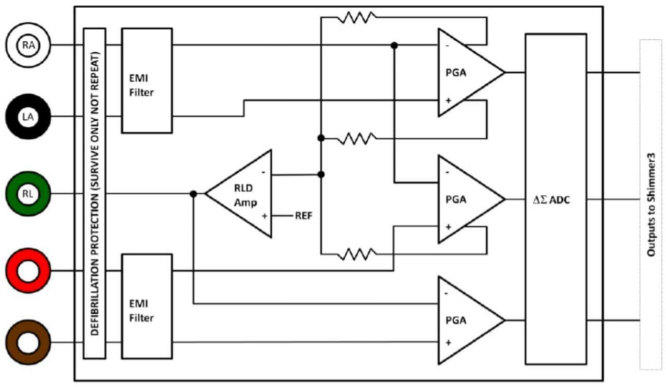

Figure 2.4: Shimmer3 EXG Unit SR47-4-0 block diagram [33].

2.1.2 PPG device and sensor

PPG signals have been acquired with *Shimmer3 GSR+ Unit SR48-3-0* module (Fig. 2.5). The *GSR+ (Galvanic Skin Response)* unit provides connections and preamplification for one channel of Galvanic Skin Response data acquisition and it is suitable for measuring the electrical characteristics or conductance of the skin, as well as capturing a PPG signal and converting to estimate HR, using the Shimmer clip (Fig. 2.6) [34]. The optical pulse circuitry includes an on-board amplifier and filter circuit for initial conditioning of the signal [35]. Moreover, the clip embeds a green light LED and a detector side by side, thus the operating configuration is the reflection ("adjacent") mode [29].

Figure 2.5: Shimmer3 GSR+ Unit SR48-3-0 for PPG recordings.

Figure 2.6: Shimmer PPG optical pulse clip to derive PPG-to-HR from the Shimmer3 GSR.

2.1.3 Software

To configure the Shimmer devices and export their data, the software *ConsensysPRO v1.6.0 – 64bit* was used. Before writing the configuration via their board (Fig. 2.7), in *Shimmer3 GSR+* only the PPG sensor was turned on (Fig. 2.8), instead with *Shimmer3 EXG* only the LA-RA derivation was recorded and only the ECG sensor was enabled (Fig. 2.9). The *EXG* module was set as master and the sampling frequency was set to 504.12 Hz (Fig. 2.10), since the ECG requires a minimum sampling frequency of 500 Hz [36] and the software allows to selection of predefined frequency values. Instead, the PPG requires a minimum sampling frequency of 100 Hz [37].

Figure 2.7: Consensys Base 6U to set the Shimmer devices and to export data from Shimmers to the calculator.

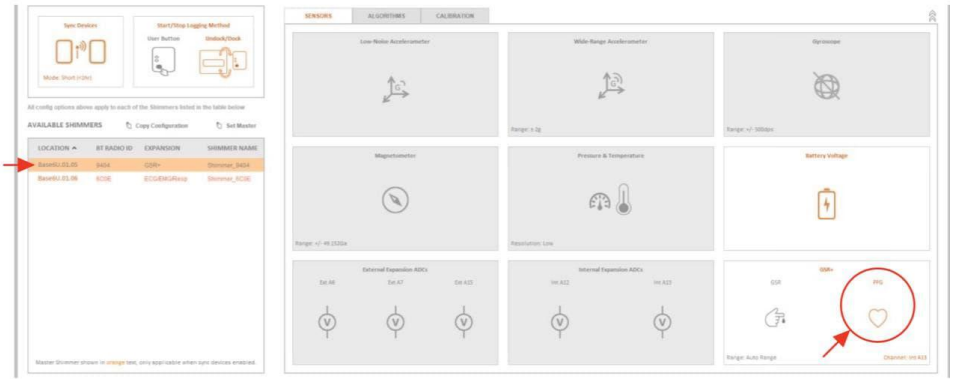

Figure 2.8: In Shimmer3 GSR+ only PPG sensor has been turned on for PPG recordings.

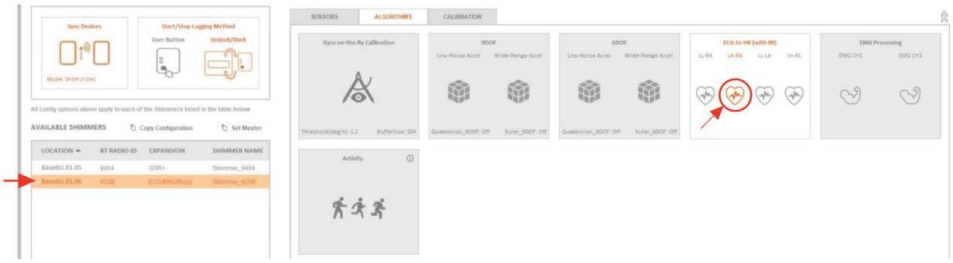

Figure 2.9: In Shimmer3 EXG only the option "LA-RA derivation" has been turned on for ECG recordings.

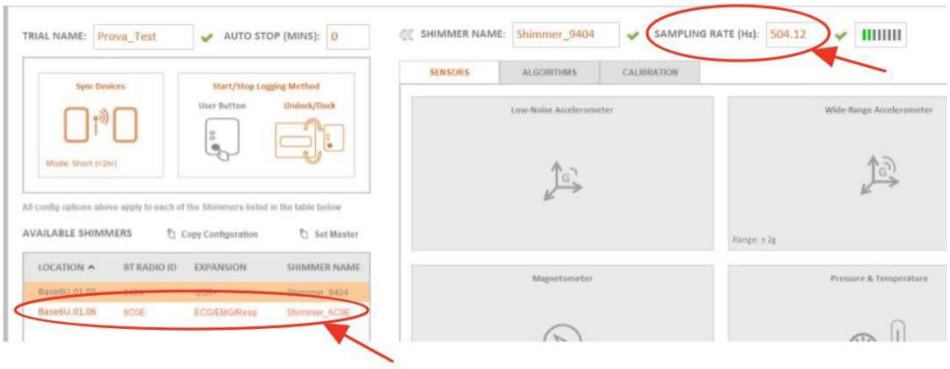

Figure 2.10: The sampling frequency has been set to 504.12 Hz and Shimmer3 EXG has been set as the master device.

To record signals, both Shimmers have to be undocked from the board and the opposite action must be performed in order to stop the recordings.

When the Shimmers are undocked, they start to record the signals synchronously thanks to the Bluetooth connection (Fig. 2.11).

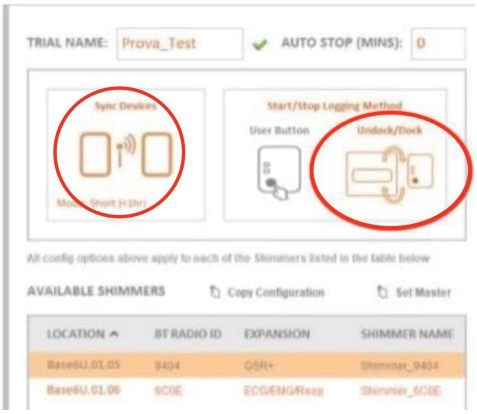

Figure 2.11: The Shimmers start to record the physiological signals when both the devices are undocked from the board; while recording, the Shimmers are synchronized through via Bluetooth.

To export data, once the Shimmers are docked to the board after recording the physiological signals, all data are transferred to the calculator as *.mat* files.

2.2 Protocols

Each subject from whom physiological signals were recorded was sit and relaxed. As said before, the recordings were acquired in different moments of the day and each one lasts about 20 minutes.

2.2.1 ECG recording

The ECG sensors configuration is shown in Fig. 2.12: the electrodes in the white and black pin were placed on the subject's chest (on the right and on the left respectively), instead the electrode in the green pin was placed on the right leg as reference.

Figure 2.12: ECG electrodes positioning for LA-RA derivation in ECG recordings.

2.2.2 PPG recording

The PPG Shimmer clip was clamped to the left index of the subject and covered with a thick black tie in order to make a better adhesion of the clip to the finger's skin, and to avoid possible external environment light interference (Fig. 2.13).

Figure 2.13: PPG optical pulse clip on the left index covered by a thick, black tie.

2.2.3 OMRON HeartGuide

The OMRON HeartGuide (Fig. 2.14) is a punctual pressure detector which returns the SBP and DBP values which are necessary to train the algorithm (Fig. 2.15). The device is worn like a watch and during pressure measurement, the arm must be positioned as in Fig. 2.16. This blood pressure monitor uses the oscillometric method for BP measurement: when the band inflates, the monitor senses the pressure pulsations of the artery underneath the band [38]. Moreover, the device returns SBP and DBP values approximately in a minute, since the cuff detects the last Korotkov noise (instant in which the pressure of the cuff is equal to the DBP) one minute after detecting the first one (instant in which instead the pressure of the cuff corresponds to the SBP) [39].
The OMRON's values are written into an *Excel* sheet which is turned into a *.csv* file after converting time values into timestamp units. Then, the file is passed to the algorithm.
Fig. 2.17 shows one of the subjects with all the attached sensors.

Figure 2.14: OMRON HeartGuide as the control device.

Figure 2.15: OMRON HeartGuide display with SBP and DBP control values [40].

Figure 2.16: Arm position while measurements are carried out with OMRON HeartGuide [40].

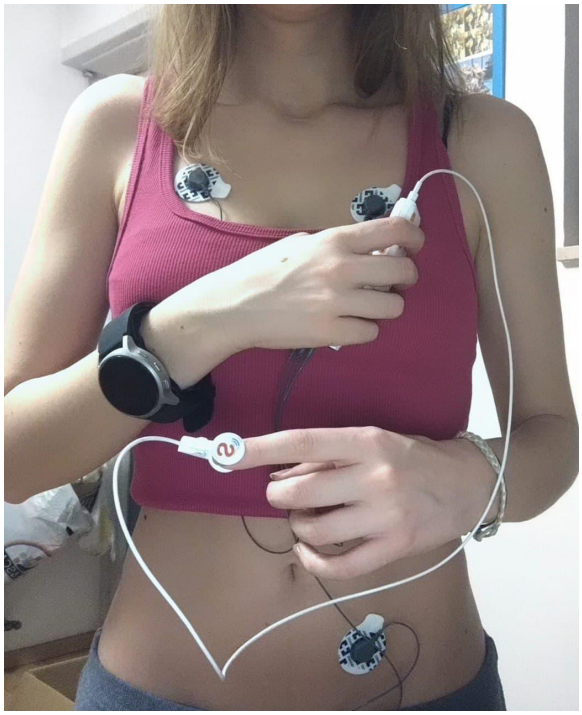

Figure 2.17: Subject 3 with all the attached sensors: Shimmer ECG module with Covidien electrodes, Shimmer PPG module with Shimmer clip and OMRON HeartGuide.

Chapter 3

The algorithm

The developed algorithm is written in *Python*, an interpreted high-level general-purpose programming language [41] and it is divided into seven sections, each one focused on a phase of the process leading to the predicted SBP and DBP values. The seven steps are signal preparing, signal filtering, peaks detection, feature extraction, OMRON data preparing, feature reduction and regression analysis.
The complete code is shown in Appendix F, while the high-level structure the algorithm is shown in Fig. 3.1.

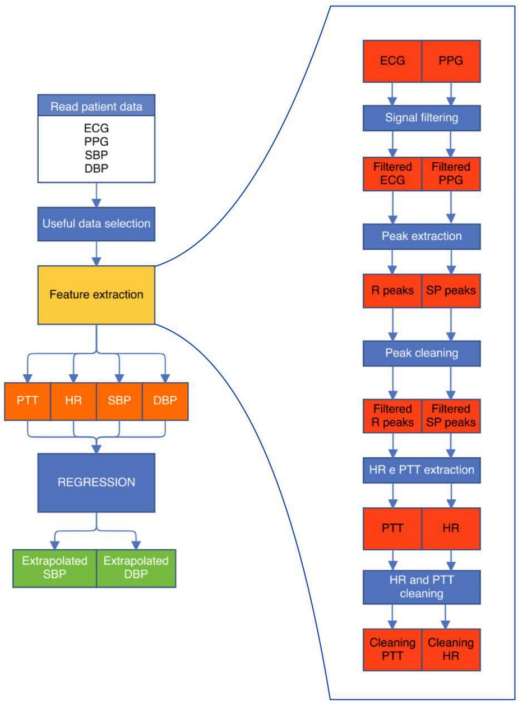

Figure 3.1: Algorithm structure, from data reading to regression process.

3.1 Preparation of signals

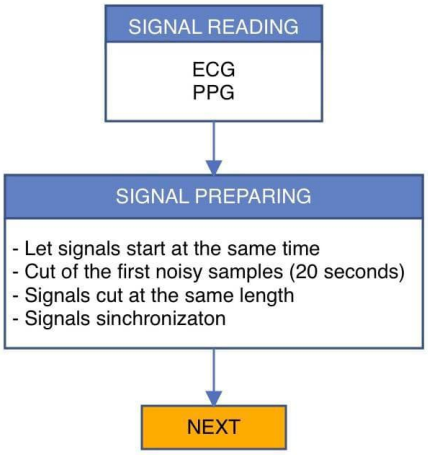

Figure 3.2: Preparation of ECG and PPG flowchart.

For each subject, first the 20-minutes ECG and PPG recordings together with the reference SBP and DBP values were acquired, then they are processed by the algorithm.
One of the fundamental requirements for the algorithm to work correctly is that the ECG and PPG signals are synchronized with each other (see Fig. 3.2). Firstly, the first sample of both signals is considered in order to make the signals start at the same time (Fig. 3.3). Then, the first samples (20 seconds) are removed because they could be affected by noise due to the undocking from the board (Fig. 3.4), and signals are cut at the same length. After that, signals are aligned through the synchronization of their timestamp arrays (Fig. 3.5): asynchrony between Shimmer devices could happen during recording because of Bluetooth connection, which could be discontinuous [42].

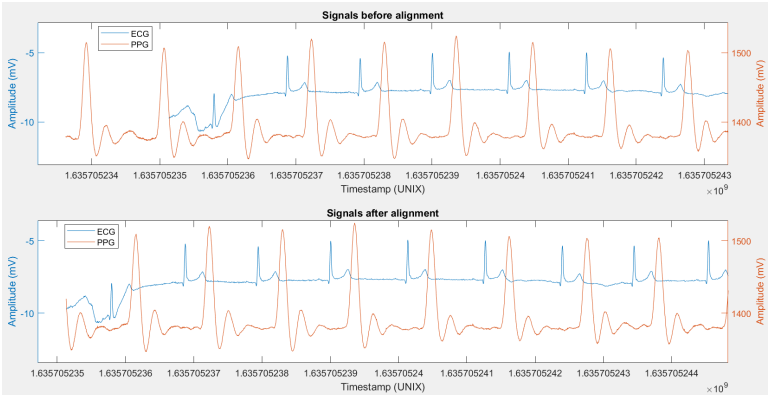

Figure 3.3: Signals before and after alignment.

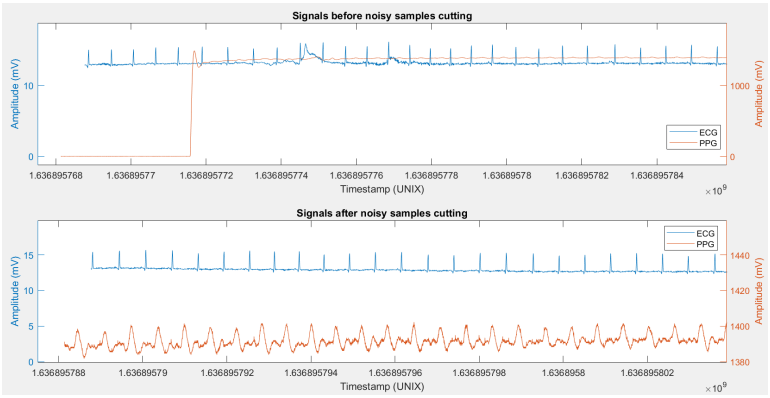

Figure 3.4: Removal of the first noisy samples (20 seconds).

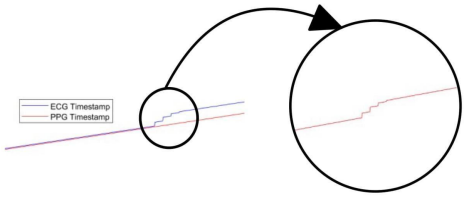

Figure 3.5: Timestamp arrays before and after the synchronization process.

3.2 Signal filtering

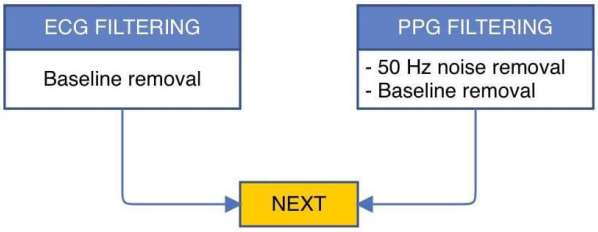

Figure 3.6: Signal filtering flowchart, relating to the baseline removal and to the PPG filtering.

Both ECG and PPG signals are affected by 50 Hz noise and by the power variation with respect to the zero (baseline), so some processing is needed (Fig. 3.6). In the case of ECG the 50 Hz noise is not a problem for the purpose of the work, because the R-peaks are clearly visible and easily detectable; thus, it is necessary only to remove the baseline through the calculation of the signal lower envelope curve and subtracting it from the signal itself (Fig. 3.7).

