CHARACTERIZATION OF INFLATIONARY AND DEFLATIONARY AUSCULTATORY BLOOD PRESSURE MEASUREMENTS

A Dissertation
Submitted to the Graduate Faculty
of the
North Dakota State University
of Agriculture and Applied Science

By

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In Partial Fulfillment of the Requirements
for the Degree of
DOCTOR OF PHILOSOPHY

Major Department:
Electrical and Computer Engineering

July 2022

Fargo, North Dakota

North Dakota State University
Graduate School

Title

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

Doctor of Philosophy

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ABSTRACT

This document is a paper-based dissertation. The dissertation is a collection of articles written by the author in the pursuit to develop a novel method to measure blood pressure (BP). The introduction chapter describes how the documents are interrelated. This work starts with the description of the development and design of a non-invasive medical device capable of measuring arterial BP with a combination of inflationary and deflationary procedures. In addition to the device, we conducted a human-based study to characterize the properties of the BP signal in the inflationary and deflationary curves. With the signals acquired, we focused on the uncertainty occurring when taking two consecutive BP measurements.

The prototype was composed of 1) a modified off-the-shelf oscillometric BP system, 2) a contact microphone with an amplifier, and 3) a high-sensitivity pulse oximeter, and its control electronics. The device captured the cuff pressure signal, arterial skin-surface acoustics, and photoplethysmography (PPG).

The captured signals were processed and analyzed. We focused our analysis on the characterization of the uncertainty of two consecutive BP measurements by studying the bio-signals captured with the custom-made apparatus.

Accurate non-invasive BP measurements are vital in preventing and treating many cardiovascular diseases. The "gold standard" for non-invasive procedures is the auscultatory method, which is based on detecting Korotkoff sounds while deflating an arm cuff. Using this method as a "gold standard" requires highly-trained technicians and has an intrinsic uncertainty in its BP predictions. In this document, we analyze and characterize the origins of BP uncertainty.

By analyzing the captured bio signals we postulate an uncertainty model for two consecutive BP measurements. Our research group developed a computer-based simulation of auscultatory BP measurement uncertainty, and these modeled results were compared to a human-subject experiment with a group of 20 diverse-conditioned individuals.

Uncertainties were categorized and quantified. The total computer-simulated uncertainty ranged between -8.4 mmHg to 8.4 mmHg in systolic BP and -8.4 mmHg to 8.3 mmHg in diastolic BP at a 95% confidence interval. The limits in the human-based study ranged from -8.3 mmHg to 8.3 mmHg in systolic BP and -16.7 mmHg to 4.2 mmHg in diastolic BP.

ACKNOWLEDGMENTS

First of all, I want to thank my family for all the support I have had during my life.

I also want to thank Dr. Ewert for being my mentor, my graduate advisor, and for helping me in my academic path. Also, many thanks to the Krisara team, Dave, and Dr. Sand I really enjoyed the weekly meetings and all the support given during this time.

Thanks Dr. Braaten and to all the NDSU Electrical and Computer Engineering faculty and staff.

Thanks, Jamie, for putting up with me.

DEDICATION

I dedicate this dissertation to all my family.

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LIST OF ABBREVIATIONS

BP.....Blood pressure.

DBP.....Diastolic blood pressure.

SBP .....Systolic blood pressure.

MAP.....Mean arterial pressure.

mmHg .....Millimeters of mercury.

OMW .....Oscillometric waveform.

OMWE.....Oscillometric waveform envelope.

PPG .....Photoplethysmography.

PVDF .....Polyvinylidene fluoride.

HR.....Heart rate.

CI.....Confidence interval.

PP .....Pulse pressure.

AHA.....American Heart Association.

CDC .....Centers for Disease Control and Prevention.

LIST OF SYMBOLS

V_p .....Peak amplitude from voltage signal.

V_{pp} .....Peak to peak amplitude from voltage signal.

e_{me} .....Method error. Error introduced by the Korotkoff method.

e_{th} .....Threshold error. Error occurred when selecting the incorrect threshold for the start and end of the Korotkoff sounds.

e_{mt}.....Moving target error. Error introduced by the physiological changes of the human being.

E_{total} .....Total error.

U_{total} .....Total uncertainty of the BP samples measured.

1. INTRODUCTION TO BLOOD PRESSURE

Arterial BP is a continuous analog signal that measures the force applied against the surface of arterial walls when blood is being pumped by the heart. The heart beats at a periodic rhythm. The two values on which most medical professionals focus are the systolic and diastolic BP values. The systolic BP is defined as the maximum pressure when the heart contracts and ejects blood into the aorta from the left ventricle [1].

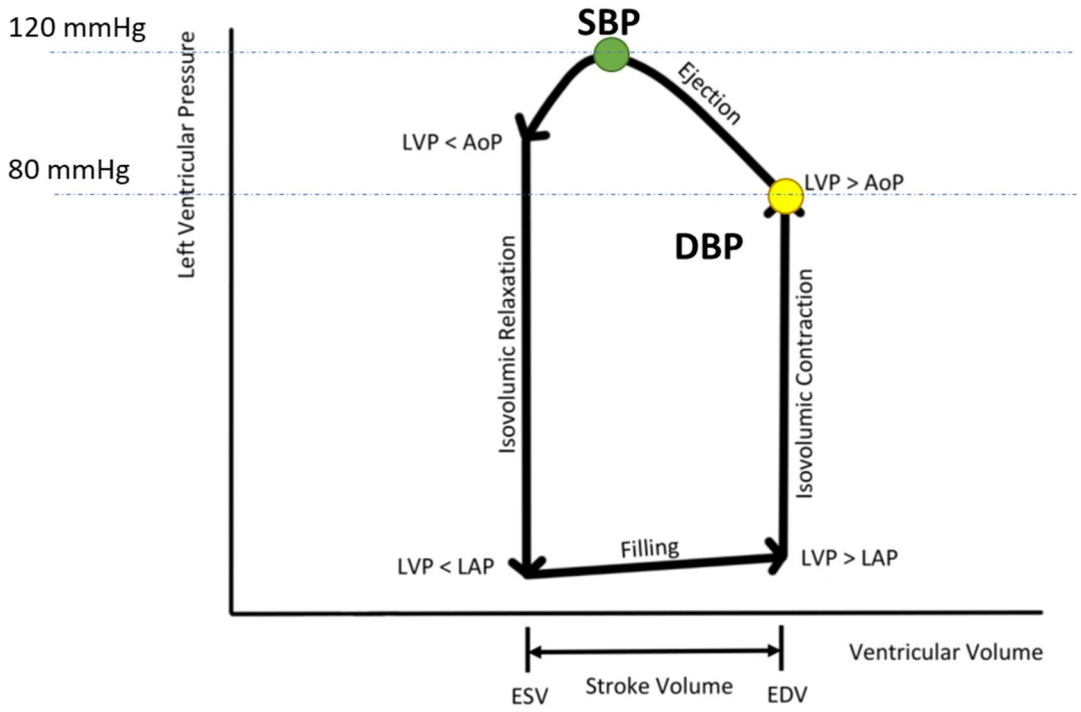


Figure 1. PV cycle showing SBP in green and DBP in yellow. Image adapted from *Cardiovascular Engineering ebook*, by Daniel Ewert, 2019.

The diastolic BP value is defined as the minimum pressure in the arterial walls in between beats. Pulse pressure (PP) is defined as the difference between SBP and DBP. For historical reasons, as most accurate pressure gauges were based on mercury [2] , BP is measured in millimeters of mercury (mmHg). A healthy value for SBP is 120 mmHg and for DBP is 80 mmHg. Thus, the associated pulse pressure in this case would be 40 mmHg. Hypertension is the

condition of having high BP, which is currently defined as having a SBP greater than 130 mmHg or DBP greater than 80 mmHg [3]. The Centers for Disease Control and Prevention (CDC) defines two levels of hypertension: stage 1 and stage 2. Stage 1 encompasses SBP values between 130 and 139 mmHg and DBP values of 80-89 mmHg. Stage 2 denotes all SBP values greater than 140 mmHg and DBP greater than 90 mmHg. It is also worthwhile to mention that the CDC defines an intermediate category called 'elevated BP' which captures the values of SBP between 120 and 129 mmHg and DBP less than 80 mmHg.

The American Heart Association (AHA) includes a level of hypertension named 'hypertensive crisis' which is defined as having an SBP greater than 180 mmHg and/or a DBP higher than 120 mmHg. These values are critical and should be dealt with a health professional immediately.

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)	and/or	DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

Figure 2. BP levels defined by the American Heart Association [4].

Hypertension is also known as the 'silent killer' since it may not have obvious symptoms, and many people don't even know they have it. This condition develops over time and doesn't have a cure [4]. Contrary to hypertension, an individual can have hypotension, which is having

too low of a BP. AHA doesn't define any limits for hypotension, and it says that as long as there are no troubling symptoms, the lower the BP reading is, the better [5].

Unhealthy levels of BP are considered a risk factor for a multitude of diseases, including ischemic heart disease and stroke [6]. Hypertension is a critical health concern in the United States. Approximately 116 million people in the country have hypertension. That is nearly 1 out of 2 adults in the United States that have hypertension [7], [8]. Consequently, accurate and readily available BP measurements are crucial to help in the understanding of cardiovascular health.