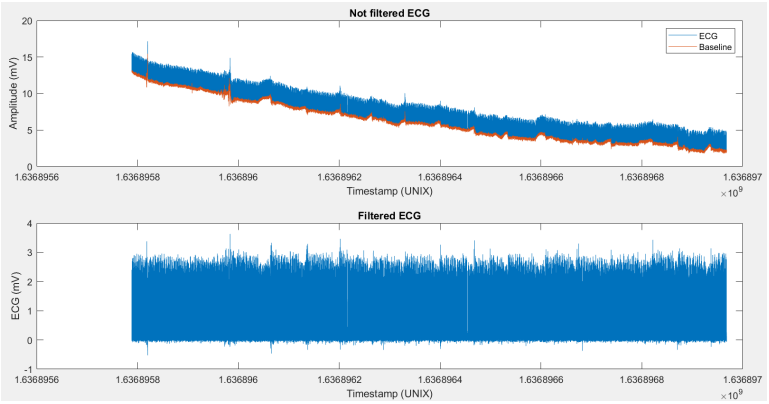

Figure 3.7: ECG baseline removal through subtracting the signal's lower envelope curve.

For PPG instead, 50 Hz noise makes the peaks detection more difficult, so a 7-order low-pass Butterworth filter (Fig. 3.8) is implemented in order to make the signal smoother (Fig. 3.9). After that, the baseline is removed at the same way as the ECG signal (Fig. 3.10).

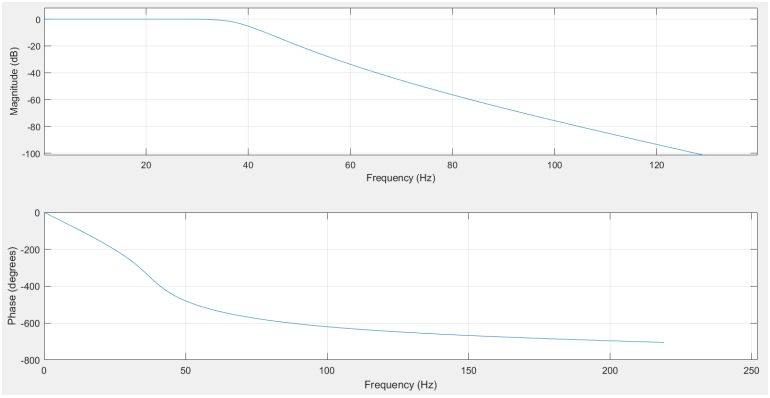

Figure 3.8: Magnitude and phase of the 7-order low-pass Butterworth filter. The choice of the order of the filter is due to the fact that 8 is the minimum coefficients number which is sufficient to obtain the required noise attenuation.

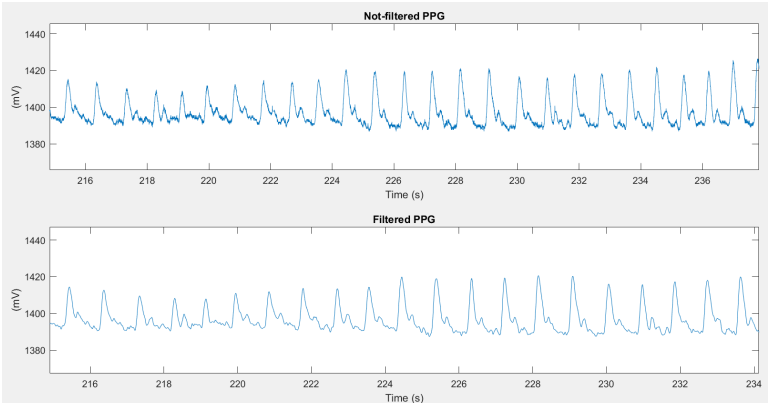

Figure 3.9: PPG before and after filtering with Butterworth filter.

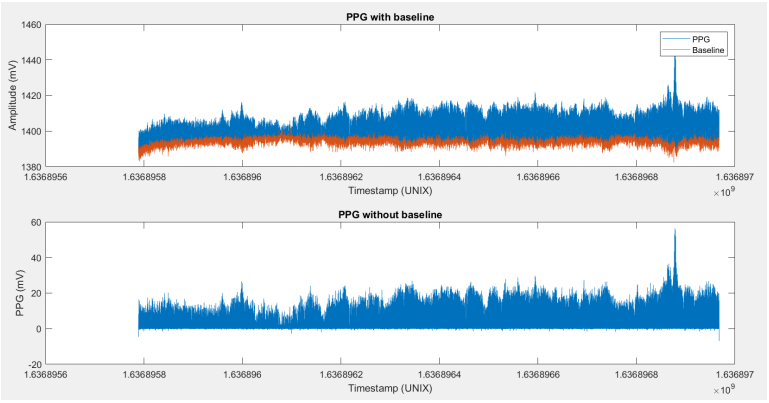

Figure 3.10: PPG baseline removal through subtracting the signal's lower envelope curve.

3.3 Peaks detection

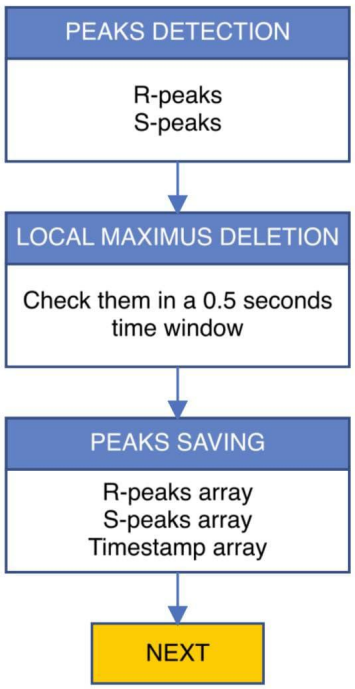

Figure 3.11: R-peaks and S-peaks detection flowchart, focusing on the parameters to reduce as much as possible any misdetection.

This part of the algorithm (Fig. 3.11) is focused on ECG and PPG peaks detection in order to calculate the features which will be discussed in the

next section.
Thanks to the *findpeaks.py* function, the algorithm scrolls the arrays containing ECG and PPG values and detects all the peaks crossing a given threshold, which is defined every time both for ECG and PPG signals (Figs. 3.12, 3.13). These thresholds change among different subjects but remain constant for measurements taken from the same individual. The thresholds are shown in the Table 5.1 in the Appendix B.
As an additional check, it is verified that no more than one peak is detected within a 0.5 seconds time window. Detected peaks are saved in two different zero arrays of the length of the reference timestamp array.
A more detailed flowchart of this part of the algorithm is reported in Fig. 3.14.

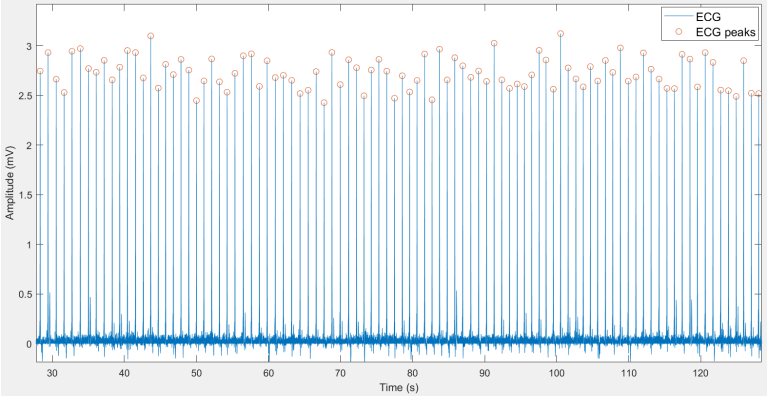

Figure 3.12: R-peaks detection.

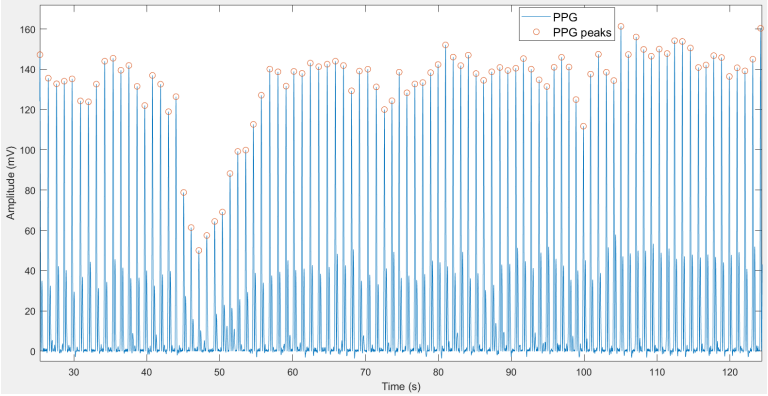

Figure 3.13: S-peaks detection.

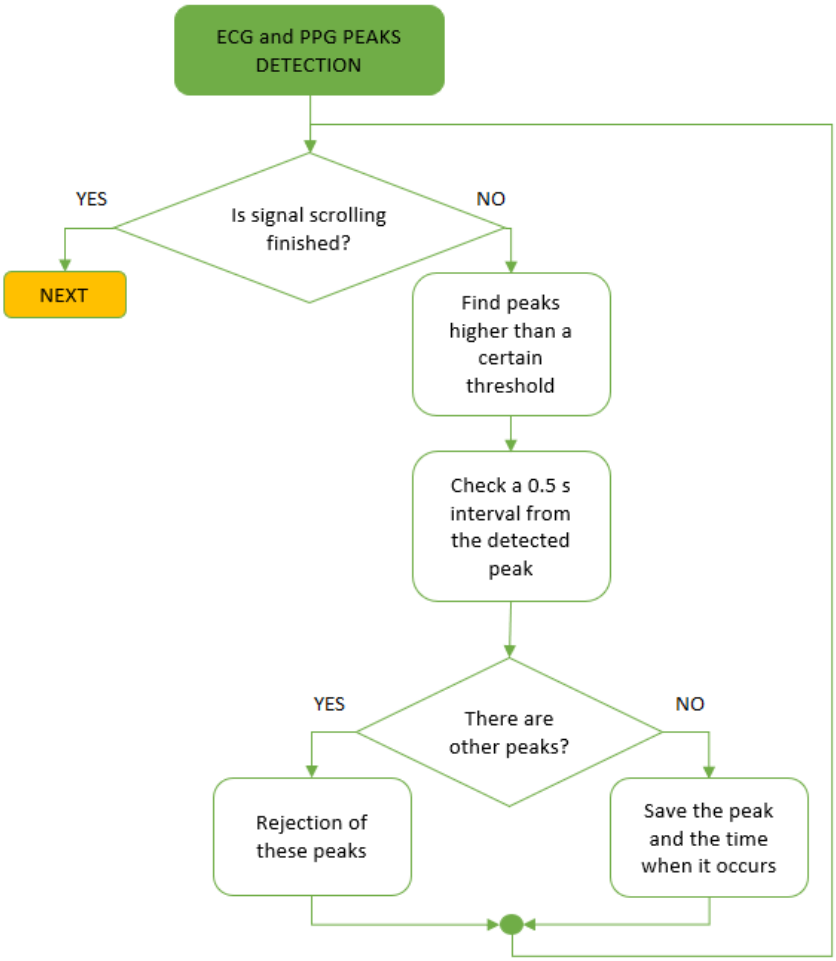

Figure 3.14: Detailed R-peaks and S-peaks detection flowchart.

3.4 Feature extraction

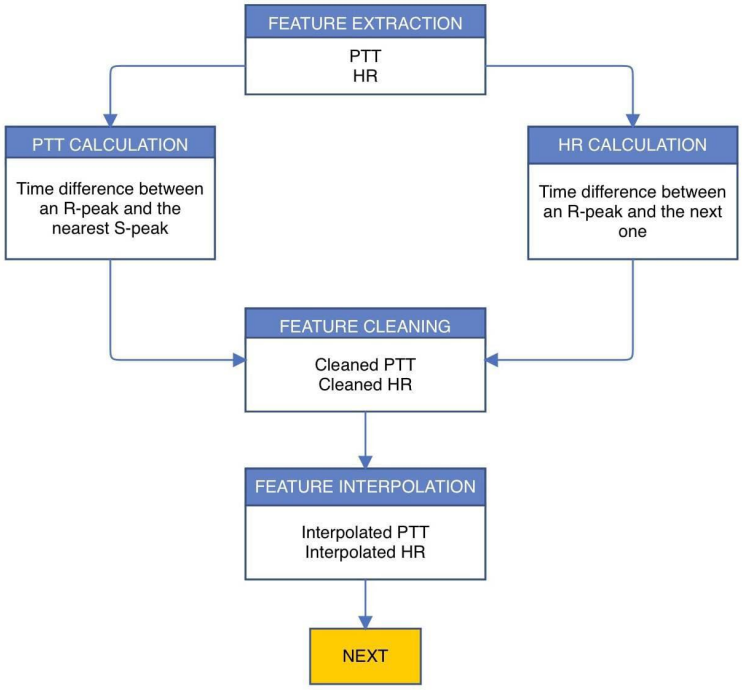

Figure 3.15: Feature extraction flowchart, from the calculation to the cleaning and the interpolation.

For what concerns the extraction of the features of interest (Fig. 3.15), PTT and HR, the basic idea consists in sliding the array in which detected R-peaks were saved at the step before, and finding the first R-peak. Starting from that time instant, the algorithm slides both R-peaks and S-peaks arrays (Fig. 3.16): if another R-peak is found before an S-peak, the previous R-peak is discarded and the new one is taken as reference; viceversa, the reference time instant is saved, pulse transit time and heart rate are calculated and saved in two arrays with the correspondent reference time instant.

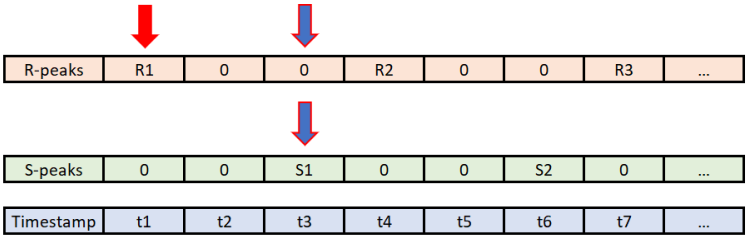

Figure 3.16: PTT and HR calculation.

After that, HR and PTT arrays are cleaned in order to avoid errors in the final SBP and DBP predictions: all those PTT and HR values which are out of range of $mean \pm SD$ related to their respective array are eliminated. These higher peaks (mainly present in the PTT array as the PPG is a more variable signal than the ECG, from which the heart rate is derived) are due to the loss of some samples caused by the momentary disconnection between Shimmer devices during the recordings (Fig. 3.17). In this case, in the feature extraction step, abnormal PTT or HR values giving rise to these peaks are calculated, and they are deleted immediately after their detection (Fig. 3.18).
In the end, PTT and HR values are interpolated along the whole signals' timestamp array, ready for the feature reduction process (Fig. 3.19).
Also for this algorithm section, a more detailed flowchart is reported (Fig. 3.20).

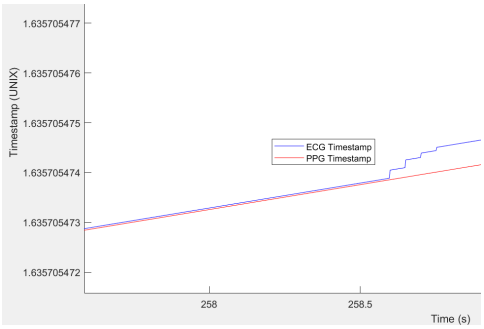

Figure 3.17: A sudden increase of the timestamp values (steps) suggests the loss of some samples of the physiological signal.

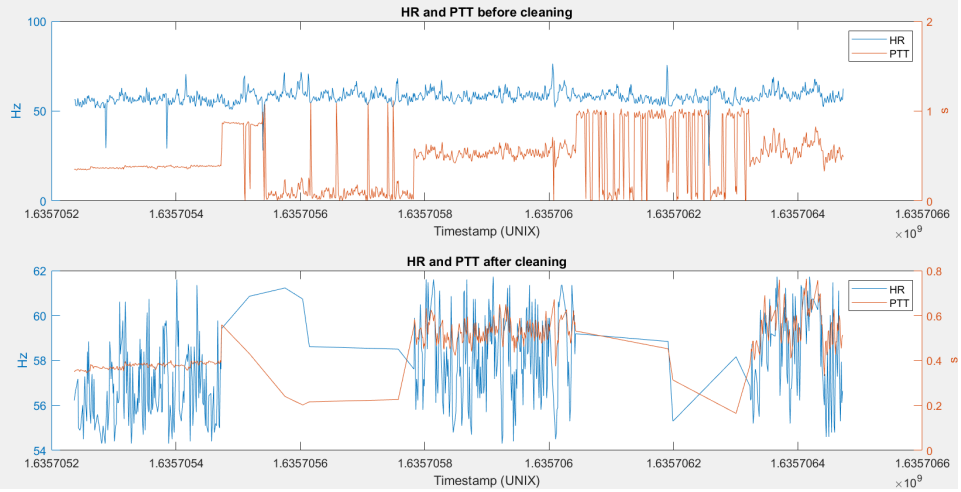

Figure 3.18: HR and PTT before and after cleaning.