In our research to discover a more accurate BP measurement, we researched different hardware approaches. We looked for a more accurate, cost-effective, comfortable, and precise procedure to get BP readings. We selected a readily-available BP measuring device (Omron BP710), and we modified both its hardware and software. These modifications allowed us to acquire and transmit real-time bio-signals while taking a custom-made procedure with the goal of obtaining a better BP measurement. For reference reasons we will call this the 'tool'.

Once the 'tool' was designed and implemented, we planned and developed a study to test the 'tool'. We first tested that the device functioned by performing some preliminary testing as well as calibrating the sensors. Once the device was validated, we drafted a human-based experiment to test the non-invasive machine with real people. We secured IRB approval, and we conducted a study with 20 participants while the COVID-19 pandemic was at its highest. Our experiment consisted of two measurements (also known as 'runs') separated five minutes apart. In each of these measurements, we recorded several bio-signals (acoustics, cuff pressure, and PPG) while pumping and releasing air to an arm cuff. Figure 2 shows a typical run where we

inflated and deflated the arm cuff at similar pumping rates. The maximum peak pressure was intended to pass brachial artery occlusion (>160 mmHg in most cases).

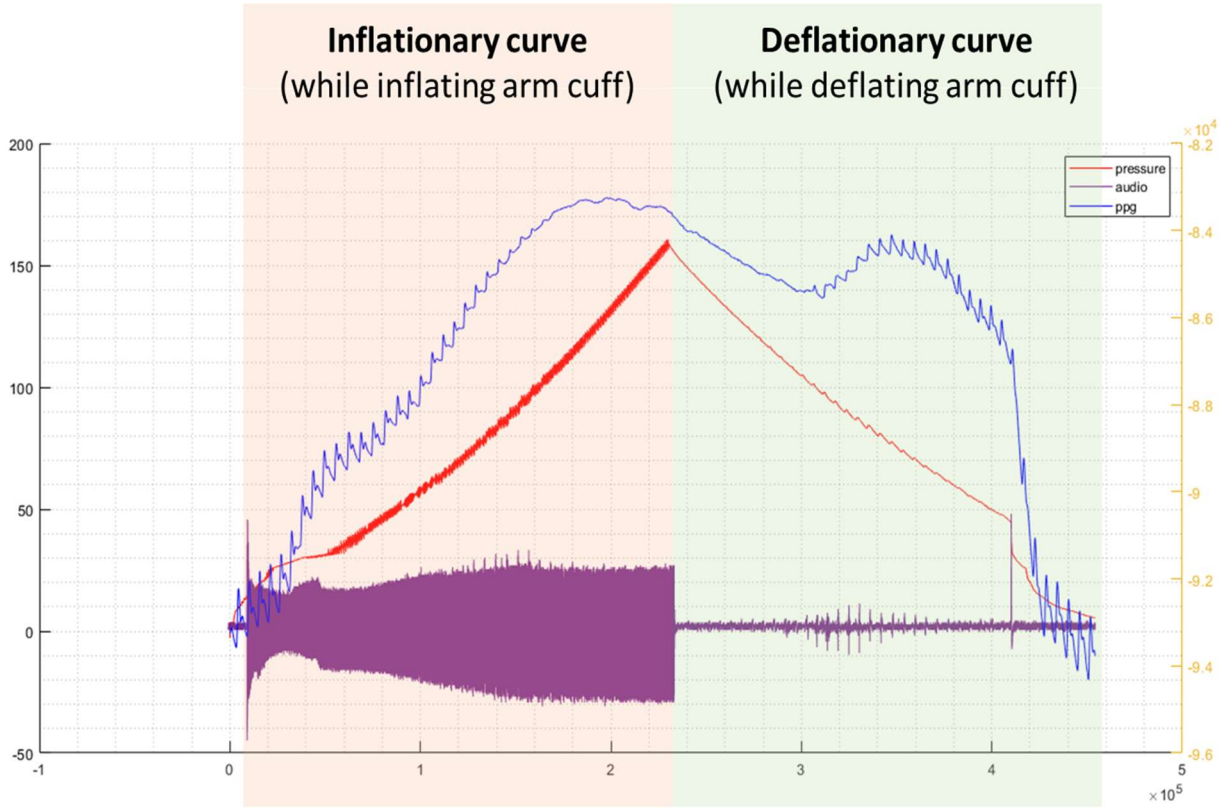


Figure 3. Experimental run while inflating and deflating the arm cuff. Korotkoff sounds are shown in purple, PPG in blue, and pressure in red. The three signals were plotted in real time and then stored for further analysis.

Once the experiment concluded, we analyzed all the data and carved a section of the analysis and data to include in this dissertation. We studied the range of uncertainty that could occur in a two-sample experiment when measuring BP using Korotkoff sounds, also known as the gold standard. Our hypothesis was that under the same measuring circumstances (using the same method), we would obtain the same numbers of SBP and DBP in both runs. However, we observed that the SBP and DBP values from run #1 and run #2 were similar but not exactly the same. Even solely focusing on Korotkoff sounds captured by our device, the values would vary within a range. To better understand this difference in values we studied the possible sources of

uncertainty that could be contributing to the measurement. After reflection and understanding of the origins of uncertainty, we developed a software model based on a Monte Carlo simulation, and we compared the model with our human-based SBP/DBP pairs from run #1 and run #2.

The first paper in this paper-based dissertation aims to characterize the customized BP measuring device. The second paper describes the software model and human-based data analysis and comparison in the proposed BP uncertainty model.

2. PAPER 1 – SENSOR FUSED BLOOD PRESSURE MEASURING DEVICE CAPABLE OF RECORDING KOROTKOFF SOUNDS IN INFLATIONARY CURVES

2.1. Abstract

This study describes a non-invasive medical device capable of measuring arterial blood pressure (BP) with a combination of inflationary and deflationary procedures. The device uses the pressure cuff pressure signal, arterial skin-surface acoustics, and photoplethysmography (PPG) to make a sensor-fusion estimation of blood pressure readings. We developed an apparatus composed of 1) a modified off-the-shelf oscillometric blood pressure system, 2) a contact microphone with an amplifier, 3) and high-sensitivity pulse oximeter, and its control electronics.

2.2. Introduction

Accurate blood pressure measurements are crucial to diagnose and understand cardiovascular health. High blood pressure is a risk factor for a multitude of diseases, including ischemic heart disease and stroke [6]. There are a multitude of forms to measure blood pressure, and we can classify these procedures as invasive or non-invasive. Invasive BP meters require the use of a catheter and may present several risks: bleeding, infection, etc. Non-invasive BP meters are less risky but may be compromised in accuracy and precision [9].

The gold standard in non-invasive BP is the auscultatory method, where a highly-trained medical provider uses a stethoscope with a combination of manually-controlled blood pressure cuff and a mercury sphygmomanometer [10]. The medical provider controls the inflation of an arm cuff, he/she pumps the cuff until a certain level (usually over 120 mmHg), and then he/she deflates the cuff slowly and listens to the Korotkoff sounds [11]. On the first Korotkoff sound the provider determines the systolic value. After further deflation, the health provider determines the

diastolic value when he/she cannot hear any more Korotkoff sounds. This method is manual, takes practice and specialized training, and requires well-calibrated instrumentation. Health providers get accuracy through continuous training and adherence to recognized protocols.

Non-invasive accurate and repeatable blood pressure measurements are more challenging. There is a trend towards automation since it provides so many benefits: home care, easy to use, a higher number of reading samples, etc. The most common automated BP protocols are based on a) plethysmography, b) tonometry, c) vascular unloading, d) automated auscultatory, e) doppler ultrasound sphygmomanometry and f) oscillometry [12].

One of the most common and simple methods used in over-the-counter BP meters is oscillometry. This method measures and analyzes small pressure oscillations within the pressurized inflatable cuff. An algorithm correlates the oscillometric pulses to the SBP and DBP readings using the OMWE. The maximum of the OMWE establishes the MAP point, after that, the system calculates the SBP and DBP by applying empirically-calculated coefficients to the left and right ramps to the MAP value in the OMWE. Pulse pressure and arterial compliance play a key role in the oscillometry's accuracy, and some studies suggest that the measurement may benefit by using patient-specific coefficients [13]. Oscillometric methods readings can significantly differ from the ones obtained by the auscultatory method, especially in non-standard populations like the elderly [14].