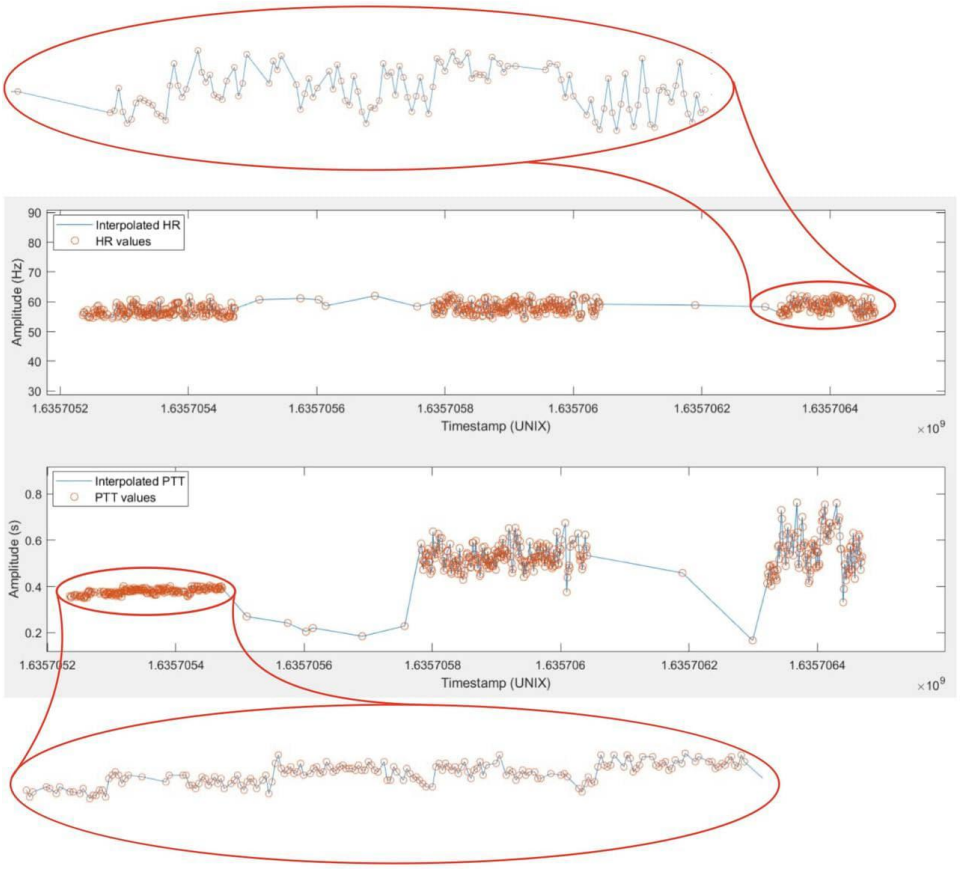

Figure 3.19: HR and PTT interpolation along the whole timestamp array.

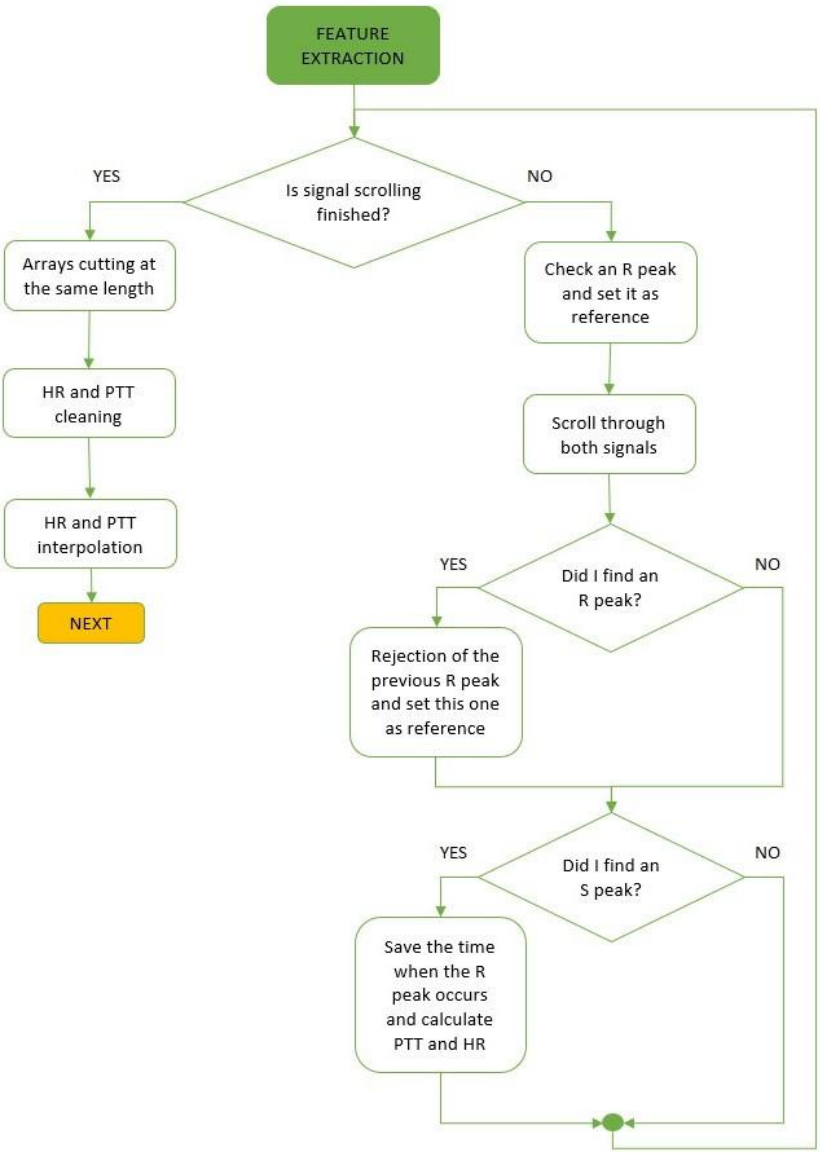

Figure 3.20: Detailed feature extraction flowchart.

3.5 OMRON HeartGuide data preparation

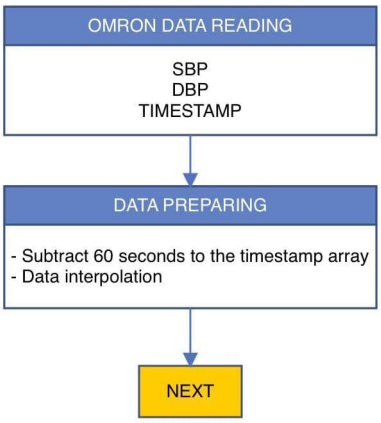

Figure 3.21: OMRON data preparing flowchart, relating to control SBP, DBP and detection time.

As previously said in section 2.2.3, OMRON device returns SBP and DBP values in about one minute after pushing the start button. For this reason, 60 seconds are subtracted from the OMRON's timestamp values, since the algorithm calculates the features starting from the instant in which the peak is detected, that is one minute before the OMRON returns the results (Fig. 3.21).
Furthermore, as said before, the OMRON device returns punctual blood pressure values, so it is necessary to interpolate them in order to distribute them along the whole signals' timestamp array (Fig. 3.22).

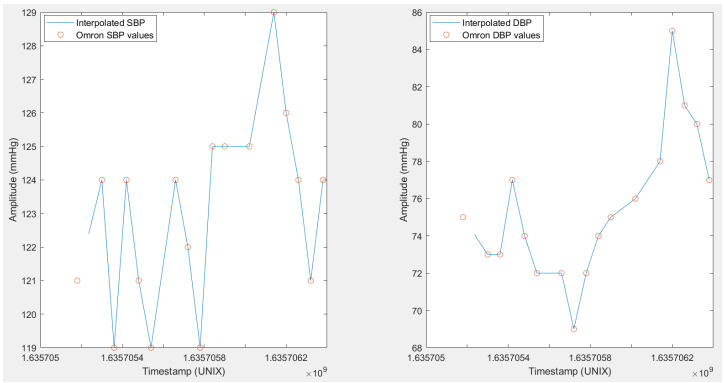

Figure 3.22: Interpolated SBP and DBP values along the whole timestamp array.

3.6 Feature reduction

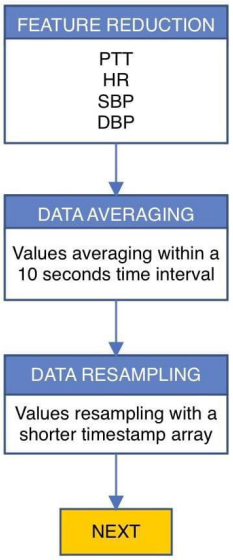

Figure 3.23: Feature reduction flowchart, from the time-window averaging to the resampling.

The algorithm performs the step described in Fig. 3.23 in order to avoid serious errors due to the imperfect synchronization of the Shimmer devices. In particular, the previously interpolated SBP and DBP values provided by the OMRON HeartGuide, together with pulse transit time and heart rate values acquired from the Shimmers are averaged within a 10 seconds time window (for robustness against any artifact and misdetections [43]), and the result of each interval is written in correspondence of each timestamp value of the same window (Fig. 3.24). After discussing with the sensors' manufacturers, it was determined that this was a possible solution to optimize the algorithm's decision-making process, while a moving average would have entailed a considerable computational complexity, in addition the algorithm's ability to predict sudden changes in blood pressure would decrease.
Moreover, HR, PTT, SBP and DBP values are resampled with a shorter timestamp array in order to reduce the computational time of the algorithm during the regression phase, which will be discussed in the next section.

SBP	99,924	100,0105	100,0998	100,1857	100,2674	100,3509	100,4347	100,5247	100,6182	...
DBP	62,6148	62,5653	62,5143	62,4652	62,4186	62,3708	62,3229	62,2715	62,2181	...
Timestamp	1635951050,78	1635951051,52	1635951052,28	1635951053,02	1635951053,72	1635951054,44	1635951055,16	1635951055,93	1635951056,93	...

SBP	100,5582	100,5582	100,5582	100,5582	100,5582	100,5582	100,5582	100,5582	100,5582	...
DBP	62,3054	62,3054	62,3054	62,3054	62,3054	62,3054	62,3054	62,3054	62,3054	...
Timestamp	1635951050,78	1635951051,52	1635951052,28	1635951053,02	1635951053,72	1635951054,44	1635951055,16	1635951055,93	1635951056,93	...

Figure 3.24: SBP and DBP values before and after the feature reduction.

3.7 Regression analisys

Linear regression has been around for a long time and it is still a useful and widely used statistical learning method [44]. It is a very straightforward simple linear approach for predicting a quantitative response Y on the basis of a single or more predictor variables X, and it assumes that there is approximately a linear relationship between X and Y [45]. For this work, there are two predictors, which are PTT and HR; so, it is necessary the use of a multivariate regression model that could be represented by the regression line in Eq. (3.1), where β_0 is the intercept, while the other β coefficients are interpreted each one as the average effect on y of a one unit increase in its respective predictor x, holding the other predictors fixed.

$$y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 \tag{3.1}$$

For the purpose of the work, the algorithm implements four different regression processes, each one with two different dataset divisions:

- Without any time interval: the dataset is divided into training set (the first 70% of the samples) and test set (the last 30% of the samples);
- With a 10-seconds time interval: the dataset division is realized through a 10-seconds window which slides across the first 70% of the samples to build the training set, which will be a matrix with many columns as predictors; the test set is built with the same time window sliding through the last 30% of the dataset samples.

The four different implemented regression processes are the following:

- Multivariate Linear Regression (MLR): instead of fitting a separate simple linear regression model for each predictor, a better approach is to extend the simple linear regression model so that it can directly accommodate multiple predictors; this can be done by giving each predictor a separate slope coefficient in a single model, as in the Eq. (3.1).
- Random Forest Regression (RFR): so called because the base constituents of the ensemble are tree-structured predictors and each of

these is constructed using an injection of randomness; a random forest is a collection of tree predictors $h(x;\theta_k)$, where x represents the observed input (covariate) vector with associated random vector X, and the θ_k are independent and identically distributed random vectors [46]. For regression, the random forest prediction is the unweighted average over the collection.

$$y(x) = \frac{1}{K}\sum_{k=1}^{K} h(x;\theta_k) \tag{3.2}$$

In the algorithm, the implemented *RandomForestRegressor().py* function requires as inputs three parameters. The first one is the *n_estimators*, representing the number of trees in the forest and which value is set to 100, as the default one. The second parameter is the *random_state*, which controls both the randomness of the trees creation and the sampling of the features to consider when looking for the best split at each node [47]. The last parameter is the error criterion and the mean absolute error (MAE) has been chosen.

- Ridge Regression (RR): it is a form of Bayesian estimation. Estimators such as ridge are the methods of choice when the a priori information is less precise [48]. The a priori assumptions are that the regression coefficients are zero except the constant term, and that the variances of the coefficients are equal [48]. The model line is the same as MLR (Eq. (3.1)).
  The *Ridge().py* function requires as input the hyperparameter α, which minimizes the mean square error of the model [49]. It is fixed to 0.01 for any subject, since a few recordings were used to find the optimal α value which could be suitable for a generic individual. These measurements are not included in the database.

- Suppor Vector Regression (SVR): as a supervised-learning approach, this method trains using a symmetrical loss function, which equally penalizes high and low misestimates; one of the main advantages of SVR is that its computational complexity does not depend on the dimensionality of the input space and it has excellent generalization capability, with high prediction accuracy [50]. For multidimensional data, x is increased by one and b is included in the w vector to simplify the mathematical notation to obtain the multivariate regression in Eq. 3.3.

$$y(x) = w^T x + b \tag{3.3}$$

  The *SVR().py* function requires as inputs the meta-parameters C and ϵ. The first one, is the regularization parameter and determines the

compromise between the model complexity and the degree to which deviations larger than ϵ are tolerated [51]. The bigger C, the stronger the regularization, and after several trials it has been set to 50 [52]. The second parameter controls the width of the insensitive zone used to fit the training data [52]. The bigger ϵ, the fewer support vectors are selected, but it returns more "flat" predictions [51].

3.7.1 Regression without time interval dataset division

For this method, the dataset is divided as shown in Fig. 3.25.

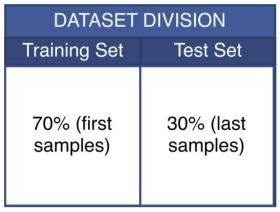

Figure 3.25: Dataset division without time interval.

For each type of regression process, the algorithm returns two models, one for SBP and the other one for DBP estimation.
Each regression function takes as input a matrix which has as many columns as predictors (PTT and HR in this case) and the array with real SBP or DBP values. After the training phase, the function returns the intercept and the coefficients for the two predictors, since the equations of the MLR, RR and SVR models are those reported in Eq. 1.1.

3.7.2 Regression with time interval dataset division

Unlike the previous method, this one makes the dataset division as shown in Fig. 3.26. This time, each regression function takes as input a matrix which has as many columns as the number of samples in a 10 seconds time interval, and the array with real SBP or DBP values. This is done to ensure that the trend of the predicted values follows that of the real ones and, trying to increase the range of the time interval, substantial improvements were not achieved.
As a consequence, each model returns the intercept and as many coefficients as the number of samples in the time interval, since the new equations are

$$\begin{cases} SBP(n) = \alpha_0 + \sum_{i=1}^{N} \alpha_i PTT_i + \sum_{i=1}^{N} \beta_i HR_i \\ DBP(n) = \beta_0 + \sum_{i=1}^{N} \gamma_i PTT_i + \sum_{i=1}^{N} \delta_i HR_i \end{cases} \tag{3.4}$$

where:

- n refers to the sample;
- N refers to the total number of the 10-seconds windows in the test phase;
- all the i-th coefficients and i-th features are the values referred to the i-th window in the test phase.

The test set is divided at the same way of the training set, and then SBP and DBP values are calculated (Fig. 3.27).

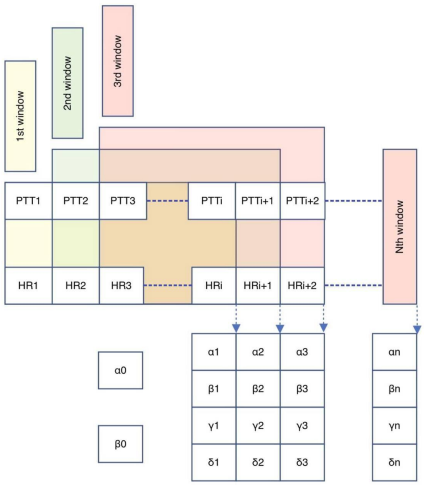

Figure 3.26: Regression coefficients calculation with time interval training set division.

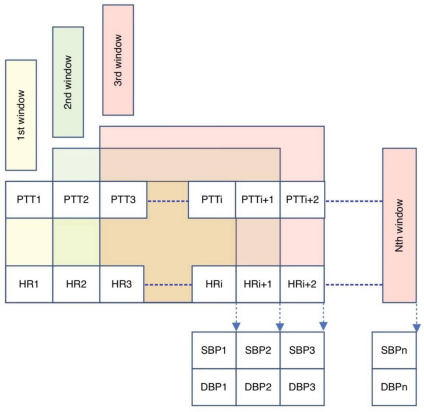

Figure 3.27: SBP and DBP prediction with the time interval test set division.

Chapter 4

Results

The algorithm has been tested for all the measurements in the database and the results are shown in the tables in the Appendix C.

4.1 Algorithm test

To understand how many measurements are to be considered as valid, it is necessary to refer to the AAMI/ESH/ISO guidelines. According to their protocol, the following pass/fail criterion is applicable in general population samples (at least 85 measurements) but also in population with a smaller sample size (at least 35 measurements): mean difference of test versus reference blood pressure measurements less or equal to 5 mmHg with an SD less or equal to 8 mmHg, both for SBP and DBP values [53]. Moreover, the reference BP values are obtained by the OMRON HeartGuide device, whose accuracy is equal to ± 3 mmHg. Thus, according to the error propagation theory [54], the conditions for considering the predicted BP values as valid are the following:

$$\begin{cases} MAE \leq 2 \ \ mmHg \\ SD \leq 8 \ \ mmHg \end{cases} \tag{4.1}$$

The number of validated measurements for each regression method is shown in the Tab. 4.1, calculated considering the occurrences below the conditions in Eq. (4.1).

	NUMBER OF VALIDATED MEASUREMENTS			
	MLR	RFR	RR	SVR
Without time interval dataset division	40 (80%)	16 (32%)	40 (80%)	20 (40%)
With time interval dataset division	13 (26%)	9 (18%)	13 (26%)	14 (28%)

Table 4.1: Number of validated measurements with respect of the total ones.

The larger number of measurements meeting the conditions in Eq. (4.1), are obtained with the multivariate linear regression and Ridge regression methods. From a first analysis, it can also be seen that the results relating to the time interval dataset division are unusable.
Instead, to conduct a more detailed analysis it is necessary to refer to the Tab. 4.2.