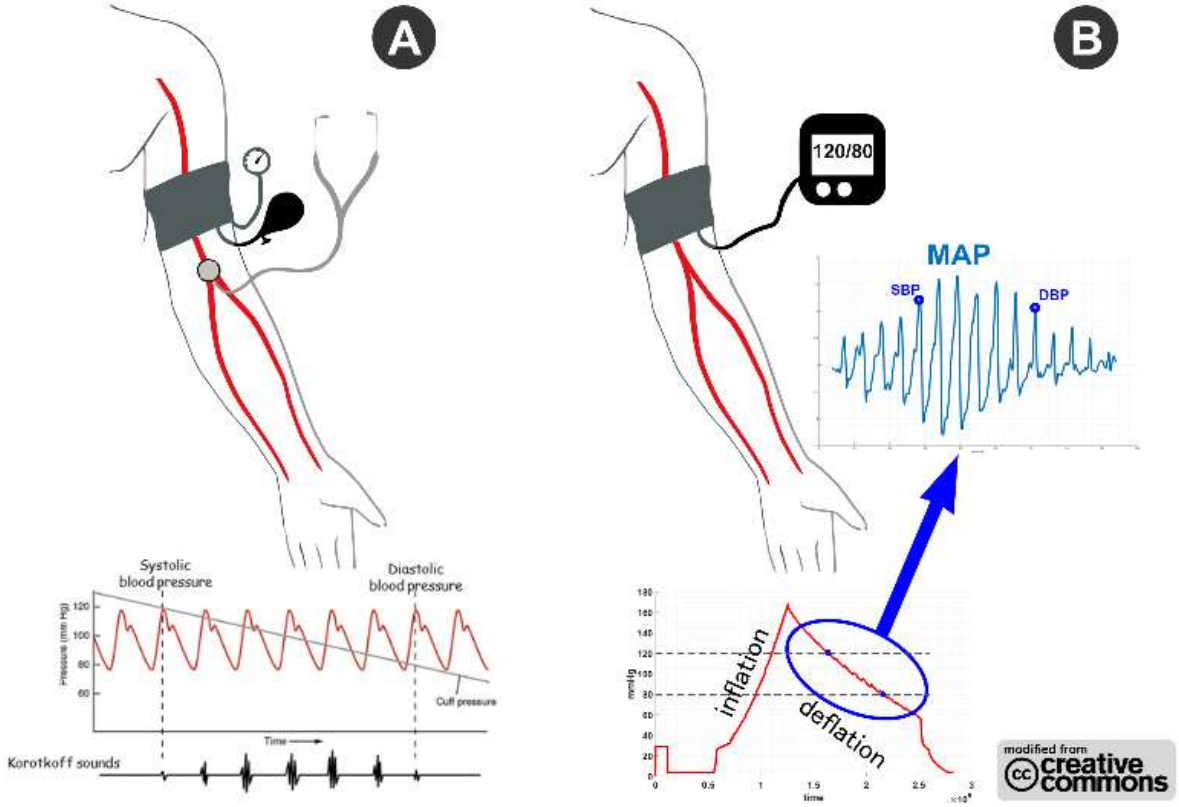


Figure 4. The traditional auscultatory methods illustrated in section A consists of listening to Korotkoff sounds by a trained medical provider while deflating the arm cuff. MOST automatic BP meters used the oscillometric envelope (section B), where a pressure sensor records artery pulsations transmitted to the arm cuff usually while deflating the arm cuff.

The most common procedure for oscillometric techniques is to obtain the OMWE in the deflation curve (deflationary devices). However, devices that measure while inflating are also available (inflationary devices). The benefits of inflationary oscillometric devices are lower cuff pressure to detect SBP and DBP and faster measurements [15], [16]. A problem with inflationary devices is that they have to deal with inflationary pumping noise due to pressurizing the cuff when conducting a reading [17].

The oscillometric estimations may differ from the gold standard (auscultatory) [14]. A similar technique to the standard healthcare-conducted auscultatory method is the machine-driven automatic auscultatory method. This technique uses a microphone near the brachial artery, in contact with the skin, that records vibrations caused by blood flow. This audio is then

processed by a machine that calculates SBP and DBP based on Korotkoff sound detection. This method doesn't need highly-trained healthcare personnel and is highly effective in quiet environments, however it lacks robustness when noise is introduced.

In addition to measuring pressure oscillations near the arm cuff, we wanted to monitor blood flow behavior when the arm was being pressurized/depressurized by the cuff. The PPG signal has been shown to provide information about arterial and venous flow [18] and valuable insights on blood pressure estimation and cardiac output [19]. PPG allows us to log arterial blood flow, venous system behavior, and blood oxygen saturation while the arm cuff inflates and deflates. Some drawbacks of PPG are that it is affected by contact pressure, usually needs calibration, and that it can carry a significant BP error (over 10 mmHg) [20].

Our research team has developed a system that simultaneously combines some of the most popular methods to measure BP readings: auscultatory, oscillometric, and plethysmography. We selected these techniques because of availability, simplicity, cost, and commonality within the non-invasive techniques. Our apparatus allows us to combine the strengths and characteristics of each of the techniques. With this device we can further understand the relationship between Korotkoff sounds, OMWE and PPG.

We intend this device to be a step towards a more accurate, cost-effective, comfortable and precise procedure to get BP readings automatically by studying how to combine the strengths of these readily-available technologies. We aim to develop hardware to study the strengths of three common techniques to improve blood pressure measurements.

2.3. Materials and methods

We have developed a prototypical system based on the combination of three off-the-shelf devices in addition to custom-designed hardware and self-implemented software. We based the

system on the following three main subsystems: 1) Omron BP meter model# BP710, 2) a Maxim MAX30101 Pulse Oximetry and Heart Rate Module and 3) a PVDF piezoelectric thin film vibration sensor CM-01B,

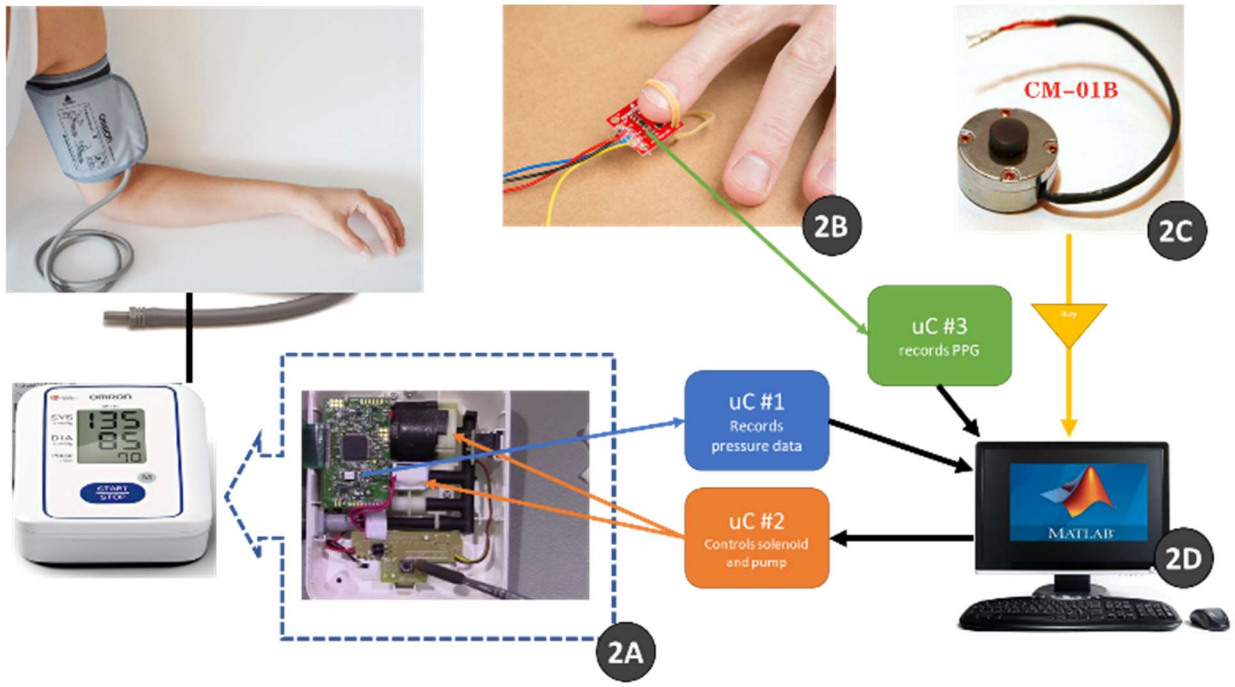


Figure 5. General device diagram. The device has three main input components: a pressure sensor (2A), an oximeter (2B), and a contact microphone (2C). All the inputs are combined and then analyzed using Matlab.

We used one microcontroller to manage the inflation/deflation parameters of the Omron meter. In addition, we had two microcontrollers tasked to sample the pressure sensor signal and the pulse oximeter. The sampling was synchronized with the help of a timestamp signal that was received by all the microcontrollers from a bus.

2.3.1. Pressure meter

The altered BP meter allows us to control the pumping rate, to open/close the solenoid valve (which is a valve that, in the OFF/open position allows the system to exhaust all the air in the cuff chamber, or in the ON/close position makes the chamber airtight), and to read the

Microelectromechanical systems (MEMS) gauge pressure sensor. This device captures the pressure signal transmitted from the arm cuff and then channels it to a 16-bit ADC (ADS1115) with a programmable gain amplifier. The ADS1115 samples the signal at 55 Hz, amplifies it, and then sends it to a microcontroller using the Inter-Integrated Circuit (I2C) protocol. Then, the microcontroller transmits the samples to the PC and into Matlab™ for further analysis.

2.3.2. Contact microphone

Korotkoff sounds are detected by using a contact microphone. Our research group selected the model CM-01B because it is widely used in digital stethoscopes and has been documented in previous research [21]. An LM741 amplifier conditions the microphone signal from the CM-01B and connects to the PC audio line-in input. Afterward, the computer samples the audio signal at 8 kHz and the signal is then transmitted to a Matlab program. The Matlab procedure amplifies the audio digitally and applies a one-dimensional 100^{th} order median filter. This process enhances the local maxima present in the signal originated from wall turbulence in the brachial artery.

2.3.3. Pulse oximeter

To obtain a PPG signal, our team selected a readily available pulse oximeter MAX3010. This chip is a well-used high-sensitivity pulse oximeter and a heart-rate sensor for wearable health. We placed the sensor on the tip of the finger. The sensor emits two wavelengths (red and green) and captures the reflection of the blood flow in the fingertip. The receiving part of the sensor then processes the signal and sends it to the microcontroller. The microcontroller samples the signal at 55Hz, inverts it and sends it to the PC using I2C.

2.4. Software analysis

The research team developed specific communication procedures to get the signals simultaneously. The PC uses a series of callback functions to store the received samples from the two microcontrollers and the audio line-in.

After storing the signals, Matlab is used to plot them. We can create custom BP measuring procedures since we can control the pumping rate and the solenoid valve on the system. Figure 6 shows an example of cuff inflation and deflation at different rates (pressure signal shown in red signal).

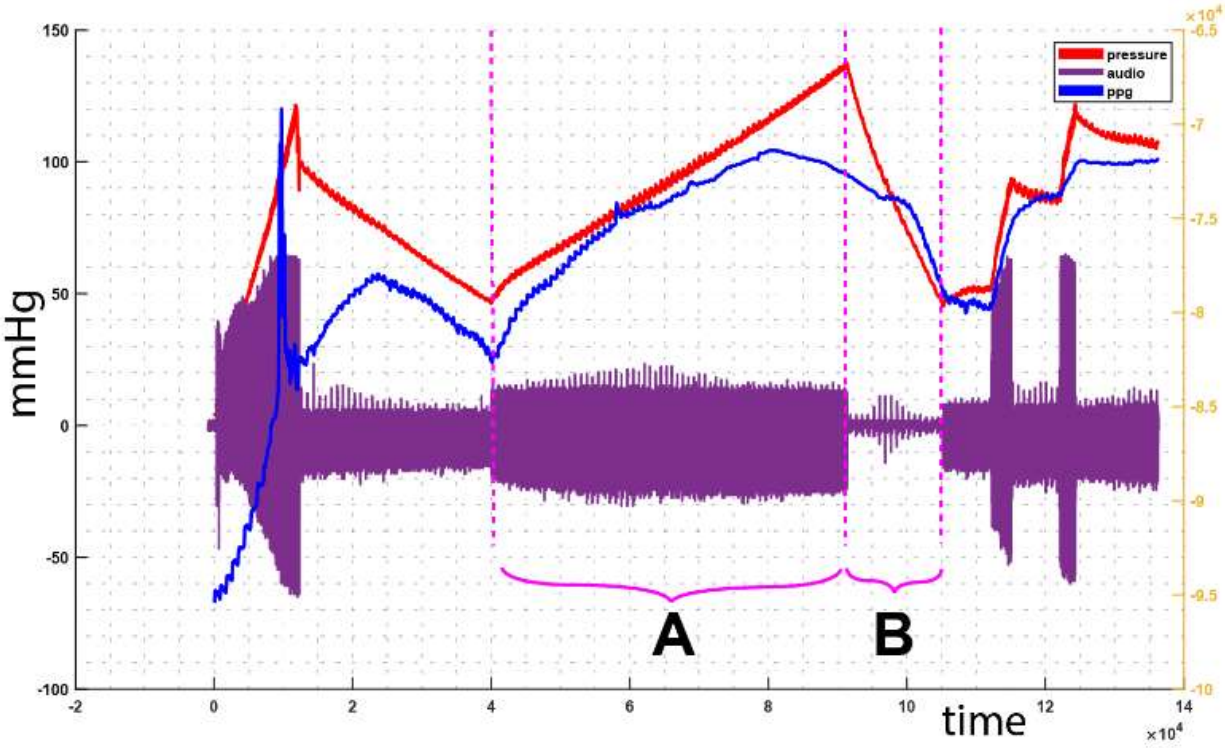


Figure 6. Raw signals plotted in real-time by the Matlab routine. Section 'A' illustrates an inflationary curve and section 'B' a deflationary curve (most commonly used in BP meters).

Two sections: 'A' and 'B' are used as an example to show how the system processes different signals.

Section ‘A’ includes an inflationary curve. The pressure signal (shown in red) increases with time due to a volume increase of air in the arm cuff.

Figure 7 illustrates the audio envelope in ‘A1’. We plotted the Korotkoff sounds by applying a threshold algorithm. In this case, the threshold is fixed and established based on signal variance and energy calculated in the Korotkoff sounds envelope. To extract the Korotkoff sounds the signal is first filtered using a one-dimensional 100^{th} order median filter. After that, a series of the local maxima are detected in the audio signal. Next, the audio envelope is defined while inflating the arm cuff. This does not require any hardware alteration.

Next, we section the pressure signal by removing the best straight-fit line from the curve and then high-pass filtering it. This results in the small pressure oscillations that characterize the oscillometric behavior of the BP signal. Next, a wavelet signal de-noising procedure improves the pulse detection. The result of this process is shown graphically in section ‘A2’ under Figure 7. We can get the OMWE from the pulses and predict an empirical estimation of BP using fixed coefficients.

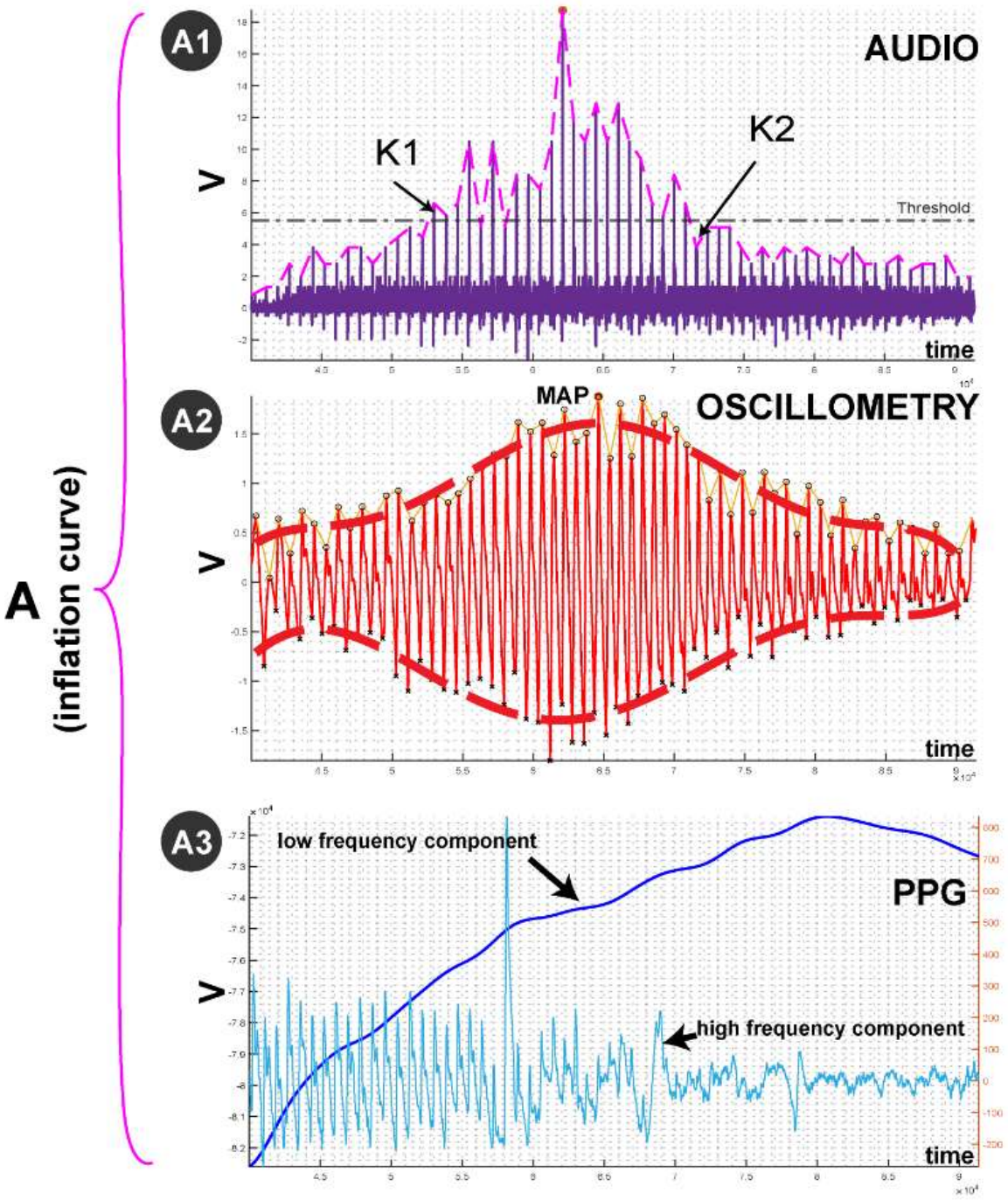


Figure 7. This figure shows the Korotkoff sounds, section A2 displays oscillometry, and section A3 shows PPG signals out of the inflationary curve from section 'A' in Figure 6.