	AVERAGE MAE (mmHg) ± AVERAGE SD (mmHg)							
	MLR		RFR		RR		SVR	
	SBP	DBP	SBP	DBP	SBP	DBP	SBP	DBP
Without time interval dataset division	1.76±1,67	1,76±1.72	2,98±3.26	2,50±2,53	1.76±1,67	1.76±1.72	2.62±0.87	2.47±0.84
With time interval dataset division	4.76±3,06	3,70±2.41	3.80±2.35	3.29±2.23	4.76±3.06	3.70±2.41	3.01±1.02	2.75±0.78

Table 4.2: Average MAE and SD related to all the regression methods.

Tabs. 4.1 and 4.2 show that multivariate linear regression and Ridge regression without any interval dataset division are equally valid regression methods for the purpose of this work, because they return the same MAE and SD values for each prediction, as well as for all the reasons previously described in the section 3.7. If a choice must be taken between the two regression methods, MLR could be chosen because it is characterized by a shorter computational time than the RR. In fact, the latter could be considered a regularization of the MLR method, as it introduces the α hyperparameter which keeps the learning weights of the function as low as possible; thus, the decision time of the algorithm increases. An example of predicted SBP and DBP values is shown in the Fig. 4.1.

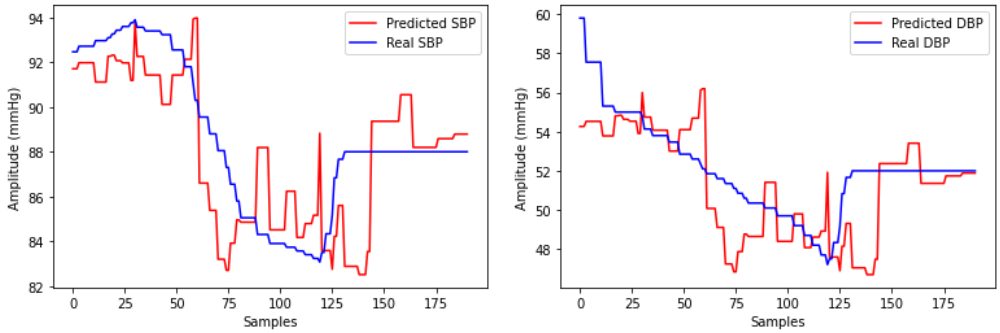

Figure 4.1: Comparison between real and predicted SBP and DBP values obtained with MLR method. $\text{MAE}_{SBP} = 1.84\pm\ 3.28$ mmHg, $\text{MAE}_{DBP} = 1.58\pm\ 2.71$ mmHg. These values belong to subject 1.

At a first glance, the signals may seem not smooth and, at some points, they seem not to follow the trend of the real signals very well. This happens because, as previously mentioned, the OMRON device does not return continuous signals, but punctual blood pressure values. Thus, after interpolating these reference values, the real BP signals may seem "edgy". Despite this, the MAEs and SDs values are acceptable.
The Random Forest regression presents the highest SD values (Fig. 4.2), while the support vector regression shows the lowest SD values but the predicted trend does not follow the real one very well (Fig. 4.3).

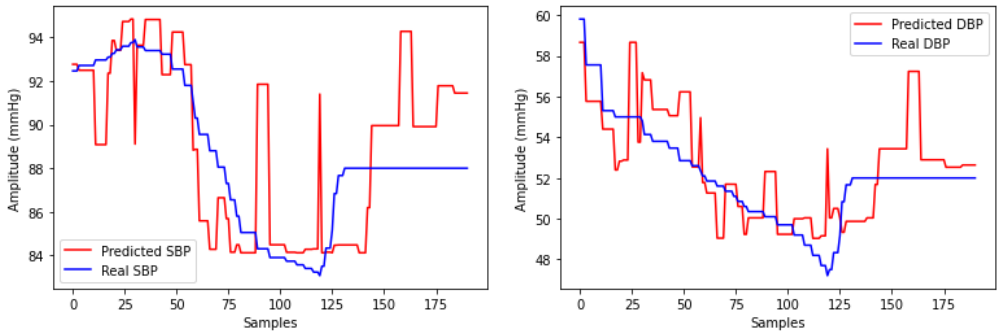

Figure 4.2: Comparison between real and predicted SBP and DBP values obtained with RFR method. $\text{MAE}_{SBP} = 2.16\pm\ 3.95$ mmHg, $\text{MAE}_{DBP} = 1.52\pm\ 2.62$ mmHg. These values belong to subject 1.

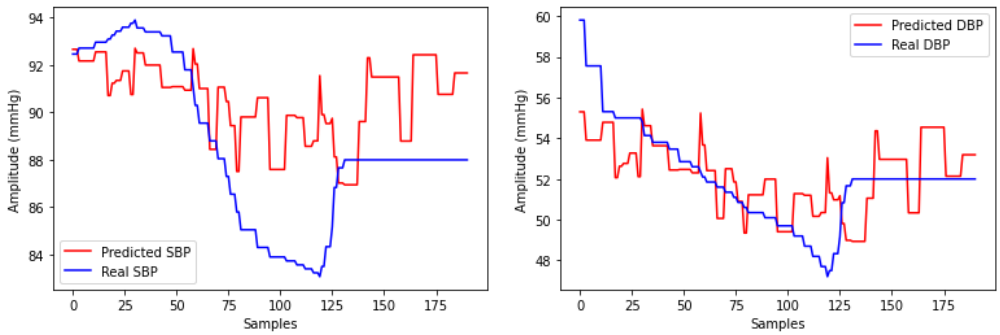

Figure 4.3: Comparison between real and predicted SBP and DBP values obtained with SVR method. $\text{MAE}_{SBP} = 2.84\pm 1.62$ mmHg, $\text{MAE}_{DBP} = 1.55\pm 1.70$ mmHg. These values belong to subject 1.

From Tab. 4.2, it is evident that in general the highest MAE and SD values belong to SBP predictions, because it is intrinsically affected by more variability than the DBP. It is due to the subject's age, genre, BMI and sympathetic nervous system activity [55].
Furthermore, the regression analysis using the time interval dataset division has been implemented because it has already been used in literature, but in this case it returns higher MAE and SD values because this dataset is made up of interpolated punctual BP values. In literature, this method has been used with arterial blood pressure (ABP) values, which constitute continuous signals taken from the *MIMIC III* database [56].
Finally, Tab. 4.1 shows the number of validated measurements according to the AAMI/ESH/ISO guidelines referring to a reduced population (at least 35 measurements). If the population were larger (a general population size of at least 85 measurements), the error tolerance would also increase. In this case, the guidelines suggest a tolerance less or equal to 10 mmHg for the MAE, while the accepted SD values are the same [53]. Including also the accuracy of the control device ($\pm$ 3 mmHg), the new conditions for considering the predictions to be validated are the following:

$$\begin{cases} MAE \leq 7 \ \ mmHg \\ SD \leq 8 \ \ mmHg \end{cases} \tag{4.2}$$

With these new tolerance values, almost all the measurements of the database created for this thesis work can be considered as valid.

4.2 Error resolution strategies

There are several causes to be attributed to the higher errors of predicted blood pressure values.

- PPG and ECG intersubject variability. It is due to subject's physiology [57]. In particular for PPG, which recording is influenced by the subject's skin conductance, sometimes the peaks are so low that it is difficult to establish a threshold value to detect them as well as possible [58]. The *Morfea3* sensor has been especially developed by *SINTEC* to improve the detection of the S-peaks and also to avoid errors due to the malposition of the Shimmer clip and to the light interference thanks to the black adhesive patch (Figs. 4.4, 4.5).

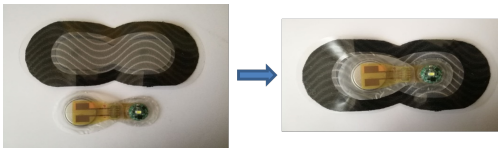

Figure 4.4: Morfea3 module.

Figure 4.5: Morfea3 position.

- Instrumental error. The guide of the *EXG* module does not report any error range because this device allows to record the ECG without visibly affecting it by noise. Thus, the instrumental error related to the *EXG* is negligible. The PPG instead, due to both its own nature and the sampling method, it is affected by noise also caused by the instrumental error, which is a tabulated average across the measurements range [59]. The bias voltage is 0.5 V and, at a typical "low" body resistance (120 kΩ or 8 μS), the bias current is approximately 5 μA; that current will decrease as the conductance increases [59]. The *SINTEC* sensors (Figs. 4.6, 4.7) would be able to decrease the instrumental error, both for ECG and PPG signals.

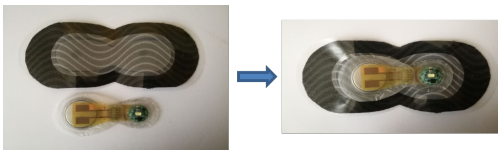

Figure 4.6: Morfea3 module for PPG.

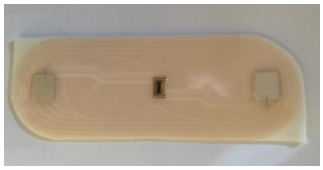

Figure 4.7: HI active patch for ECG.

- OMRON HearthGuide size, tolerance and procedure. The control device is currently available for wrists with a circumference of 160-190

mm [40]. Furthermore, the OMRON HeartGuide can return BP values each minute, but the device's guide suggests to wait 2-3 minutes between measurements in order to allow the arteries to decompress and return to their pre-measurements state [38]. Finally, the device's accuracy in BP measurements is equal to ±3 mmHg [38]. The solution to this problem could be to use a device with a cuff that can be adapted to all wrist circumferences, or that can use cuffs of different sizes. Moreover, it could be able to return BP values every minute at least.

- SBP variability. As previously said, SBP is affected by a major variability than DBP because of the subject's physiology [55]. This problem has been partially avoided because the physiological signals are recorded while the subject is seated and resting, but it could be further avoided by adding other features to better show SBP variability, such as the hour of the recording and if there were changes in the subject's activity.

- HR and PTT array cleaning. Values that are out of range $mean \pm SD$ are deleted and this leads to an improvement of BP predictions. This is done because of the reasons previously discussed in section 3.4. The disadvantage of the cleaning phase is the loss of information for the BP predictions, and although several solutions have been implemented to solve the problem, none of these leads to an improvement of the BP predicted values. Fat-IBC technology, as one of the goal of the *SINTEC* project, would be able to solve this problem because it uses a direct connection between sensors and the interior of the body, which is represented by the skin's fat [60].

4.3 Algorithm calibration time

Wearable technologies aim to be as more comfortable as possible. One of the aspect which could threaten the patient's comfort is about waiting too long for the device calibration. For this reason, the algorithm returns for each subject the minimum calibration time in order to make the individual wear the control device only for the necessary period for the algorithm to train satisfactorily.
Therefore, for each measurement the calibration time is reported in Tab. 5.6 in Appendix D, and it is defined as the minimum time for the algorithm to return the blood pressure values with an acceptable error, as reported in Eq. (4.1).
The average calibration time for each subject has been calculated in Tab. 4.3 only for BP values predicted without any time interval dataset division because, as the Tab. 4.1 has shown, the results in the second row are

unusable.

SUBJECT	AVERAGE CALIBRATION TIME (min)
1	8.39
2	8.60
3	11.71
4	5
5	10.5
6	8

Table 4.3: Average calibration time for all subjects.

As previously said, these values are calculated considering the errors defined in the AAMI/ESH/ISO guidelines and considering the OMRON HeartGuide accuracy. Instead, they do not take into account the goodness of the trend of the predicted BP values compared to the real ones. In this case, the minimum calibration time would be larger for all subjects.

4.3.1 Regression coefficients statistical analysis

The statistical analysis of the regression coefficients was carried out to see if their values related to the same subject remain more or less constant. This was done by calculating for the four regression coefficients of each subject (two for the SBP and two for the DBP) two statistical variables:

- Arithmetic mean (μ): it synthetically describes the average value assumed by a given regression coefficient [61]. It is generally defined as:

$$\mu_X = \frac{1}{N}\sum_{i=1}^{N} x_i \tag{4.3}$$

- Variance (σ^2): it provides a measure of how much the values assumed by a given regression coefficient deviate quadratically from their arithmetic mean [62]. It is generally defined as:

$$\sigma_X^2 = \frac{1}{N-1}\sum_{i=1}^{N}(x_i - \mu_X)^2 \tag{4.4}$$

In order for the statistical analysis to be consistent, it was carried out on the regression coefficients of the subject from whom the greatest number of recordings was acquired. This is a 23-year-old woman, whose coefficients are shown in Tab. 5.7 in Appendix E, and whose statistical variables are shown in Tabs. 4.4 and 4.5.

MEAN (μ)			
α	β	γ	δ
-10.32	0.07774	-5.3648	0.03348

Table 4.4: Regression coefficients' mean related to the subject 1.

VARIANCE (σ^2)			
α	β	γ	δ
288.622	0.05299	402.878	0.06026

Table 4.5: Regression coefficients' variance related to the subject 1.

From Eq. (1.1), it is recalled that α and γ are the coefficients associated with the PTT, which is the feature extracted from the PPG signal, that has a larger variability than ECG (as previously said in section 3.4). For this reason, from Tab. 4.5 it is noted that the variance of the α and γ coefficients is much higher than that of the β and δ coefficients which, on the other hand, are associated with the heart rate (feature extracted from the ECG) and is extremely low.
Now, trying to divide the regression coefficients related to the ante meridiem (AM) measurements by those related to the post meridiem (PM) ones, the variance was calculated again to see if there was any change. The results are shown in Tab. 4.6.

	VARIANCE (σ^2)			
	α	β	γ	δ
AM	42.7755	0.02173	269.209	0.02339
PM	358.017	0.06568	437.157	0.07976

Table 4.6: Regression coefficients' variance related to the AM and PM recordings of subject 1.

As we can see, the AM coefficients present a much lower variability than that calculated considering all the values of a single coefficient. On the other hand, the variability related to the regression coefficients of the PM recordings are higher than the total one, and this happens because in the PM hour range there are the main daily meals, lunch and dinner. There are some studies in the literature which demonstrate that one of the factors which influence blood pressure variability is the proximity of the measurement to the mealtime [63].
This kind of BP variability also occurs in subject 3, whose regression coefficients and their mean and variance are respectively listed in the Tabs. 5.13, 5.14 and 5.15 in Appendix E. After collecting a sufficient number of recordings from the subject 3, the same considerations were made with respect to subject 1 (see Tab. 4.7).

	VARIANCE (σ^2)			
	α	β	γ	δ
AM	224.702	0.07008	505.288	0.10022
PM	957.154	0.59921	427.302	0.16111

Table 4.7: Regression coefficients' variance related to the AM and PM recordings of subject 3.

Chapter 5

Conclusions

The thesis work aimed to find a method capable of monitoring blood pressure values in a non-invasive way through wearable sensors. The goal has been achieved through the ECG and PPG preprocessing and using regression techniques with the features related to them, which are heart rate and pulse transit time.
From the study, it was found that the algorithm using the MLR method returns BP values with a low acceptable error, according to the AAMI/ISO/ESH guidelines (see Eq. (4.1)), with a large number of measurements taken with *SHIMMER* devices.
Previous studies have shown that a similar processing of ECG, PPG and arterial blood pressure signals extracted from the MIMIC III database [64] returns estimated BP values with an error less than 5 mmHg, according to the same guidelines. But as previously said, ABP is acquired in an invasive way which may cause discomfort and several vascular damage to the patients, not to mention that the subject must be in hospital or any other clinical setting for the procedure.
Instead, the proposed approach can be considered as the first step towards continuous cuff-less BP monitoring in a non-invasive way, and with the algorithm uploaded on the wearable sensors developed by *SINTEC*, BP values could be measured at any time in any place, whatever activity the subject is carrying out.
The final device intended by *SINTEC* project is shown in Fig. 5.1. The main idea is based on the use of a new technology consisting of a strain gauge able to resist to mechanical solicitations (it is flexible and stretchable), covered by a transparent patch to realize the adhesion to the skin and to make the device water-repellent. The design is imperceptible in appearance and size and ideal for an active life.

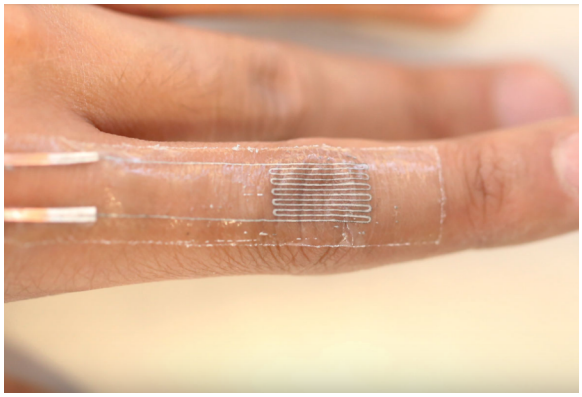

Figure 5.1: Final intended *SINTEC* device for a non-invasive continuous BP monitoring.

5.1 Future developments

Although the algorithm works quite satisfactorily, there are many aspects that can definitely be improved.
Firstly, since the algorithm uses different regression methods, it could be tried to modify the input parameters of Random Forest regression, Ridge regression and support vector regression methods to see if the algorithm could return blood pressure values with a lower error, so a larger number of measurements could be considered as valid. This can be useful also in order to obtain a shorter calibration time and, as a consequence, to make the recording period more comfortable.
After that, the dimension (number of measurements) and the heterogeneity of the population must be increasing in order to verify that the regression coefficients of the same subject do not deviate too much from their mean, and to prove that the coefficients related to subjects with the same physiological features are similar. Also, as previously said in section 4.1, a larger population allows the inclusion of more measurements, accepting a higher error tolerance.
According to the previous point, when the *SINTEC* devices will be used in experimental and/or clinical environment, patients and volunteers will be asked about some information as selection conditions for the experimentation, such as age, gender, BMI, anamnesis, medicament and if they follow any therapy which could affect the BP variability. Also, if the OMRON HeartGuide will continue to be used as a control device, it will be asked a wrist circumference between 160 and 190 mm.
Furthermore, having a larger and more heterogeneous database available, it can be verified that the predicted BP values related to the same subject do not vary over the time if the ECG and PPG signals are recorded under the

same physiological conditions. This aspect translates into the calculation of the time range within a new calibration of the *SINTEC* devices must be carried out.
For what concerns the signals sampling instead, ECG and PPG should be upsampled using higher frequency rates because for *SINTEC* design, as wearable devices, it was chosen to save the battery life in the face of a lower sample frequency.
Finally, it would be useful if the device is calibrated on the ECG and PPG thresholds of the subject it is intended for before using it. The algorithm has been developed also taking into account this aspect.