The PPG signal was inverted and divided into a low-frequency component and a high-frequency component. 'Figure 7 A3' shows how the behavior of both components change in time while we inflate the arm cuff.

Similar to the ramp-up, we can apply the same algorithm to the ramp down. We sectioned the ramp down curve in Figure 6 and we named it ‘B’.

Section ‘B’ includes the pressure signal in red, the audio signal in purple, and the PPG signal in dark blue. We applied the same analysis described in section ‘A’ to section ‘B’, and we plotted the graphs shown in Figure 8. We gathered the Korotkoff sounds using again a threshold algorithm; we calculated the OMWE and MAP on the pressure signal and we decomposed the PPG signal in low and high-frequency components. Please note that the ‘B’ section is shorter. However, this section requires inflating the arm cuff pressure to a high level of mmHg in order to be effective and to produce valid BP readings.

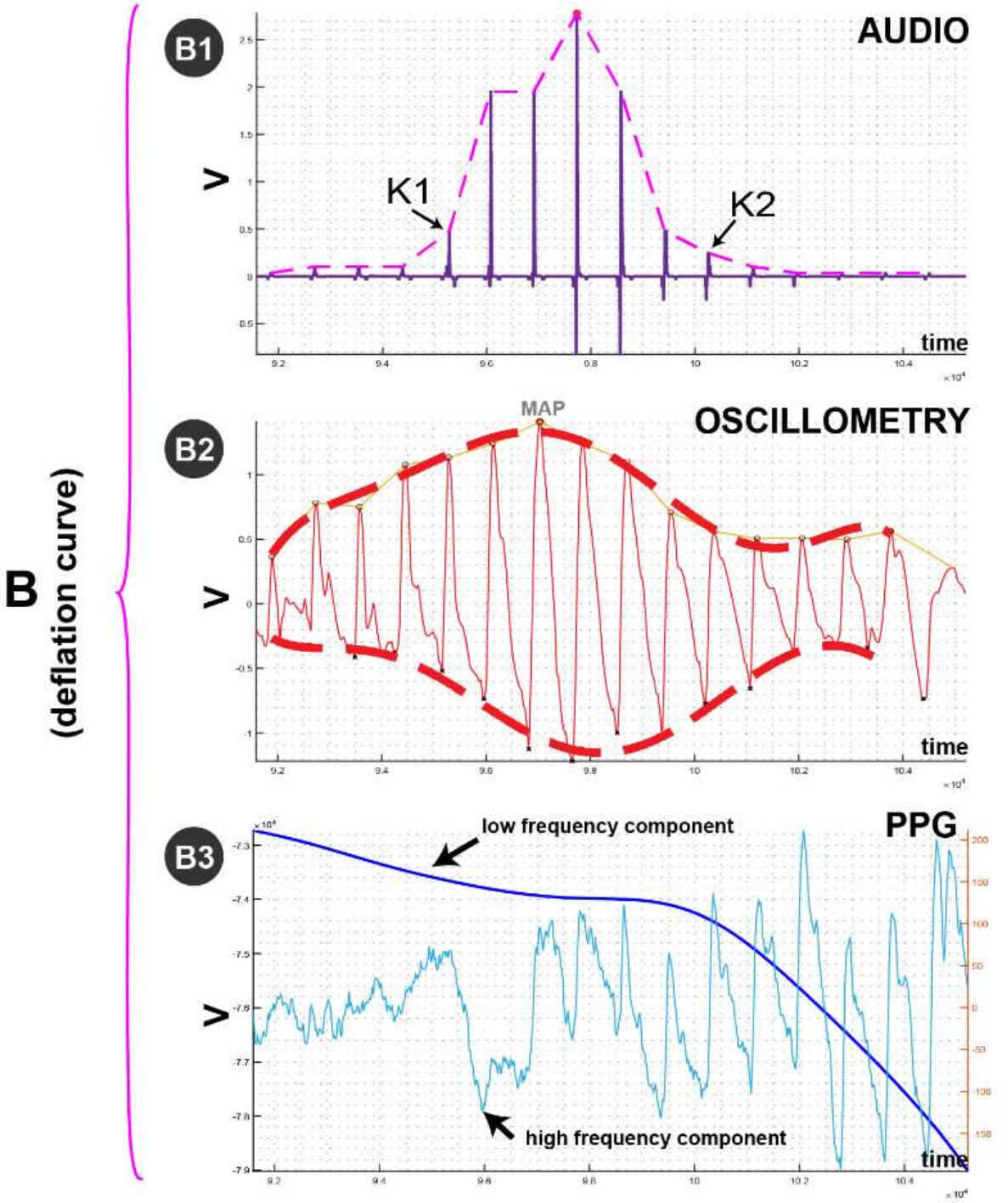


Figure 8. Section 'B' describes the behavior of our algorithm in the deflationary curve. Section B1 shows the deflationary Korotkoff Sounds. B2 displays the OMWE while deflating the cuff and B3 displays the two frequency components of the PPG signal.

2.5. Results and discussion

Estimations of BP using the inflationary curve are more challenging. The pump noise makes it difficult to get a reliable automatic auscultatory reading. However, Korotkoff sounds were obtained by adapting the pumping rate of the arm cuff and by applying specific digital signal analysis to the data. We have made minimal hardware modifications to keep the cost of future developments low as well as to maintain simplicity in the data collection methods.

2.5.1. Possibilities with custom procedures

This work shows pressure signals, PPG, and vessel acoustics can be detected and applied to different procedures and in different environmental conditions. With the help of our custom device, we can control the cuff's air volume, inflation, and deflation rates. Our team will be able to develop custom procedures using various inflationary and deflationary curves. With the use of these protocols, we will be able to compare Korotkoff sounds on both types of curves and analyze our three sensors in a variety of self-made procedures.

We intend to further understand how the three signals can be combined and how we can generate a more accurate BP measurement.

2.5.2. Future work

Our research group has acquired bio-signals from a few participants as a measure of feasibility. With feasibility established, we will test this on a larger number of diverse subjects to better investigate the possibilities brought by this equipment to create a patient-specific model of BP. Within this dataset of subjects, we intend to include atypical conditions such as participants with high or low values of BP, obesity, and the elderly. We will specifically study how these bio-signals can be optimally-fused to produce a more accurate BP estimation.

With proper fusion, the investigation team hopes to focus on obtaining patient-specific coefficients using automatic auscultatory procedures that we could then apply to patient-specific OMWE.

We also seek a more comfortable BP measurement experience. If we can acquire BP readings by sensor-fusion while keeping a lower arm cuff pressure, we could create a more pleasant and reliable experience for patients while taking BP measurements.

Further research is needed to develop a robust model that integrates all the signals and creates a strong sensor fused model.

2.6. Conclusion

Our team has designed and implemented a low-cost BP device capable of recording PPG, Korotkoff sounds, and pressure signals at the same time. The signals are processed and stored in Matlab files for further analysis. Our group has detected Korotkoff sounds in the inflationary curve with the use of digital signal analysis and with no major hardware changes applied to an off-the-shelf BP meter.

3. PAPER 2 - ASSESSMENT OF THE UNCERTAINTY ASSOCIATED WITH TWO CONSECUTIVE BLOOD PRESSURE MEASUREMENTS USING THE AUSCULTATORY METHOD

3.1. Abstract

Accurate non-invasive blood pressure measurements are vital in preventing and treating many cardiovascular diseases. The “gold standard” for non-invasive procedures is the auscultatory method, which is based on detecting Korotkoff sounds while deflating an arm cuff. Using this method as a “gold standard” requires highly-trained technicians and has an intrinsic uncertainty in its blood pressure predictions. In this paper, we analyze and characterize the origins of this uncertainty.

This paper defines an uncertainty model for two consecutive blood pressure measurements. Our research group developed a computer-based simulation of auscultatory blood pressure measurement uncertainty, and these results were compared to a human-subject experiment with a group of 20 diverse-conditioned individuals.

Uncertainties were categorized and quantified. The total computer-simulated uncertainty ranged between -8.4 mmHg to 8.4 mmHg in systolic blood pressure and -8.4 mmHg to 8.3 mmHg in diastolic blood pressure at a 95% confidence interval, while the limits in the human-based study ranged from -8.3 mmHg to 8.3 mmHg in systolic blood pressure and -16.7 mmHg to 4.2 mmHg in diastolic blood pressure.

3.2. Introduction

This paper describes the uncertainty present in the non-invasive gold standard method to measure blood pressure (BP). The auscultatory method, also known as the gold standard for non-invasive BP methods, is widely used as a valid reference to categorize the general population's health. Depending on the BP measured, patients may be prescribed medication or recommended to make lifestyle changes. The auscultatory method also evaluates existing and new BP measuring techniques. Understanding and quantifying the range of uncertainty of the auscultatory method is important because there can be a considerable range of errors in the gold standard (error understood as the difference between the actual value of BP and the measured value of BP). This work evaluates the sources and the impact of the uncertainty intrinsic to the auscultatory method by calculating the range of uncertainty in two consecutive auscultatory BP readings separated by five minutes.

BP measurements are important [22], [23]. Cardiovascular diseases are the number one cause of death in the United States [24] and the world [25]. Cardiovascular diseases can be prevented and treated early if BP measurements are readily available and accurate. Accuracy can be a problem when dealing with special patient populations (elderly, hypertensive, obese, etc.) [26]–[28]

The most accurate technique to obtain an arterial BP measurement is the intraarterial technique (IABP) [29]. In this method, a high-fidelity BP catheter captures the pressure waves occurring in an artery and translates these biological signals to analog electric signals, where a machine stores and displays the measurements [30]. This method is the gold standard for invasive BP measurements [29]. However, it is invasive, non-home-friendly, and is not widely

available because it requires a specialized clinical setting to be used. IABP meters require a catheter and may present several risks: infection, hematomas, blood loss, etc. [31].

A series of non-invasive methods were developed as an alternative to invasive methods. These methods don't require puncturing the skin and are widely available worldwide. However, their accuracy is not equivalent to invasive methods [9] and depends on patient characteristics [32]. The two most common non-invasive BP methods are auscultation and oscillometric [33].

This paper will focus on the auscultatory method because it is considered the gold standard for non-invasive methods [10]. In this technique, a highly trained medical specialist listens to the acoustics occurring in a patient's arm (Korotkoff sounds) while pressure is applied to their arm using an inflatable arm cuff. The specialist uses a stethoscope to listen to the sounds when the blood in the brachial artery rushes through the artery after being occluded or partially occluded [34], [35]. Korotkoff sounds are related to blood turbulence that occurs internally in the vessel. These measurements are based on the onset and disappearance values of the sounds captured with the help of a sphygmomanometer [36]. Based on these sounds, professionals can determine the values of systolic BP (SBP) and diastolic BP (DBP).

The auscultatory method requires a highly trained specialist to accurately make measurements, a reasonably quiet space, and a relaxed and still patient [37]. There have been attempts to automate this process by using automatic auscultatory devices. The automated method determines the SBP and DBP values by applying a threshold to the audio signal; in other words, the automatic method replaces the specialist with an algorithm [38], [39].

BP measurements are highly variable [40]–[42]. It is known that a BP reading can vary depending on the subject's emotional and/or physical status [43], [44]. Other influences on BP can include the patient's arm position [45], the stethoscope's location [46], the time of the day

[47], etc. Besides these circumstantial situations, physiological reasons also cause normal BP variation. BP variability can be classified as follows: very-short term, short term, and long term [48].

We can think of BP as a continuously changing signal where measuring a single static repeatable value is unrealistic [49], [50]. A way to measure the validity of BP measurements is by understanding and evaluating the various uncertainties that occur while measuring BP [51].

Uncertainty can be understood as the probabilistic range of difference between the actual value (reference) of BP in the system and the measured value of BP (estimation) for any one measurement. *Lee et al.* [52] estimated BP uncertainty by analyzing the difference between consecutive BP measurements obtained by the oscillometric method and comparing them to a reference value attained by the auscultatory method (non-invasive gold standard).

This paper extends the work of *Lee et al.* by examining the idea that the auscultatory method also contributes to uncertainty (i.e., the gold standard has uncertainty). Auscultatory methods, both automatic and manual (specialist), contain sources of uncertainty. The sphygmomanometer used (with a ±1 mmHg [53]) and the personnel that make the estimation introduce uncertainties in the measurement. Some common mitigating factors are using several trained observers and taking an average value of their measurements [54].

Our team has studied the origins of potential sources of uncertainty in the non-invasive gold standard. It has developed a computational model of BP uncertainty focused on the auscultatory method. A human-subject experiment was conducted to verify the model by taking two consecutive auscultatory BP measurements five minutes apart. This report documents the expected uncertainty of two consecutive single-sample BP measurements in the “gold standard.”

3.3. Description of uncertainties

We have identified the following categories of BP uncertainty: a) measuring method uncertainty, b) threshold detection uncertainty and c) the moving target uncertainty.

3.3.1. Uncertainty from the 'measuring method'

The arm cuff pressure is continuously reduced while taking a BP measurement using the auscultatory method. Meanwhile, the specialist is hearing Korotkoff sounds produced by blood pulses that happen periodically due to the patient's heart rate (HR). In other words, we are only taking measurements/samples at a frequency of HR while the arm cuff is deflating. We know the SBP value occurs anywhere in between beats, but we don't know where in between beats because we are only taking snapshots of the system at a specific interval while the applied pressure is reduced. The 'method' uncertainty reflects the possible difference between the actual value of BP and the estimated value by the specialist, based on Korotkoff sounds (Figure 9).

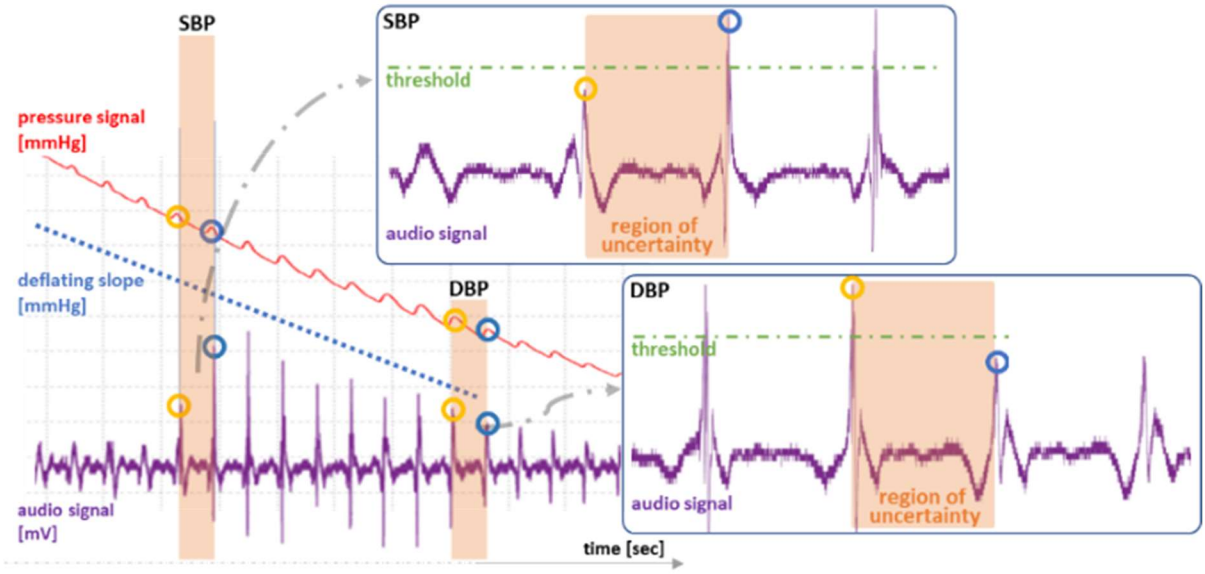


Figure 9. Measuring method uncertainty. The top red signal shows the arm cuff pressure, where we can notice small pressure oscillations. The second blue dotted signal shows the deflation slope. And the purple bottom signal shows the audio recorded with the device. The region shaded in orange displays the potential real SBP value that could land anywhere between the adjacent pulses caused by the periodic heart contracting. The adjacent pulses are illustrated with yellow and blue circles.

Since we cannot know where the real BP value is between those two wave peaks, we assume that this distribution of uncertainty is uniformly distributed. This uncertainty is directly correlated to the slope of the cuff's deflation and the heart rate (HR) of the individual. The slower the deflation is, the smaller the error introduced in the measurement, and the higher the HR the less error.

$$e_{me} = \frac{-(p_2 - p_1)}{(t_2 - t_1)} * \frac{1}{HR}$$

Where e_{me} is the 'measuring method error', $\frac{-(p_2-p_1)}{(t_2-t_1)}$ is the slope of deflation of the arm cuff in mmHg per minute, and HR refers to the heart rate in beats per minute.

3.3.2. Uncertainty from selecting the 'detection threshold'

This uncertainty simulates the potential error committed by selecting the incorrect threshold to select the values of SBP and DBP. In the case of manual auscultatory, the model mimics when a specialist determines the Korotkoff sound associated with a pulse that is not aligned with the actual value of SBP/DBP. In the case of automatic auscultatory, this uncertainty models the potential range of error if the threshold is not selected correctly. We understand that this error will be zero in most cases because most specialists/machines have been trained to minimize this error. However, there may be times when a pulse is misinterpreted, and the next (or previous) Korotkoff sound is taken as the reference to determine systole or diastole (Figure 10).