Appendix A

This appendix shows the informed consent which each subject signed before proceeding with the recording of the physiological signals. The information note relating to the *SINTEC* project is also shown below.

CONSENSO INFORMATO

Titolo della ricerca: **Implementazione di un algoritmo per il monitoraggio della pressione arteriosa in modo non invasivo partendo dai segnali elettrocardiografici (ECG) e fotopletismografici (PPG).**

Sperimentatore: **Dott.ssa Sofia Galici**

Tesista magistrale del Politecnico di Torino

Tesi svolta presso LINKS Foundation

Torino (TO), Italy

Io sottoscritto/a _____, nato/a a _____, il _____, indirizzo _____, telefono _____ ,

Dichiaro

- Di partecipare volontariamente allo studio **Implementazione di un algoritmo per il monitoraggio della pressione arteriosa in modo non invasivo partendo dai segnali elettrocardiografici (ECG) e fotopletismografici (PPG)** avente lo scopo di Testare l'accuratezza dell'algoritmo per la stima della pressione sanguigna in modo non invasivo nell'ambito del progetto europeo SINTEC;

- Di aver ricevuto dalla Dott.ssa **Sofia Galici** esaurienti spiegazioni in merito alla richiesta di partecipazione alla ricerca, in particolare sulle finalità e procedure:
- Di aver avuto la possibilità di porre domande e di aver avuto risposte soddisfacenti su tutta la sperimentazione;
- Di essere stato informato sui possibili rischi o disagi ragionevolmente prevedibili;
- Di essere consapevole che la partecipazione è volontaria;
- Di essere stato assicurato:
  - che potrò ritirarmi dalla sperimentazione già iniziata in qualsiasi momento senza l'obbligo da parte mia di motivarne la decisione;
  - che i dati saranno utilizzati con le finalità indicate nello studio;
  - che è mio diritto avere accesso alla documentazione che mi riguarda;
  - che una copia del consenso informato e della documentazione di cui ho preso visione rimarrà in mio possesso;
  - che per ogni problema o per eventuali ulteriori informazioni potrò rivolgermi alla Dott.ssa Sofia Galici.

Pertanto, confermo di aver avuto risposte esaurienti a tutti i miei quesiti e, preso atto della situazione illustrata,

ACCONSENTO

LIBERAMENTE, SPONTANEAMENTE E IN PIENA COSCIENZA ALLA SPERIMENTAZIONE PROPOSTAMI. Dichiaro inoltre di essere a conoscenza della possibilità di revocare il presente consenso in qualsiasi momento prima, durante e dopo l'avvio della sperimentazione.

Data registrazione	Ora inizio	Ora fine	Firma del partecipante

Eventuali testimoni presenti (nome, cognome, firma): _____

Firma del partecipante: Firma dello sperimentatore:

_____ _____

OPPURE

NON ACCONSENTO

LIBERAMENTE, SPONTANEAMENTE E IN PIENA COSCIENZA ALLA SPERIMENTAZIONE PROPOSTAMI.

Data: _____

Eventuali testimoni presenti (nome, cognome, firma): _____

Firma del partecipante: Firma dello sperimentatore:

_____ _____

NOTA INFORMATIVA

Il progetto ***SINTEC-Soft intelligence epidermal communication platform*** è un progetto europeo nato a giugno del 2019 che si propone di sviluppare una tecnologia innovativa in grado di monitorare la salute di chi la indossa.
SINTEC è supportato da un'ampia varietà di organizzazioni con esperti in tutti i settori d'interesse come l'ingegneria, lo studio dei materiali, l'elettronica, la medicina, lo sport, l'economia e la divulgazione. Gran parte delle attività vengono svolte utilizzando un approccio interdisciplinare. Il progetto vuole rispondere alla necessità di sviluppare nuove tecnologie di interconnessione, non invasive e che non interferiscano con la vita del soggetto che le indossa. I dispositivi indossabili smart sono il passo successivo nell'evoluzione dei dispositivi indossabili di Internet of Things (IoT). Il primo obiettivo che il progetto SINTEC si propone di raggiungere è dimostrare i vantaggi di questa nuova tecnologia nell'ambiente clinico.
Per far ciò si sta sperimentando una tecnologia PCB con substrato estensibile e lega liquida con l'integrazione di sistemi embedded complessi all'interno del substrato al fine di applicarla in differenti situazioni complesse della vita di tutti i giorni.
Il contributo di *LINKS foundation* è orientato all'analisi ed elaborazione dei segnali fisiologici registrati, nello specifico del segnale elettrocardiografico (ECG) e fotopletismografico (PPG). La prima parte del lavoro è focalizzata sulla valutazione delle prestazioni di sensori e antenne tramite confronto con i dispositivi allo stato dell'arte presenti nei laboratori. I sensori esplorati saranno elettrodi per segnali elettrofisiologici (bioimpedenza) per ECG e sensori ottici (LED e fotodiodo) per PPG. Il risultato di queste analisi ha orientato ed orienterà l'architettura del sistema finale che è in continuo aggiornamento. Verranno inoltre integrati e testati firmware e algoritmi per l'estrazione dei parametri fisiologici (es. Frequenza cardiaca, Pressione sanguigna ecc.). I risultati ottenuti dalla validazione forniranno feedback per l'ottimizzazione del dispositivo.

Ulteriori informazioni sul *Progetto SINTEC* sono disponibili qui:
https://www.sintec-project.eu/
Firmando il modulo di consenso ivi allegato, si accetta di partecipare allo studio **Implementazione di un algoritmo per il monitoraggio della pressione arteriosa in modo non invasivo partendo dai segnali elettrocardiografici (ECG) e Fotopletismografici (PPG).**

Qual è lo scopo della sperimentazione?
Lo studio ha lo scopo di testare l'accuratezza dell'algoritmo per la stima della pressione sanguigna in modo non invasivo partendo dai segnali ECG e PPG registrati con dispositivi wearable (Shimmer3 ECG e GRS+).

Sono obbligato a partecipare?
No. La decisione di partecipare alla sperimentazione dipende solo da Lei. È completamente volontaria.

Come si svolgerà la sperimentazione?
Ai volontari sarà richiesto di indossare i dispositivi Shimmer e il dispositivo di riferimento Omron Heartguide. Dovranno restare in posizione rilassata per 20 minuti durante i quali verranno registrati i segnali ECG e PPG in maniera continuativa ed i valori di pressione sistolica e diastolica ogni minuto.

Quanto dura la sperimentazione?
La Sua partecipazione alla sperimentazione durerà fino alla fine della registrazione dei segnali, i volontari che lo desidereranno potranno partecipare più volte alla registrazione.

Dovrò sostenere spese?
No. La Sua partecipazione alla sperimentazione sarà completamente gratuita.

Cosa dovrò fare se decido di partecipare alla sperimentazione?
Le sarà consegnata questa nota informativa, da leggere e conservare. Le sarà chiesto di firmare il modulo di consenso, ivi allegato. Le sarà richiesto di dedicarci il tempo necessario per la registrazione dei segnali.

Potrò cambiare idea dopo aver accettato di partecipare?
Sì. Lei potrà decidere di ritirare il consenso e interrompere la partecipazione alla sperimentazione, in qualsiasi momento, anche a studio avviato, senza dover fornire giustificazioni. Qualora decidesse di ritirare il consenso, Le chiediamo di inviare una comunicazione al seguente recapito: sofia.galici@studenti.polito.it

Come saranno usati i miei dati personali?
I Suoi dati personali saranno resi anonimi, nessuna informazione che La identifichi o La renda identificabile, direttamente o indirettamente, o che possa fornire informazioni sulle Sue caratteristiche, le Sue abitudini, il Suo stile di vita, le Sue relazioni personali, la Sua situazione economica, verrà conservata. I segnali registrati verranno elaborati per la stima della pressione sanguigna e i risultati ottenuti non potranno in alcun modo ricondurre a Lei.

Per quanto tempo saranno conservati i miei dati personali?
I Suoi dati personali saranno resi anonimi, nessuna informazione che La identifichi o La renda identificabile, direttamente o indirettamente, o che

possa fornire informazioni sulle Sue caratteristiche, le Sue abitudini, il Suo stile di vita, le Sue relazioni personali, la Sua situazione economica, verrà conservata. I segnali da Lei registrati saranno utilizzati esclusivamente per il lavoro di tesi della dott.ssa Sofia Galici che terminerà a Marzo 2022.

I miei dati saranno sfruttati commercialmente?
I Suoi dati non saranno in alcun modo sfruttati commercialmente.

Con chi verranno condivisi i miei dati personali?
I Suoi dati personali saranno resi anonimi e solo i risultati da essi ottenuti saranno condivisi con il consorzio SINTEC.

Chi devo contattare nel caso in cui abbia delle domande o reclami da sottoporre?
Nel caso in cui avesse domande o reclami relativi alla sperimentazione, può contattare: sofia.galici@studenti.polito.it

Quali benefici potrò avere partecipando alla sperimentazione?
Lei parteciperà ad uno studio che punta ad avere un impatto rivoluzionario sulla vita dei pazienti per le patologie cardiovascolari. Si spera che fornendo un mezzo di monitoraggio conveniente e affidabile, aumenti il numero di persone che rilevano sistematicamente la propria pressione sanguigna. In questo modo si potrebbe prevenire l'insorgenza o la degenerazione di malattie cardiovascolari che sono ancora oggi la prima causa di mortalità nel mondo.

Cosa accadrà ai risultati della sperimentazione?
I risultati della sperimentazione saranno resi anonimi, quindi Lei non sarà identificabile. I risultati anonimizzati saranno utilizzati ai fini del Progetto SINTEC, condivisi con il consorzio SINTEC, in conferenze nazionali e internazionali, e pubblicati su riviste scientifiche.

Verranno effettuate riprese fotografiche o videografiche durante la mia partecipazione alla sperimentazione?
Durante la Sua partecipazione alla sperimentazione, non saranno scattate fotografie e non saranno effettuati filmati delle sessioni di test.

Quali potrebbero essere i rischi?
Il prelievo dei segnali avviene in modo non invasivo ed indolore, si percepirà solo una pressione al polso su cui verrà posizionato il dispositivo Omron HeartGuide (smartwatch con cuffia che restituisce i valori pressori gonfiandosi e sgonfiandosi). I rischi relativi alla fase di prelievo sono quelli legati all'eventuale mal posizionamento dei sensori con conseguente registrazione di segnali non utilizzabili. In ogni caso il soggetto potrà scegliere in totale libertà di sottoporsi nuovamente alla sperimentazione o meno.

Appendix B

This appendix shows the table containing the peaks detection thresholds, both for ECG and PPG signals, related to all measurements.

THRESHOLDS (mV)		
Measurements	ECG	PPG
1	1.25	30
2	1.25	30
3	1.25	25
4	1.25	9
5	1.25	9
6	1.25	7
7	1.25	4
8	0.5	15
9	1.25	30
10	1.25	30
11	1.25	10
12	0.5	10
13	1.25	30
14	1.25	10
15	1.25	30
16	1.25	30
17	1.25	30
18	1.25	10
19	1.25	10
20	1.25	5
20	1.25	5
21	1.25	8
22	1.25	10
23	1.25	30
24	1.25	20
25	1.25	25
26	1.25	8
27	1.25	5

THRESHOLDS (mV)		
Measurement	ECG	PPG
28	1.25	5
29	1.25	20
30	1.25	3
31	1.25	2
32	1.25	20
33	1.25	10
34	1.25	30
35	0.5	8
36	0.5	20
37	0.5	30
38	0.5	30
39	0.5	5
40	0.5	30
41	0.5	9
42	0.5	25
43	0.5	7
44	0.5	10
45	0.5	30
46	0.5	20
47	0.5	20
48	0.5	20
49	0.5	25
50	0.5	4

Table 5.1: ECG and PPG thresholds for all measurements.

Appendix C

This appendix shows the tables with the MAEs and the SDs related to all measurements for each regression method.

MEA (mmHg) ± SD (mmHg)			
NUMBER OF MEASUREMENTS		MLR	
		SBP	DBP
1	Without time interval dataset division	0.96±0.66	0.77±0.17
	With time interval dataset division	1.48±0.94	0.63±0.49
2	Without time interval dataset division	1.23±1.49	1.69±2.32
	With time interval dataset division	2.10±1.78	2.26±2.51
3	Without time interval dataset division	1.87±4.17	1.58±2.78
	With time interval dataset division	4.59±3.25	4.05±2.70
4	Without time interval dataset division	0.76±0.48	0.79±0.39
	With time interval dataset division	0.81±0.36	1.63±0.51
5	Without time interval dataset division	1.64±4.17	1.40±2.78
	With time interval dataset division	7.78±3.25	2.23±2.70
6	Without time interval dataset division	0.40±1.43	0.70±1.02
	With time interval dataset division	0.44±1.37	0.67±0.80
7	Without time interval dataset division	6.49±2.07	3.02±0.86
	With time interval dataset division	2.97±2.19	1.10±0.97
8	Without time interval dataset division	1.21±1.36	1.95±3.44
	With time interval dataset division	3.62±3.90	4.25±7.13
9	Without time interval dataset division	1.82±3.10	0.95±0.80
	With time interval dataset division	2.68±2.41	0.91±0.60

10	Without time interval dataset division	1.57±3.23	1.65±2.26
	With time interval dataset division	2.70±3.30	2.31±1.89
11	Without time interval dataset division	1.99±1.26	1.05±0.25
	With time interval dataset division	4.45±2.37	1.55±0.73
12	Without time interval dataset division	1.66±2.57	1.87±0.99
	With time interval dataset division	24.53±2.10	1.10±0.67
13	Without time interval dataset division	0.73±1.34	1.76±2.68
	With time interval dataset division	0.96±1.28	2.74±2.70
14	Without time interval dataset division	2.03±1.25	2.54±0.51
	With time interval dataset division	1.16±0.80	1.90±2.58
15	Without time interval dataset division	1.33±0.98	1.47±0.83
	With time interval dataset division	2.58±1.24	1.95±0.67
16	Without time interval dataset division	0.52±0.47	0.97±0.85
	With time interval dataset division	0.77±0.81	0.66±0.60
17	Without time interval dataset division	1.25±0.43	2.00±5.44
	With time interval dataset division	2.64±2.07	8.96±6.55
18	Without time interval dataset division	1.99±1.69	1.77±1.20
	With time interval dataset division	1.87±1.39	1.07±1.02
19	Without time interval dataset division	1.36±1.29	1.90±2.55
	With time interval dataset division	2.10±1.64	3.80±0.95
20	Without time interval dataset division	2.75±7.02	4.45±7.58
	With time interval dataset division	9.14±10.91	9.80±8.28
21	Without time interval dataset division	1.44±1.91	1.32±1.24
	With time interval dataset division	5.51±2.83	2.45±1.63
22	Without time interval dataset division	2.00±3.86	1.68±1.83
	With time interval dataset division	4.47±1.79	3.67±2.80
23	Without time interval dataset division	0.88±2.09	1.95±3.01
	With time interval dataset division	2.62±2.02	7.32±3.69
24	Without time interval dataset division	1.46±1.33	1.31±1.26
	With time interval dataset division	1.99±1.45	2.90±0.93

25	Without time interval dataset division	0.95±0.59	1.86±0.25
	With time interval dataset division	0.84±0.24	1.60±0.38
26	Without time interval dataset division	1.58±1.49	1.38±3.71
	With time interval dataset division	2.63±1.73	2.66±2.59
27	Without time interval dataset division	0.66±0.22	0.78±0.55
	With time interval dataset division	0.76±0.12	1.02±1.07
28	Without time interval dataset division	0.71±0.77	1.15±0.02
	With time interval dataset division	1.61±1.39	0.90±0.63
29	Without time interval dataset division	1.87±0.94	1.85±0.67
	With time interval dataset division	1.21±0.52	1.97±0.76
30	Without time interval dataset division	4.48±0.93	2.05±0.27
	With time interval dataset division	3.82±2.32	2.08±0.64
31	Without time interval dataset division	3.79±1.06	4.34±1.72
	With time interval dataset division	3.31±2.21	4.20±0.32
32	Without time interval dataset division	1.14±0.72	0.98±0.78
	With time interval dataset division	4.16±0.68	3.22±0.63
33	Without time interval dataset division	0.60±0.66	0.98±1.14
	With time interval dataset division	1.12±1.01	1.59±0.63
34	Without time interval dataset division	1.36±1.29	1.32±1.39
	With time interval dataset division	20.33±23.60	19.16±21.58
35	Without time interval dataset division	3.62±0.71	4.05±0.87
	With time interval dataset division	6.63±5.56	4.60±3.68
36	Without time interval dataset division	2.00±2.72	1.99±3.04
	With time interval dataset division	2.74±2.68	2.77±2.97
37	Without time interval dataset division	0.87±0.59	0.55±0.39
	With time interval dataset division	3.64±2.54	4.48±3.32
38	Without time interval dataset division	1.81±1.40	1.88±2.64
	With time interval dataset division	3.23±1.43	5.55±0.60
39	Without time interval dataset division	4.23±2.56	3.31±1.79
	With time interval dataset division	36.78±17.71	17.89±10.39
40	Without time interval dataset division	0.82±0.59	0.66±0.69
	With time interval dataset division	5.74±5.14	2.21±1.26

41	Without time interval dataset division	1.43±0.78	1.47±1.53
	With time interval dataset division	1.55±1.72	2.08±1.47
42	Without time interval dataset division	0.86±0.92	1.55±2.37
	With time interval dataset division	3.57±0.86	5.12±0.18
43	Without time interval dataset division	0.55±0.21	0.84±0.77
	With time interval dataset division	0.93±0.50	1.78±0.69
44	Without time interval dataset division	1.83±0.79	2.00±3.33
	With time interval dataset division	3.50±2.29	5.01±1.38
45	Without time interval dataset division	0.71±0.45	2.74±2.88
	With time interval dataset division	7.84±7.01	4.28±0.93
46	Without time interval dataset division	1.00±0.63	0.91±0.32
	With time interval dataset division	1.83±1.93	1.32±1.03
47	Without time interval dataset division	1.94±2.98	1.32±1.25
	With time interval dataset division	4.73±3.80	4.70±0.85
48	Without time interval dataset division	6.72±2.84	4.93±0.12
	With time interval dataset division	12.17±4.51	5.29±1.65
49	Without time interval dataset division	1.92±6.99	1.92±6.20
	With time interval dataset division	8.52±5.49	7.89±6.02
50	Without time interval dataset division	1.04±0.21	0.53±0.22
	With time interval dataset division	0.79±0.60	1.83±0.52

Table 5.2: All measurements' MAE and SD referred to the MLR method.