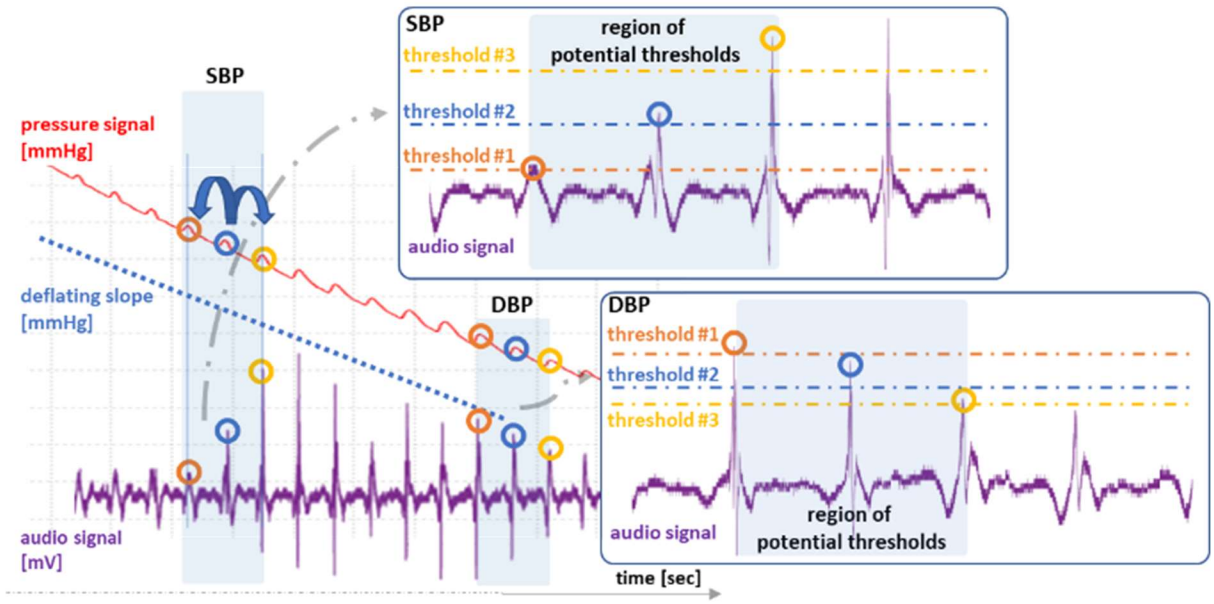


Figure 10. Detection threshold uncertainty. The top red signal is the pressure wave captured with the device, while the bottom purple signal is the audio recordings while deflating the arm cuff. The orange, blue and yellow circles show the potential candidates as the first Korotkoff sound for SBP and DBP.

We modeled this error as an asymmetric non-linear discrete distribution. In SBP, we set the error distribution to have an error equal to zero in 85% of the cases. In 10% of the cases, we simulated that we have a BP detecting threshold too sensitive, so we overestimated the actual value of SBP by a complete pulse difference (delta of pressure corresponding to the distance between the orange circle and blue circle in Figure 10). In other words, we will have at least a negative error equal to the maximum range of the 'method error.' In 5% of the cases, we estimated that we had the threshold not sensitive enough. We missed our target SBP by a full pulse (delta of pressure corresponding to the distance between the blue circle and orange circle in Figure 10).

$$e_{th_{SBP}} = \begin{cases} -e_{th}, & prob = 0.10 \\ 0, & prob = 0.85 \\ e_{th}, & prob = 0.05 \end{cases}$$

where

$$e_{th} = \max(e_{me})$$

Similarly, for DBP, we assumed that detecting the absence of Korotkoff sounds was more challenging to detect than the onset of Korotkoff sounds. Thus, we modeled the zero-error case with 75% of the occurrences, 5% with a difference of one pulse for a too sensitive threshold scenario, and 20% with the difference of one pulse for an unresponsive threshold.

$$e_{th_{DBP}} = \begin{cases} -e_{th}, & prob = 0.05 \\ 0, & prob = 0.75 \\ e_{th}, & prob = 0.20 \end{cases}$$

where

$$e_{th} = \max(e_{me})$$

3.3.3. Uncertainty due to BP being a 'moving target'

BP naturally oscillates with time due to respiration and normal cardiac control. Measuring accurate BP is like hitting a moving target. Based on the present literature, we know that there are specific factors that change BP, such as sitting still, circadian cycles, etc. [55]–[59].

The gold standard follows a strict protocol to minimize these effects [37]. However, even with those precautions, we still encounter physiological changes that make BP fluctuate in time. Some of these physiological phenomena are Mayer and Traube-Hering waves [60]–[62].

We know that these biological oscillations may have an impact within very-short term BP variability. In our model, we programmed this uncertainty using a periodic wave that would modulate an underlying BP signal. The peak values of this oscillatory wave were estimated to be 4 mmHg, with a period of 10 seconds (Figure 11). The values were modeled based on [63] and are well within the range of expected BP variability.

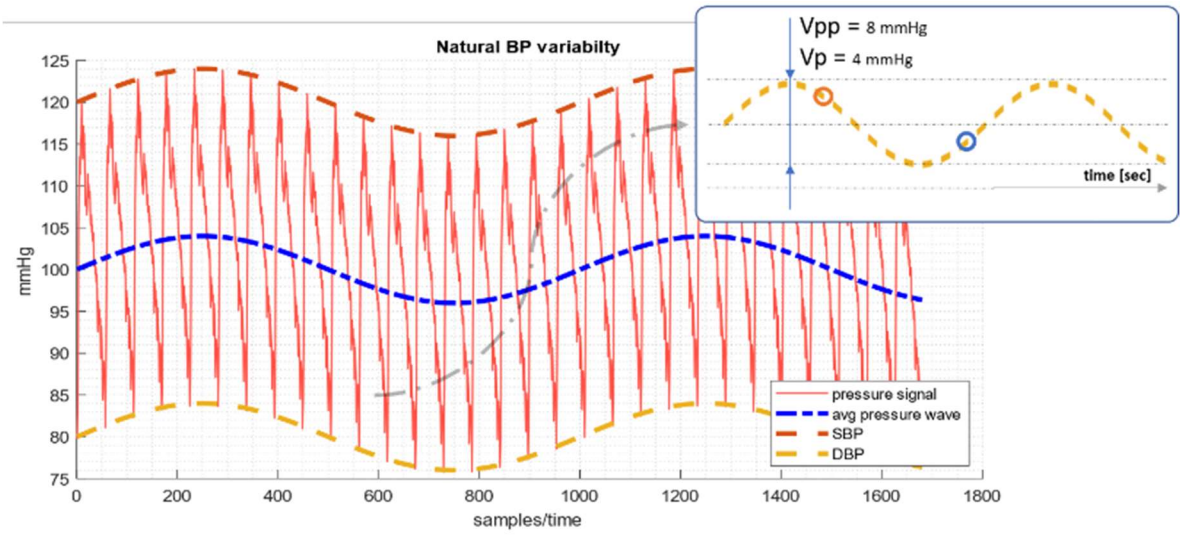


Figure 11. Simulated moving-target uncertainty. SBP and DBP oscillate in time. These values are simulated by modulating a low-frequency wave on top of the BP signal. The peaks of the BP signal show SBP, while the minimums illustrate DBP. In this case, SBP varies between 124 mmHg and 116 mmHg; in other words, 4 mmHg of peak amplitude in variability (V_p) or 8 mmHg in variability peak-to-peak (V_{pp}). Similarly, DBP varies between 84 mmHg and 76 mmHg.

These natural oscillations have a considerable effect on BP. Even under controlled conditions, where we take sequential measurements very close to each other, this effect can be observed. *Hansen et al*. [64] found that, within a few heartbeats, shifts of 20 mmHg can be observed because of these physiological oscillations.

All these uncertainties above have a direct impact on the final measurement. The total range of uncertainty can be studied by analyzing the interactions of these individual errors. We calculated the total error (E_{total}) summing potential errors from the 'method' error (e_{me}), the 'detection threshold' error (e_{th}), and the 'moving target' (e_{mt}) effects using a Monte Carlo simulation. Thus, the postulated formula below:

$$E_{total} = \sum(e_{me}, e_{th}, e_{mt})$$

$$U_{total} = f(E_{total})$$

Where E_{total} is the cumulative total error that originates from the three sources of error. U_{total} is the probabilistic range of error for a single sample of BP (e.g., 68% confidence interval (CI) or 95% CI). In our case, we calculate the total uncertainty by analyzing the histogram of a Monte Carlo simulation with 10,000 samples of BP measurements to determine these CIs (denoted as the function *f*).

In circumstances where these individual components were similar, the summation of all errors would tend to create a normal distribution [65]. However, this is only true under the assumption that all uncertainties are similar in magnitude. When these components have different magnitudes, the summation may not converge to a normal distribution and would trend towards uncertainty distribution with the most significant influence.