MEA (mmHg) ± SD (mmHg)			
NUMBER OF MEASUREMENTS		RFR	
		SBP	DBP
1	Without time interval dataset division	1.19±1.08	0.67±0.77
	With time interval dataset division	2.14±0.53	0.72±0.78
2	Without time interval dataset division	2.38±3.06	3.58±3.87
	With time interval dataset division	1.79±1.34	4.91±3.91
3	Without time interval dataset division	1.97±3.58	1.42±1.96
	With time interval dataset division	4.21±2.15	4.07±2.83
4	Without time interval dataset division	1.35±1.63	1.49±0.98
	With time interval dataset division	1.34±1.55	1.69±0.42
5	Without time interval dataset division	2.19±3.58	2.87±1.96
	With time interval dataset division	5.60±2.15	3.52±2.83
6	Without time interval dataset division	0.95±2.64	1.14±1.45
	With time interval dataset division	0.79±2.55	1.42±1.47
7	Without time interval dataset division	8.24±5.69	3.82±2.97
	With time interval dataset division	8.12±4.03	3.98±1.98
8	Without time interval dataset division	1.80±2.20	2.51±3.46
	With time interval dataset division	3.96±6.30	6.30±9.77
9	Without time interval dataset division	1.82±3.31	0.95±2.97
	With time interval dataset division	2.68±2.94	0.91±2.70
10	Without time interval dataset division	5.11±5.54	1.99±1.20
	With time interval dataset division	6.83±3.50	2.10±1.09
11	Without time interval dataset division	1.90±6.91	1.63±1.98
	With time interval dataset division	2.96±6.10	1.25±1.29
12	Without time interval dataset division	5.49±5.35	1.87±0.85
	With time interval dataset division	19.87±2.63	1.10±2.53
13	Without time interval dataset division	1.66±2.10	5.36±5.44
	With time interval dataset division	1.46±0.44	5.66±1.32
14	Without time interval dataset division	2.30±1.87	3.67±2.34
	With time interval dataset division	2.27±1.85	2.22±1.34

15	Without time interval dataset division	1.79±1.38	1.93±1.30
	With time interval dataset division	4.25±2.63	2.61±1.27
16	Without time interval dataset division	1.14±0.73	0.64±0.82
	With time interval dataset division	5.25±1.40	0.60±0.24
17	Without time interval dataset division	1.30±1.19	3.34±5.08
	With time interval dataset division	1.75±0.89	5.24±1.81
18	Without time interval dataset division	2.00±1.77	2.79±2.73
	With time interval dataset division	2.48±1.91	2.97±2.94
19	Without time interval dataset division	2.66±6.67	2.60±4.01
	With time interval dataset division	3.37±5.08	7.34±6.83
20	Without time interval dataset division	3.79±7.75	5.67±7.13
	With time interval dataset division	5.36±4.47	8.74±5.04
21	Without time interval dataset division	2.38±3.94	1.75±2.29
	With time interval dataset division	5.36±2.85	1.13±1.72
22	Without time interval dataset division	1.95±2.15	1.96±1.96
	With time interval dataset division	4.45±1.18	3.37±1.90
23	Without time interval dataset division	3.13±1.99	2.13±2.18
	With time interval dataset division	2.47±1.10	3.17±2.87
24	Without time interval dataset division	2.70±7.39	2.62±3.75
	With time interval dataset division	3.70±2.79	4.43±1.48
25	Without time interval dataset division	1.43±1.78	1.66±1.52
	With time interval dataset division	0.98±0.64	1.39±1.36
26	Without time interval dataset division	2.91±3.43	2.00±2.06
	With time interval dataset division	3.70±2.71	3.04±4.58
27	Without time interval dataset division	0.56±0.46	2.84±3.05
	With time interval dataset division	0.79±0.32	3.98±2.70
28	Without time interval dataset division	1.68±1.10	1.40±1.15
	With time interval dataset division	1.79±1.51	1.50±1.10
29	Without time interval dataset division	2.14±1.01	2.82±1.35
	With time interval dataset division	1.75±1.03	2.46±1.02
30	Without time interval dataset division	4.06±1.79	2.10±1.07
	With time interval dataset division	3.13±2.44	1.96±0.54

31	Without time interval dataset division	4.30±2.94	4.15±3.23
	With time interval dataset division	3.19±1.47	3.98±1.38
32	Without time interval dataset division	2.20±1.86	3.48±3.41
	With time interval dataset division	4.24±1.72	3.24±2.12
33	Without time interval dataset division	1.11±2.12	1.05±1.85
	With time interval dataset division	1.99±1.35	1.68±0.86
34	Without time interval dataset division	3.47±4.02	1.89±2.50
	With time interval dataset division	3.24±0.82	6.64±1.90
35	Without time interval dataset division	3.93±2.30	2.01±1.57
	With time interval dataset division	5.84±0.93	6.07±1.46
36	Without time interval dataset division	4.57±3.20	3.86±3.37
	With time interval dataset division	3.49±2.61	3.50±3.07
37	Without time interval dataset division	3.27±2.41	2.31±2.03
	With time interval dataset division	3.65±2.23	1.58±1.65
38	Without time interval dataset division	2.58±2.48	2.01±2.42
	With time interval dataset division	3.40±0.23	5.45±1.31
39	Without time interval dataset division	7.93±6.36	5.22±4.04
	With time interval dataset division	4.41±2.13	1.86±1.39
40	Without time interval dataset division	1.33±1.47	1.29±1.40
	With time interval dataset division	1.69±1.81	1.11±1.61
41	Without time interval dataset division	2.10±2.30	2.22±2.20
	With time interval dataset division	2.91±3.53	2.05±1.76
42	Without time interval dataset division	2.46±2.59	1.70±3.20
	With time interval dataset division	2.85±2.76	4.09±3.72
43	Without time interval dataset division	1.04±1.09	1.56±1.97
	With time interval dataset division	2.26±2.14	2.54±1.18
44	Without time interval dataset division	3.75±3.78	5.43±5.96
	With time interval dataset division	3.75±3.56	5.55±5.89
45	Without time interval dataset division	9.42±11.35	2.57±2.52
	With time interval dataset division	7.89±3.78	3.59±2.04

46	Without time interval dataset division	2.49±2.56	2.03±2.34
	With time interval dataset division	1.51±1.20	1.68±1.64
47	Without time interval dataset division	4.37±4.52	1.20±1.23
	With time interval dataset division	4.03±4.52	4.99±1.34
48	Without time interval dataset division	8.18±8.26	4.71±2.18
	With time interval dataset division	7.87±6.43	5.06±1.85
49	Without time interval dataset division	5.22±2.56	3.49±3.95
	With time interval dataset division	6.18±2.39	5.08±3.01
50	Without time interval dataset division	1.06±1.86	1.42±1.51
	With time interval dataset division	1.15±0.66	0.74±0.41

Table 5.3: All measurements' MAE and SD referred to the RFR method.

MEA (mmHg) ± SD (mmHg)			
NUMBER OF MEASUREMENTS		RR	
		SBP	DBP
1	Without time interval dataset division	0.96±0.66	0.77±0.17
	With time interval dataset division	1.48±0.94	0.63±0.49
2	Without time interval dataset division	1.23±1.49	1.69±2.32
	With time interval dataset division	2.10±1.78	2.26±2.51
3	Without time interval dataset division	1.87±4.17	1.58±2.78
	With time interval dataset division	4.59±3.25	4.05±2.70
4	Without time interval dataset division	0.76±0.48	0.79±0.39
	With time interval dataset division	0.81±0.36	1.63±0.51
5	Without time interval dataset division	1.64±4.17	1.40±2.78
	With time interval dataset division	7.78±3.25	2.23±2.70
6	Without time interval dataset division	0.40±1.43	0.70±1.02
	With time interval dataset division	0.44±1.37	0.67±0.80
7	Without time interval dataset division	6.49±2.07	3.02±0.86
	With time interval dataset division	2.97±2.19	1.10±0.97
8	Without time interval dataset division	1.21±1.36	1.95±3.44
	With time interval dataset division	3.62±3.90	4.25±7.13
9	Without time interval dataset division	1.82±3.10	0.95±0.80
	With time interval dataset division	2.68±2.41	0.91±0.60
10	Without time interval dataset division	1.57±3.23	1.65±2.26
	With time interval dataset division	2.70±3.30	2.31±1.89
11	Without time interval dataset division	1.99±1.26	1.05±0.25
	With time interval dataset division	4.45±2.37	1.55±0.73
12	Without time interval dataset division	1.66±2.57	1.87±0.99
	With time interval dataset division	24.53±2.10	1.10±0.67
13	Without time interval dataset division	0.73±1.34	1.76±2.68
	With time interval dataset division	0.96±1.28	2.74±2.70
14	Without time interval dataset division	2.03±1.25	2.54±0.51
	With time interval dataset division	1.16±0.80	1.90±2.58

15	Without time interval dataset division	1.33±0.98	1.47±0.83
	With time interval dataset division	2.58±1.24	1.95±0.67
16	Without time interval dataset division	0.52±0.47	0.97±0.85
	With time interval dataset division	0.77±0.81	0.66±0.60
17	Without time interval dataset division	1.25±0.43	2.00±5.44
	With time interval dataset division	2.64±2.07	8.96±6.55
18	Without time interval dataset division	1.99±1.69	1.77±1.20
	With time interval dataset division	1.87±1.39	1.07±1.02
19	Without time interval dataset division	1.36±1.29	1.90±2.55
	With time interval dataset division	2.10±1.64	3.80±0.95
20	Without time interval dataset division	2.75±7.02	4.45±7.58
	With time interval dataset division	9.14±10.91	9.80±8.28
21	Without time interval dataset division	1.44±1.91	1.32±1.24
	With time interval dataset division	5.51±2.83	2.45±1.63
22	Without time interval dataset division	2.00±3.86	1.68±1.83
	With time interval dataset division	4.47±1.79	3.67±2.80
23	Without time interval dataset division	0.88±2.09	1.95±3.01
	With time interval dataset division	2.62±2.02	7.32±3.69
24	Without time interval dataset division	1.46±1.33	1.31±1.26
	With time interval dataset division	1.99±1.45	2.90±0.93
25	Without time interval dataset division	0.95±0.59	1.86±0.25
	With time interval dataset division	0.84±0.24	1.60±0.38
26	Without time interval dataset division	1.58±1.49	1.38±3.71
	With time interval dataset division	2.63±1.73	2.66±2.59
27	Without time interval dataset division	0.66±0.22	0.78±0.55
	With time interval dataset division	0.76±0.12	1.02±1.07
28	Without time interval dataset division	0.71±0.77	1.15±0.02
	With time interval dataset division	1.61±1.39	0.90±0.63
29	Without time interval dataset division	1.87±0.94	1.85±0.67
	With time interval dataset division	1.21±0.52	1.97±0.76
30	Without time interval dataset division	4.48±0.93	2.05±0.27
	With time interval dataset division	3.82±2.32	2.08±0.64

31	Without time interval dataset division	3.79±1.06	4.34±1.72
	With time interval dataset division	3.31±2.21	4.20±0.32
32	Without time interval dataset division	1.14±0.72	0.98±0.78
	With time interval dataset division	4.16±0.68	3.22±0.63
33	Without time interval dataset division	0.60±0.66	0.98±1.14
	With time interval dataset division	1.12±1.01	1.59±0.63
34	Without time interval dataset division	1.36±1.29	1.32±1.39
	With time interval dataset division	20.33±23.60	19.16±21.58
35	Without time interval dataset division	3.62±0.71	4.05±0.87
	With time interval dataset division	6.63±5.56	4.60±3.68
36	Without time interval dataset division	2.00±2.72	1.99±3.04
	With time interval dataset division	2.74±2.68	2.77±2.97
37	Without time interval dataset division	0.87±0.59	0.55±0.39
	With time interval dataset division	3.64±2.54	4.48±3.32
38	Without time interval dataset division	1.81±1.40	1.88±2.64
	With time interval dataset division	3.23±1.43	5.55±0.60
39	Without time interval dataset division	4.23±2.56	3.31±1.79
	With time interval dataset division	36.78±17.71	17.89±10.39
40	Without time interval dataset division	0.82±0.59	0.66±0.69
	With time interval dataset division	5.74±5.14	2.21±1.26
41	Without time interval dataset division	1.43±0.78	1.47±1.53
	With time interval dataset division	1.55±1.72	2.08±1.47
42	Without time interval dataset division	0.86±0.92	1.55±2.37
	With time interval dataset division	3.57±0.86	5.12±0.18
43	Without time interval dataset division	0.55±0.21	0.84±0.77
	With time interval dataset division	0.93±0.50	1.78±0.69
44	Without time interval dataset division	1.83±0.79	2.00±3.33
	With time interval dataset division	3.50±2.29	5.01±1.38
45	Without time interval dataset division	0.71±0.45	2.74±2.88
	With time interval dataset division	7.84±7.01	4.28±0.93

46	Without time interval dataset division	1.00±0.63	0.91±0.32
	With time interval dataset division	1.83±1.93	1.32±1.03
47	Without time interval dataset division	1.94±2.98	1.32±1.25
	With time interval dataset division	4.73±3.80	4.70±0.85
48	Without time interval dataset division	6.72±2.84	4.93±0.12
	With time interval dataset division	12.17±4.51	5.29±1.65
49	Without time interval dataset division	1.92±6.99	1.92±6.20
	With time interval dataset division	8.52±5.49	7.89±6.02
50	Without time interval dataset division	1.04±0.21	0.53±0.22
	With time interval dataset division	0.79±0.60	1.83±0.52

Table 5.4: All measurements' MAE and SD referred to the RR method.

MEA (mmHg) ± SD (mmHg)			
NUMBER OF MEASUREMENTS		SVR	
		SBP	DBP
1	Without time interval dataset division	1.12±0.81	0.80±0.47
	With time interval dataset division	1.05±1.04	0.90±0.77
2	Without time interval dataset division	1.48±0.43	2.22±0.56
	With time interval dataset division	1.97±1.59	2.29±2.61
3	Without time interval dataset division	3.11±2.29	1.44±1.63
	With time interval dataset division	4.13±1.70	1.92±0.89
4	Without time interval dataset division	1.37±0.78	0.93±0.55
	With time interval dataset division	2.01±0.41	0.79±0.19
5	Without time interval dataset division	9.22±2.29	3.96±1.63
	With time interval dataset division	9.82±1.70	4.50±0.89
6	Without time interval dataset division	0.52±0.34	1.48±0.01
	With time interval dataset division	0.42±63	1.45±0.05
7	Without time interval dataset division	2.79±0.60	2.04±0.28
	With time interval dataset division	4.09±0.96	2.84±0.52
8	Without time interval dataset division	1.65±0.79	2.18±0.57
	With time interval dataset division	1.35±0.28	2.15±0.11
9	Without time interval dataset division	1.82±0.66	0.95±0.32
	With time interval dataset division	2.68±1.12	0.91±0.10
10	Without time interval dataset division	5.08±2.28	1.89±1.78
	With time interval dataset division	2.85±3.17	2.20±0.56
11	Without time interval dataset division	4.19±0.40	1.12±0.66
	With time interval dataset division	4.34±0.13	1.12±0.70
12	Without time interval dataset division	7.66±0.62	1.87±0.61
	With time interval dataset division	10.26±1.71	1.10±0.28
13	Without time interval dataset division	0.89±0.89	2.85±0.05
	With time interval dataset division	0.93±1.57	2.68±0.70
14	Without time interval dataset division	1.52±0.21	2.44±0.19
	With time interval dataset division	1.38±0.80	2.71±2.57

15	Without time interval dataset division	1.49±0.87	2.54±0.53
	With time interval dataset division	1.64±0.86	2.69±0.68
16	Without time interval dataset division	0.42±0.25	0.92±0.68
	With time interval dataset division	0.34±0.28	0.64±0.57
17	Without time interval dataset division	1.51±1.24	5.57±0.71
	With time interval dataset division	1.28±1.38	5.81±1.00
18	Without time interval dataset division	1.12±0.63	1.95±1.58
	With time interval dataset division	1.65±1.24	1.27±1.36
19	Without time interval dataset division	1.30±2.08	3.00±4.93
	With time interval dataset division	1.95±2.02	3.37±0.15
20	Without time interval dataset division	6.19±0.24	9.22±0.26
	With time interval dataset division	6.35±0.69	9.58±1.15
21	Without time interval dataset division	1.50±1.54	0.68±0.24
	With time interval dataset division	4.72±2.14	2.20±1.41
22	Without time interval dataset division	2.55±0.15	1.62±0.59
	With time interval dataset division	3.00±0.58	1.37±0.82
23	Without time interval dataset division	1.68±0.35	3.88±1.55
	With time interval dataset division	1.81±0.06	3.40±0.94
24	Without time interval dataset division	1.38±0.17	1.99±0.88
	With time interval dataset division	1.52±0.48	3.92±0.26
25	Without time interval dataset division	0.64±0.07	1.75±0.16
	With time interval dataset division	0.74±0.11	1.82±0.05
26	Without time interval dataset division	1.47±2.02	1.94±0.98
	With time interval dataset division	2.40±1.86	2.14±0.31
27	Without time interval dataset division	0.82±0.16	0.69±0.19
	With time interval dataset division	0.81±0.15	0.84±0.37
28	Without time interval dataset division	0.92±0.17	1.26±0.07
	With time interval dataset division	1.42±0.24	0.83±0.52
29	Without time interval dataset division	0.65±0.53	1.65±1.22
	With time interval dataset division	1.27±0.93	1.52±0.90
30	Without time interval dataset division	5.64±0.65	1.89±0.34
	With time interval dataset division	6.38±1.07	1.90±0.31

31	Without time interval dataset division	3.29±0.21	3.80±1.02
	With time interval dataset division	3.32±0.28	4.45±0.27
32	Without time interval dataset division	2.19±0.57	2.94±0.74
	With time interval dataset division	3.65±0.73	3.88±0.09
33	Without time interval dataset division	1.37±1.55	1.38±1.62
	With time interval dataset division	1.24±1.30	1.66±1.00
34	Without time interval dataset division	1.63±1.89	0.49±0.05
	With time interval dataset division	1.89±1.64	0.77±0.74
35	Without time interval dataset division	5.28±0.75	2.79±1.19
	With time interval dataset division	5.96±0.20	3.90±0.84
36	Without time interval dataset division	3.71±2.37	3.79±2.85
	With time interval dataset division	5.82±2.56	6.14±2.81
37	Without time interval dataset division	3.08±0.29	0.87±0.62
	With time interval dataset division	3.93±0.24	1.02±0.56
38	Without time interval dataset division	2.81±0.52	4.76±0.50
	With time interval dataset division	2.93±0.67	4.86±1.15
39	Without time interval dataset division	4.05±1.13	4.15±2.94
	With time interval dataset division	3.06±0.60	2.70±0.97
40	Without time interval dataset division	1.45±0.37	1.82±0.16
	With time interval dataset division	1.57±0.35	2.03±0.42
41	Without time interval dataset division	1.46±0.71	1.41±0.29
	With time interval dataset division	1.76±0.42	1.64±0.97
42	Without time interval dataset division	1.38±0.74	4.48±0.92
	With time interval dataset division	1.35±0.37	4.24±1.69
43	Without time interval dataset division	0.59±0.79	0.92±0.75
	With time interval dataset division	0.69±0.55	1.78±0.57
44	Without time interval dataset division	1.96±0.84	5.35±1.29
	With time interval dataset division	2.45±1.43	6.12±0.57
45	Without time interval dataset division	6.20±0.90	3.77±1.44
	With time interval dataset division	6.40±2.99	3.57±2.86

46	Without time interval dataset division	0.81±0.32	0.80±0.32
	With time interval dataset division	0.90±0.21	0.97±0.88
47	Without time interval dataset division	3.80±2.27	2.05±0.19
	With time interval dataset division	4.82±4.11	2.13±0.21
48	Without time interval dataset division	5.86±1.92	5.19±0.26
	With time interval dataset division	6.38±0.02	5.33±0.21
49	Without time interval dataset division	6.49±0.57	5.41±0.13
	With time interval dataset division	6.32±1.20	5.47±0.10
50	Without time interval dataset division	1.79±0.09	0.68±0.41
	With time interval dataset division	1.46±0.26	0.76±0.24

Table 5.5: All measurements' MAE and SD referred to the SVR method.

Appendix D

This appendix shows the table with the minimum calibration time of the algorithm related to all measurements both within and without the time interval dataset division.

MINIMUM CALIBRATION TIME (min)		
Measurement	Without time interval dataset division	With time interval dataset division
1	6	9
2	13	/
3	5	/
4	5	5
5	7	/
6	5	5
7	/	/
8	7	/
9	5	/
10	8	/
11	6	/
12	17	/
13	8	/
14	/	5
15	8	/
16	7	7
17	7	/
18	8	5
19	14	/
20	/	/
21	16	/
22	16	/
23	11	/
24	10	/
25	5	5
26	8	/
27	6	5

MINIMUM CALIBRATION TIME (min)		
Measurement	Without time interval dataset division	With time interval dataset division
28	5	9
29	7	5
30	/	/
31	/	/
32	12	/
33	5	9
34	15	15
35	/	/
36	5	/
37	13	/
38	11	/
39	/	/
40	10	/
41	6	10
42	15	/
43	13	13
44	17	/
45	/	/
46	15	15
47	15	/
48	/	/
49	15	/
50	5	5

Table 5.6: Algorithm calibration time for all measurements.

Appendix E

This appendix shows the tables with the values of the four regression coefficients related to all subjects from whom more than two measurement were recorded. There are also the tables that show the mean and variance values of the coefficients themselves.

Subject 1	Measurements	MLR SBP coefficients		MLR DBP coefficients	
		α	β	γ	δ
Female 23 years BMI: 18.75 Thin wrist	1	-32.58	0.15	-27.26	0.06
	2	-1.95	0.15	1.95	-0.13
	3	-56.76	0.11	-23.97	0.17
	4	-2.45	0.08	8.57	-0.17
	5	-48.01	0.3	4.21	0.05
	6	-11.97	-0.09	-1.44	0.1
	7	-26.38	-0.17	-3.78	0.57
	8	1.45	-0.61	37.49	-0.71
	9	10.85	0.59	16.28	0.27
	10	12.03	0.01	-25.33	-0.05
	11	-15.3	0.1	-52.28	-0.07
	12	-10.71	0.01	-40.49	0.13
	13	-9.87	0.13	-4.17	0.04
	14	-5.32	0.33	30.52	-0.26
	15	-3.98	0.01	-7.22	-0.11
	16	-5.35	-0.21	-0.18	-0.01
	17	-17.89	-0.002	-15.27	0.17
	18	7.6	-0.05	7.63	-0.1
	19	-10.15	0.3	-7.98	0.21
	20	5.79	0.23	-2.1	0.09
	21	-13.86	0.17	-18.22	0.41
	22	7.6	-0.05	7.63	-0.1
	23	-10.15	0.3	-7.98	0.21

Table 5.7: Regression coefficients related to subject 1.

MEAN (μ)			
α	β	γ	δ
-10.32	0.07774	-5.3648	0.03348

Table 5.8: Regression coefficients' mean related to subject 1.

VARIANCE (σ^2)			
α	β	γ	δ
288.622	0.05299	402.878	0.06026

Table 5.9: Regression coefficients' variance related to subject 1.

Subject 2	Measurements	MLR SBP coefficients		MLR DBP coefficients	
		α	β	γ	δ
Male 25 years BMI: 21.50	1	4.93	0.2	-4.38	0.48
	2	14.67	-0.27	4.47	-0.12
	3	-16.52	-0.14	-21.07	0.14
	4	10.2	0.44	-50.95	-0.4
	5	-0.11	-0.25	5.06	0.12

Table 5.10: Regression coefficients related to subject 2.

MEAN (μ)			
α	β	γ	δ
2.634	-0.004	-13.374	0.044

Table 5.11: Regression coefficients' mean related to subject 2.

VARIANCE (σ^2)			
α	β	γ	δ
116.357	0.0777	442.059	0.08582

Table 5.12: Regression coefficients' variance related to subject 2.

Subject 3	Measurements	MLR SBP coefficients		MLR DBP coefficients	
		α	β	γ	δ
Female 28 years BMI: 17.69 Thin wrist	1	-0.48	-0.61	-2.79	-0.87
	2	-86.76	2.22	5.25	0.46
	3	-11.66	0.1	2.1	0.36
	4	20.06	0.65	17.5	0.88
	5	-19.91	0.12	-14.07	0.13
	6	25.07	0.04	48.41	0.04
	7	0.07	-0.59	-14.84	-0.43
	8	2.53	0.21	-9.39	-0.02
	9	12.19	0.19	31.6	-0.01
	10	-9.91	-0.04	28.34	0.001
	11	-0.74	-0.12	2	0.2
	12	0.56	0.25	-31.25	0.62
	13	-3.56	-0.11	-23.78	0.1
	14	-4.66	0.02	-11.29	0,26
	15	-15.82	-0.06	-16.38	-0.13
	16	35.34	-0.98	-2.78	0.01
	17	-46.2	0.26	-44.93	0.13
	18	-5.01	-0.02	5.01	-0.12

Table 5.13: Regression coefficients related to subject 3.

MEAN (μ)			
α	β	γ	δ
-6.0494	0.085	-1.7383	0.0895

Table 5.14: Regression coefficients' mean related to subject 3.

VARIANCE (σ^2)			
α	β	γ	δ
687.737	0.39835	496.476	0.13792

Table 5.15: Regression coefficients' variance related to subject 3.

Appendix F

This appendix shows the implemented *Python* code related to the entire algorithm.

```
@author Sofia Galici
import csv
import operator
import numpy as np
import scipy
import matplotlib.pyplot as plt
import scipy.signal
import scipy.io
from scipy.signal import butter, find_peaks
from sklearn import linear_model
from sklearn.ensemble import RandomForestRegressor
from sklearn.linear_model import Ridge
from sklearn.svm import SVR
from sklearn.metrics import mean_absolute_error

# DEFINITION OF ENVELOPE FUNCTION
def hl_envelopes_idx(s, dmin=1, dmax=1, split=False):
    # Locals max
    lmax = (np.diff(np.sign(np.diff(s)))<0).nonzero()[0]+1

    if split:
        # s_mid is zero if s centered around x-axis
        or more generally mean of signal
        s_mid = np.mean(s)
        # Pre-sorting of local max based on
        relative position with respect to s_mid
        lmax = lmax[s[lmax]>s_mid]

    # Global min of dmin-chunks of locals min
    lmax = lmax[[i+np.argmax(s[lmax[i:i+dmax]]) for i in
```

```
    range(0,len(lmax),dmax)]]

    s_filt=np.zeros(len(s))
    n=0
    for i in range(len(s)):
        if i==lmax[n]:
            s_filt[i]=s[i]-s[lmax[n]]
            if n<len(lmax)-1:
                n=n+1
        else:
            s_filt[i]=s[i]-s[lmax[n]]

    return s_filt

# PEAKS DETECTION FUNCTION
def peaks_detection(s_filt,ts,time,th):

    pks=find_peaks(s_filt,height=th)
    ind_pks=pks[0]
    ts_pks=np.zeros(len(ts))
    vect_pks=np.zeros(len(ts))
    vect_pks[ind_pks]=s_filt[ind_pks]
    ts_pks[ind_pks]=ts[ind_pks]

    # Local maximus deletion
    int_t=round(0.5/(time[-1]/len(time)))
    for i in range(len(vect_pks)):
        if i>len(vect_pks)-int_t:
            break
        if vect_pks[i]>0:
            for j in range(1,int_t):
                if vect_pks[i+j]>0:
                    vect_pks[i+j]=0
                    ts_pks[i+j]=0

    return vect_pks,ts_pks

# FEATURE REDUCTION FUNCTION
def feat_reduction(feat,t_fitted):

    row=np.zeros(len(t_fitted))
    T=0
    for i in range(len(t_fitted)-1):
        if i>=T:
```

```
            for j in range(i+1,len(t_fitted)):
                # Time window of 10 seconds
                if t_fitted[j]-t_fitted[i]>=10:
                    ind1=np.arange(i,j)

                    # Feature averaging
                    vect_feat=feat[ind1]
                    val_feat=np.mean(vect_feat)
                    row[ind1]=val_feat
                    T=j
                    break

    # If the last window is smaller than 10 s, the last
    values are averaged and fitted in a 10 s time window
    for i in range(len(row)):
        if row[i]==0:
            ind1=np.arange(i,len(row))

            # Feature averaging
            val_feat=np.mean(feat[ind1])
            row[ind1]=val_feat
            break

    return row

# REGRESSION PROCESS FUNCTION
def regression_process(model,matr_train,matr_test,i_train,
i_test,sbp,dbp):

    # SBP
    # Model training
    modelfit_SBP = model.fit(matr_train,sbp[i_train])
    sbp_pred=modelfit_SBP.predict(matr_test)
# Model testing
    mae_sbp=mean_absolute_error(sbp[i_test], sbp_pred)
# SBP MEA (mmHg)
    dev_sbp=np.std(sbp_pred)
# SBP dev std (mmHg)
    err_sbp=abs(sbp_pred-sbp[i_test])
    n=np.array(np.where(err_sbp>5))
    num_sbp=len(np.transpose(n))

    # DBP
    # Model training
```

```
    modelfit_DBP = model.fit(matr_train,dbp[i_train])
    dbp_pred=modelfit_DBP.predict(matr_test)
# Model testing
    mae_dbp=mean_absolute_error(dbp[i_test], dbp_pred)
# DBP MEA (mmHg)
    dev_dbp=np.std(dbp_pred)
# SBP dev std (mmHg)
    err_dbp=abs(dbp_pred-dbp[i_test])
    n=np.array(np.where(err_dbp>5))
    num_dbp=len(np.transpose(n))

    return sbp_pred,dbp_pred,mae_sbp,mae_dbp,dev_sbp,
    dev_dbp,num_sbp,num_dbp

# CALIBRATION TIME WITHOUT TIME INTERVAL DATASET DIVISION
FUNCTION
def calibration_time(t_min,t_table,mae_sbp,mae_dbp,dev_sbp,
dev_dbp,sbp,dbp,model):

    N=0
    while(mae_sbp>5 or mae_dbp>5 or dev_sbp>8 or dev_dbp>8):
        t_min=t_min+60

        for i in range(len(t_table)):
            if t_table[i]-t_table[0]>=t_min: # Time (s)
                ind_train=np.arange(0,i)
                ind_test=np.arange(i,len(t_table))
                break

        trainData_PTT=ptt[ind_train]
        testData_PTT = ptt[ind_test]
        trainData_HR=hr[ind_train]
        testData_HR = hr[ind_test]
        X_train=np.transpose(np.array([trainData_PTT,
        trainData_HR]))
        X_test=np.transpose(np.array([testData_PTT,
        testData_HR]))

        # Regression process
        SBP_pred,DBP_pred,mae_sbp,mae_dbp,dev_sbp,dev_dbp,
        num_SBP,
        num_DBP=regression_process(model,X_train,X_test,
        ind_train,ind_test,sbp,dbp)
```

```
        N=N+1
        if N>11
            t_min=0
            break

    return t_min

# CALIBRATION TIME WITHIN TIME INTERVAL DATASET DIVISION
FUNCTION
def calibration_time_window(t_min,t_table,mae_sbp,mae_dbp,
dev_sbp,dev_dbp,sbp,dbp,model,ptt,hr,index):

    N=0
    while(mae_sbp>5 or mae_dbp>5 or dev_sbp>8 or dev_dbp>8):
        t_min=t_min+60

        for i in range(len(t_table)):
            if t_table[i]-t_table[0]>=t_min:
# Time (s)
                ind_train=np.arange(0,i)
                ind_test=np.arange(i,len(t_table))
                break

        trainData_PTT=ptt[ind_train]
        testData_PTT = ptt[ind_test]
        trainData_HR=hr[ind_train]
        testData_HR = hr[ind_test]
        X_train=np.array([trainData_PTT,trainData_HR])
        X_test=np.array([testData_PTT,testData_HR])

        # Windows concatenation in a single training matrix
        PTT_temp=trainData_PTT
        HR_temp=trainData_HR
        PTT_regr=np.zeros((len(ind_train),
        np.dtype('int64').type(index)))
        HR_regr=np.zeros((len(ind_train),
        np.dtype('int64').type(index)))
        ind_temp=np.arange(index)

        for i in range(len(trainData_PTT)):
            PTT_regr[i,:]=PTT_temp[ind_temp]
            PTT_temp=np.roll(PTT_temp,1)
            HR_regr[i,:]=HR_temp[ind_temp]
            HR_temp=np.roll(HR_temp,1)
```

```
            X_train=np.concatenate((PTT_regr,HR_regr), axis=1)

            # Windows concatenation in a single test matrix
            PTT_temp=testData_PTT
            HR_temp=testData_HR
            PTT_regr=np.zeros((len(ind_test),
            np.dtype('int64').type(ind)))
            HR_regr=np.zeros((len(ind_test),
            np.dtype('int64').type(ind)))
            ind_temp=np.arange(ind)

            for i in range(len(testData_PTT)):
                PTT_regr[i,:]=PTT_temp[ind_temp]
                PTT_temp=np.roll(PTT_temp,1)
                HR_regr[i,:]=HR_temp[ind_temp]
                HR_temp=np.roll(HR_temp,1)

            X_test=np.concatenate((PTT_regr,HR_regr), axis=1)

            # Regression process
            SBP_pred,DBP_pred,mae_sbp,mae_dbp,dev_sbp,dev_dbp,
            num_SBP,num_DBP=regression_process(model,X_train,
            X_test,ind_train,ind_test,sbp,dbp)

            N=N+1
            if N>11
                t_min=0
                break

        return t_min

# START
#============
# FILES LOADING
#============
ecg_mat=scipy.io.loadmat('Test1_Session1_Shimmer_6C0E_
Calibrated_SD.mat')
ecg=ecg_mat['Shimmer_6C0E_ECG_LA_RA_24BIT_CAL']
tsecg=ecg_mat['Shimmer_6C0E_TimestampSync_Unix_CAL']
ppg_mat=scipy.io.loadmat('Test1_Session1_Shimmer_9404_
Calibrated_SD.mat')
ppg=ppg_mat['Shimmer_9404_PPG_A13_CAL']
tsppg=ppg_mat['Shimmer_9404_TimestampSync_Unix_CAL']
```

```
# Creation of numpy arrays
ecg_head=np.zeros(len(ecg))
ts_ecg=np.zeros(len(ecg))
ppg_head=np.zeros(len(ppg))
ts_ppg=np.zeros(len(ppg))
for i in range(len(ecg)):
    ecg_head[i]=ecg[i]
    ts_ecg[i]=tsecg[i]/1000

for i in range(len(ppg)):
    ppg_head[i]=ppg[i]
    ts_ppg[i]=tsppg[i]/1000

fs=504.12  # Sampling frequency (Hz)
rec_time_mins_ppg = ((len(ppg_head)-1)/fs)/60
t_ppg = np.arange(0,len(ppg_head))/fs
rec_time_mins_ecg = ((len(ecg_head)-1)/fs)/60
t_ecg = np.arange(0,len(ecg_head))/fs

#================
# SIGNAL PREPARING
#================
# Cut of the first noisy samples (first 20 seconds)
cut_int=round(20/(t_ppg[-1]/len(t_ppg)))
ind=np.arange(0,cut_int)
ppg_head=np.delete(ppg_head,ind)
ts_ppg=np.delete(ts_ppg,ind)
t_ppg=np.delete(t_ppg,ind)
cut_int=round(20/(t_ecg[-1]/len(t_ecg)))
ind=np.arange(0,cut_int)
ecg_head=np.delete(ecg_head,ind)
ts_ecg=np.delete(ts_ecg,ind)
t_ecg=np.delete(t_ecg,ind)

# Signal synchronization
if ts_ecg[0]<ts_ppg[0]:
    for i in range(len(ts_ecg)):
        if ts_ecg[i]>ts_ppg[0]:
            ind=np.arange(0,i-1)
            ecg_head=np.delete(ecg_head,ind)
            ts_ecg=np.delete(ts_ecg,ind)
            t_ecg=np.delete(t_ecg,ind)
            break
```

```
else:
    for i in range(len(ts_ppg)):
        if ts_ppg[i]>ts_ecg[0]:
            ind=np.arange(0,i-1)
            ppg_head=np.delete(ppg_head,ind)
            ts_ppg=np.delete(ts_ppg,ind)
            t_ppg=np.delete(t_ppg,ind)
            break

# Signals cut at the same length
if len(ts_ecg)>len(ts_ppg):
    t=t_ppg
    ind=np.arange(0,len(ts_ppg))
    ecg_head=ecg_head[ind]
    ts_ecg=ts_ecg[ind]
else:
    t=t_ecg
    ind=np.arange(0,len(ts_ecg))
    ppg_head=ppg_head[ind]
    ts_ppg=ts_ppg[ind]

# Signals alignment
int_t=ts_ppg[0]-ts_ecg[0]
for i in range(len(ts_ecg)):
    if abs(ts_ppg[i]-ts_ecg[i])>int_t:
        ts_ppg[i]=ts_ecg[i]-int_t

#===============
# SIGNAL FILTERING
#===============
# ECG
ecg_filt = hl_envelopes_idx(ecg_head)   # Baseline removal

# PPG
fNy = fs/2    # Nyquist frequency (Hz)
ft = 50        # Cut off frequency (Hz) (experimental)
ws=0.1         # Passaband ripple (dB) (experimental)
wp=15          # Stopband attenuation (dB) (experimental)
fa=30          # Attenuation frequenzy (Hz) (experimental)
n,wn=scipy.signal.buttord(ft/fNy,fa/fNy,ws,wp)
# 7-orer low-pass Butterworth filter
b,a=scipy.signal.butter(n+1,wn)
ppg_filt1=scipy.signal.filtfilt(b,a,ppg_head)
# Baseline removal
```

```
ppg_filt = hl_envelopes_idx(ppg_filt1)

#================
# PEAKS DETECTION
#================
# ECG
th_ecg=1.25      # Change the threshold eventually
vect_R, ts_R=peaks_detection(ecg_filt, ts_ecg, t, th_ecg)

plt.plot(t,ecg_filt)
plt.plot(t,vect_R,'o')

# PPG
th_ppg=25        # Change the threshold eventually
vect_P, ts_P=peaks_detection(ppg_filt, ts_ppg, t, th_ppg)

plt.plot(t,ppg_filt)
plt.plot(t,vect_P,'o')

#==================
# FEATURE EXTRACTION
#==================
n=0
T=0
found=0
ptt=np.zeros(len(ecg_filt))          # PTT array
hr=np.zeros(len(ecg_filt))           # HR array
timetable=np.zeros(len(ecg_filt))    # Timestamp array
for i in range(len(vect_R)):
    if i>=T:
        if vect_R[i]>0:
            found=0
            for j in range(i+1,len(vect_R)):
                if found==1:
                    break
                if vect_R[j]>0:
                    break
                else:
                    if vect_P[j]>0:
                        ptt[n]=ts_P[j]-ts_R[i]
                        for k in range(i+1,len(vect_R)):
                            if vect_R[k]>0:
                                hr[n]=60/(ts_R[k]-ts_R[i])
                                timetable[n]=ts_R[i]
```

```
                                        n=n+1
                                        T=k
                                        found=1
                                        break

# Zero elements deletion and arrays cut at the same length
ind=np.array(np.where(ptt==0))
ptt=np.delete(ptt,ind)
ind=np.array(np.where(hr==0))
hr=np.delete(hr,ind)
ind=np.array(np.where(timetable==0))
timetable=np.delete(timetable,ind)

if len(ptt)>len(hr):
    ind=np.arange(0,len(hr))
    ptt=ptt[ind]
    timetable=timetable[ind]
else:
    ind=np.arange(0,len(ptt))
    hr=hr[ind]
    timetable=timetable[ind]

# Arrays cleaning
mean_PTT=np.mean(ptt)
dev_PTT=np.std(ptt)
mean_HR=np.mean(hr)
dev_HR=np.std(hr)

for i in range(len(timetable)):
    if ptt[i]>mean_PTT+dev_PTT or ptt[i]<mean_PTT-dev_PTT or
    hr[i]>mean_HR+dev_HR or hr[i]<mean_HR-dev_HR:
        ptt[i]=0
        hr[i]=0
        timetable[i]=0

ind=np.array(np.where(ptt==0))
ptt=np.delete(ptt,ind)
ind=np.array(np.where(hr==0))
hr=np.delete(hr,ind)
ind=np.array(np.where(timetable==0))
timetable=np.delete(timetable,ind)

#=============================
# OMRON HeartGuide DATA LOADING
```

```
#=============================
with open("Test1.csv") as filecsv:
    reader=csv.reader(filecsv,delimiter=";")
    ts_omron=np.array(list(map(float,[(line[0]) for line
    in reader])))
with open("Test1.csv") as filecsv:
    reader=csv.reader(filecsv,delimiter=";")
    sbp=np.array(list(map(float,[(line[1]) for line in
    reader])))
with open("Test1.csv") as filecsv:
    reader=csv.reader(filecsv,delimiter=";")
    dbp=np.array(list(map(float,[(line[2]) for line in
    reader])))

# Omron's time values correspond to the time in which
the device returns the pressure values
ts_omron=ts_omron-60*np.ones(len(ts_omron))

# Creation of the interpolating time array
n=np.array(np.where(ts_ecg==timetable[0]))
m=np.array(np.where(ts_ecg==timetable[-1]))
ind=np.arange(n,m)
t_fit=ts_ecg[ind]

# Interpolation of the Omron's data
SBP_fit=np.interp(t_fit,ts_omron,sbp)
DBP_fit=np.interp(t_fit,ts_omron,dbp)

# Interpolation of PTT and HR values
HR_fit=np.interp(t_fit,timetable,hr)
PTT_fit=np.interp(t_fit,timetable,ptt)

#================
# FEATURE REDUCTION
#================
row1=feat_reduction(PTT_fit,t_fit)      # PTT
row2=feat_reduction(HR_fit,t_fit)       # HR
row3=feat_reduction(SBP_fit,t_fit)      # SBP
row4=feat_reduction(DBP_fit,t_fit)      # DBP

# Arrays resampling
row1=np.interp(timetable,t_fit,row1)
row2=np.interp(timetable,t_fit,row2)
row3=np.transpose(np.interp(timetable,t_fit,row3))
```

```
row4=np.transpose(np.interp(timetable,t_fit,row4))

#====================
# REGRESSION METHODS
#====================
# Preparing data
# Training set contains the 70% of the whole dataset, the
test set the remaining 30%
sz_train=round(0.7*len(row1))
ind_train=np.arange(0,sz_train)
ind_test=np.arange(sz_train,len(row1))
trainData_PTT=row1[ind_train]
testData_PTT = row1[ind_test]
trainData_HR=row2[ind_train]
testData_HR = row2[ind_test]
X_train=np.transpose(np.array([trainData_PTT,trainData_HR]))
X_test=np.transpose(np.array([testData_PTT,testData_HR]))
perc=round(0.2*len(ind_test))

# MULTIVARIATE LINEAR REGRESSION
regr = linear_model.LinearRegression() # Parameters definition
MLR_SBP_pred,MLR_DBP_pred,MLR_mae_SBP,MLR_mae_DBP,MLR_dev_SBP,
MLR_dev_DBP,num_SBP,num_DBP=regression_process(regr,X_train,
X_test,ind_train,ind_test,row3,row4)

# Do the following plots for the other regression methods too
# SBP plot
plt.plot(np.arange(0,len(ind_test)),MLR_SBP_pred,'r',
label="Predicted SBP")
plt.plot(np.arange(0,len(ind_test)),row3[ind_test],'b',
label="Real SBP")
plt.xlabel('Samples')
plt.ylabel('Amplitude (mmHg)')
plt.legend()

# DBP plot
plt.plot(np.arange(0,len(ind_test)),MLR_DBP_pred,'r',
label="Predicted DBP")
plt.plot(np.arange(0,len(ind_test)),row4[ind_test],'b',
label="Real DBP")
plt.xlabel('Samples')
plt.ylabel('Amplitude (mmHg)')
plt.legend()
```

```
# RANDOM FOREST REGRESSION
regr = RandomForestRegressor(n_estimators=100,random_state=7,
criterion='mae') # Parameters definition
RFR_SBP_pred,RFR_DBP_pred,RFR_mae_SBP,RFR_mae_DBP,RFR_dev_SBP,
RFR_dev_DBP,num_SBP,num_DBP=regression_process(regr,X_train,
X_test,ind_train,ind_test,row3,row4)

# RIDGE REGRESSION
regr = Ridge(alpha=.01)
RR_SBP_pred,RR_DBP_pred,RR_mae_SBP,RR_mae_DBP,RR_dev_SBP,
RR_dev_DBP,num_SBP,num_DBP=regression_process(regr,X_train,
X_test,ind_train,ind_test,row3,row4)

# SUPPORT VECTOR REGRESSION
regr = SVR(C=50, epsilon=0.2)
SVR_SBP_pred,SVR_DBP_pred,SVR_mae_SBP,SVR_mae_DBP,SVR_dev_SBP,
SVR_dev_DBP,num_SBP,num_DBP=regression_process(regr,X_train,
X_test,ind_train,ind_test,row3,row4)

#=====================================
# REGRESSION METHODS WITHIN A 10s WINDOW
#=====================================
# Preparing data
# Definition of a 10 seconds window
for i in range (1,len(row1)):
    if abs(timetable[i]-timetable[0])>=10:
        ind=i  # Samples
        break

# Windows concatenation in a single training matrix
PTT_temp=trainData_PTT
HR_temp=trainData_HR
PTT_regr=np.zeros((len(ind_train),np.dtype('int64').type(ind)))
HR_regr=np.zeros((len(ind_train),np.dtype('int64').type(ind)))
ind_temp=np.arange(ind)
for i in range(len(trainData_PTT)):
    PTT_regr[i,:]=PTT_temp[ind_temp]
    PTT_temp=np.roll(PTT_temp,1)
    HR_regr[i,:]=HR_temp[ind_temp]
    HR_temp=np.roll(HR_temp,1)

X_train=np.concatenate((PTT_regr,HR_regr), axis=1)

# Windows concatenation in a single test matrix
```

```
PTT_temp=testData_PTT
HR_temp=testData_HR
PTT_regr=np.zeros((len(ind_test),np.dtype('int64').type(ind)))
HR_regr=np.zeros((len(ind_test),np.dtype('int64').type(ind)))
ind_temp=np.arange(ind)
for i in range(len(testData_PTT)):
    PTT_regr[i,:]=PTT_temp[ind_temp]
    PTT_temp=np.roll(PTT_temp,1)
    HR_regr[i,:]=HR_temp[ind_temp]
    HR_temp=np.roll(HR_temp,1)

X_test=np.concatenate((PTT_regr,HR_regr), axis=1)

# MULTIVARIATE LINEAR REGRESSION
regr = linear_model.LinearRegression() # Parameters definition
MLR_SBP_pred,MLR_DBP_pred,MLR_mae_SBP,MLR_mae_DBP,MLR_dev_SBP,
MLR_dev_DBP,num_SBP,num_DBP=regression_process(regr,X_train,
X_test,ind_train,ind_test,row3,row4)

# RANDOM FOREST REGRESSION
regr = RandomForestRegressor(n_estimators=100,random_state=7,
criterion='mae') # Parameters definition
RFR_SBP_pred,RFR_DBP_pred,RFR_mae_SBP,RFR_mae_DBP,RFR_dev_SBP,
RFR_dev_DBP,num_SBP,num_DBP=regression_process(regr,X_train,
X_test,ind_train,ind_test,row3,row4)

# RIDGE REGRESSION
regr = Ridge(alpha=.01)
RR_SBP_pred,RR_DBP_pred,RR_mae_SBP,RR_mae_DBP,RR_dev_SBP,
RR_dev_DBP,num_SBP,num_DBP=regression_process(regr,X_train,
X_test,ind_train,ind_test,row3,row4)

# SUPPORT VECTOR REGRESSION
regr = SVR(C=50, epsilon=0.2)
SVR_SBP_pred,SVR_DBP_pred,SVR_mae_SBP,SVR_mae_DBP,SVR_dev_SBP,
SVR_dev_DBP,num_SBP,num_DBP=regression_process(regr,X_train,
X_test,ind_train,ind_test,row3,row4)

#=========================
# MINIMUM CALIBRATION TIME
#=========================
# Without time interval dataset division
min_calib_t=300
```

```
for i in range(len(timetable)):
    if timetable[i]-timetable[0]>=min_calib_t:
# Time (s)
        ind_train=np.arange(0,i)
        ind_test=np.arange(i,len(timetable))
        break

trainData_PTT=ptt[ind_train]
testData_PTT = ptt[ind_test]
trainData_HR=hr[ind_train]
testData_HR = hr[ind_test]
X_train=np.transpose(np.array([trainData_PTT,trainData_HR]))
X_test=np.transpose(np.array([testData_PTT,testData_HR]))

regr=linear_model.LinearRegression() # Change eventually
SBP_pred,DBP_pred,mae_SBP,mae_DBP,dev_SBP,dev_DBP,num_SBP,
num_DBP=regression_process(regr,X_train,X_test,ind_train,
ind_test,row3,row4)
calib_time=calibration_time(min_calib_t,timetable,mae_SBP,
mae_DBP,dev_SBP,dev_DBP,row3,row4,regr)

# Within time interval dataset division
min_calib_wind_t=300

for i in range(len(timetable)):
    if timetable[i]-timetable[0]>=min_calib_wind_t:
# Time (s)
        ind_train=np.arange(0,i)
        ind_test=np.arange(i,len(timetable))
        break

trainData_PTT=row1[ind_train]
testData_PTT = row1[ind_test]
trainData_HR=row2[ind_train]
testData_HR = row2[ind_test]
X_train=np.array([trainData_PTT,trainData_HR])
X_test=np.array([testData_PTT,testData_HR])
perc=round(0.2*len(ind_test))

# Windows concatenation in a single training matrix
PTT_temp=trainData_PTT
HR_temp=trainData_HR
PTT_regr=np.zeros((len(ind_train),np.dtype('int64').type(ind)))
HR_regr=np.zeros((len(ind_train),np.dtype('int64').type(ind)))
```

```
ind_temp=np.arange(ind)
for i in range(len(trainData_PTT)):
    PTT_regr[i,:]=PTT_temp[ind_temp]
    PTT_temp=np.roll(PTT_temp,1)
    HR_regr[i,:]=HR_temp[ind_temp]
    HR_temp=np.roll(HR_temp,1)

X_train=np.concatenate((PTT_regr,HR_regr), axis=1)

# Windows concatenation in a single test matrix
PTT_temp=testData_PTT
HR_temp=testData_HR
PTT_regr=np.zeros((len(ind_test),np.dtype('int64').type(ind)))
HR_regr=np.zeros((len(ind_test),np.dtype('int64').type(ind)))
ind_temp=np.arange(ind)
for i in range(len(testData_PTT)):
    PTT_regr[i,:]=PTT_temp[ind_temp]
    PTT_temp=np.roll(PTT_temp,1)
    HR_regr[i,:]=HR_temp[ind_temp]
    HR_temp=np.roll(HR_temp,1)

X_test=np.concatenate((PTT_regr,HR_regr), axis=1)

regr=linear_model.LinearRegression() # Change eventually
SBP_pred,DBP_pred,mae_SBP,mae_DBP,dev_SBP,dev_DBP,num_SBP,
num_DBP=regression_process(regr,X_train,X_test,ind_train,
ind_test,row3,row4)
calib_time_wind=calibration_time_window(min_calib_wind_t,
timetable,mae_SBP,mae_DBP,dev_SBP,dev_DBP,row3,row4,regr,row1,
row2,ind)
```

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