So far, we have described the potential sources of uncertainty of a single sample experiment. However, in this work, we calculate the uncertainty when two consecutive blood pressure measurements are taken using the auscultatory method. Similar to a single sample uncertainty, when dealing with the uncertainty of the difference between two samples, each has its range of uncertainty. The sample from run #1 has its range of uncertainty (defined by the sources of 'method,' 'threshold,' and 'moving-target'), and run #2 has a similar range (also defined by the sources of uncertainty). We aim to characterize the difference between two consecutive BP measurements for two-sample measurement uncertainty without the aid of an intraarterial line.

$$E_{diff} = \sum(e_{me}, e_{th}, e_{mt}) - \sum(e'_{me}, e'_{th}, e'_{mt})$$

$$U_{Diff} = f(E_{diff})$$

Where E_{diff} is the difference between the first sample (E_{total}) and the second sample (E'_{total}). In other words, the difference in the summation of errors from the first sample ($\sum(e_{me}, e_{th}, e_{mt})$) and from the estimate of the second BP reading ($\sum(e'_{me}, e'_{th}, e'_{mt})$).

Finally, U_{Diff} is the uncertainty (i.e., probabilistic range) calculated based on the histogram's CI of the difference between the two samples.

3.4. Methods

We followed a two-phase approach to determine the range of uncertainty that occurs when measuring two consecutive samples of BP while using the auscultatory method. First, we predicted the probability of multiple outcomes of uncertainty by a Monte Carlo simulation in Matlab. Second, we measured arterial non-invasive BP within an IRB-approved human-subject experiment (IRB0003287). In this experiment, we took BP measurements using specialized hardware. This hardware combined a flat microphone and a fully-controlled modified over-the-counter BP measuring device [66].

3.4.1. Matlab simulation

We developed a software program to predict BP uncertainty using a Monte Carlo simulation. We calculated 10,000 potential BP errors with various heart rates. We modeled heart rate based on [67] using a normalized distribution with the mean (mu) at 75.8 beats per minute (bpm) and standard deviation (sigma) of 23 bpm. Having a wide realizable HR distribution was key since HR directly impacts the 'measuring method' uncertainty and the 'detection threshold' uncertainty.

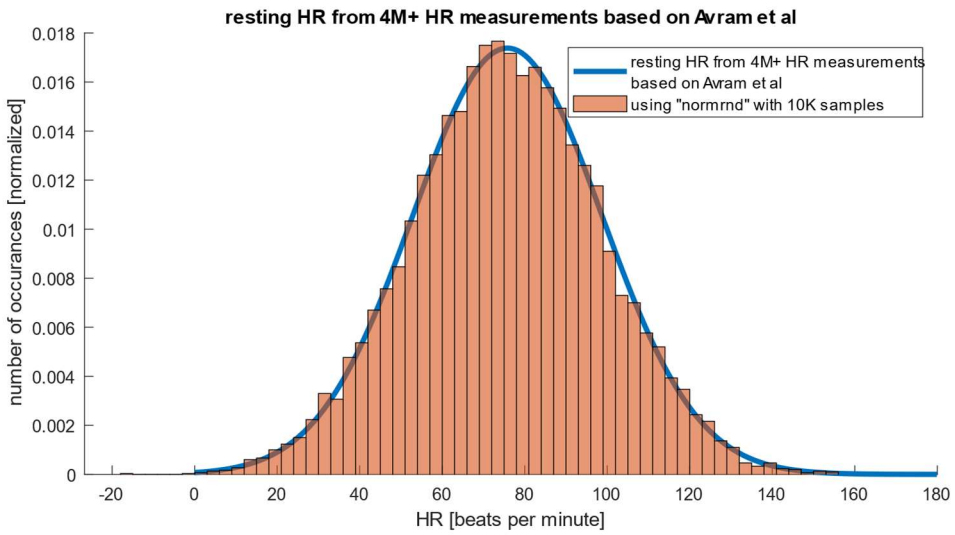


Figure 12. Normal distribution of heart rates based on Avram et al. HR mean is 75.8 bpm with a standard deviation of 23 bpm. Randomly selected values from this distribution were used to populate the single-sample uncertainties.

We randomly selected values from the HR normalized distribution and used them in the formulas for 'measuring' and 'detection threshold' uncertainties. As shown in the flow chart (Figure 13), we first calculated each uncertainty and then summed the individual error components. At the end of the simulation, we finished with a vector of 10,000 possible values of BP errors. Within those 10,000 samples, we stored the individual error components and saved them for future analysis using a histogram and CIs to estimate the uncertainty.

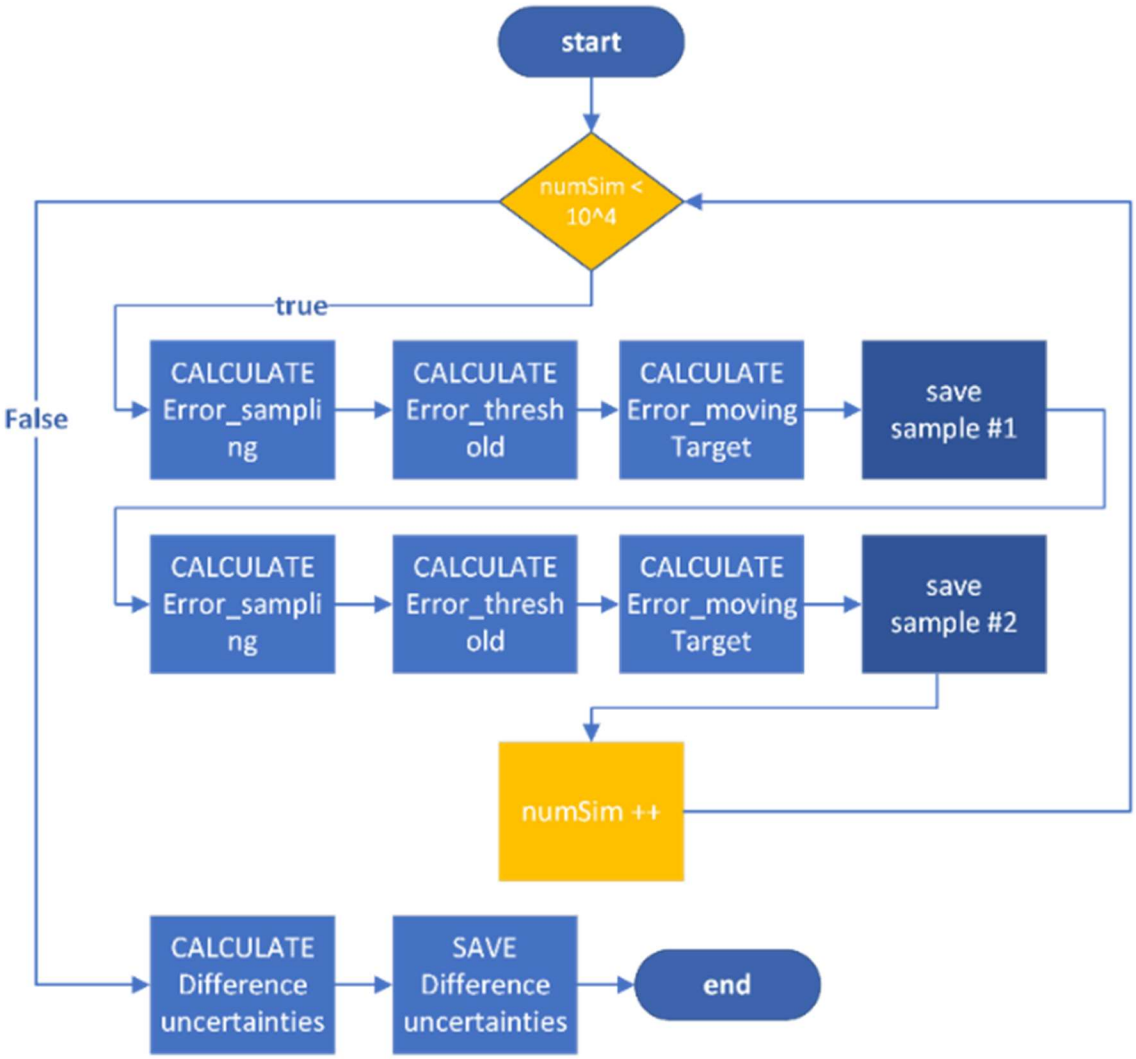


Figure 13. Flowchart showing the computer algorithm that we implemented. We looped through 10,000 errors that could occur when measuring blood pressure. The uncertainty of each sample was determined by considering all the components of uncertainty. Once we had the two samples computed, the differential error was calculated by obtaining the difference between two samples. Finally, we saved the results for further analysis at the end of the program.

When calculating uncertainty BP estimations, a critical factor to consider was the deflation rate of the arm cuff. The deflation rate directly influences the 'measuring method' uncertainty and the 'detection threshold' uncertainty. Intuitively, the slowest deflation rate results in a smaller uncertainty in the measurement. We had to search for a balance between speed of the measurement, comfort level, tissue dynamics, and reliability. We used the deflation

rate provided in an over-the-counter BP measuring Omron BP710 (Figure 14). The deflation rate was measured at a consistent 5 mmHg/sec. These devices use a fixed-rate release valve.

3.4.2. Human-subject experimental setup

Twenty adults were recruited at North Dakota State University (NDSU), Fargo, ND. Among these individuals, some self-identified with higher than average BP (SBP > 130 mmHg and/or DBP > 80 mmHg), and within this group, some were on BP medication. Before conducting the study, we received NDSU's Institutional Review Board (IRB) approval (IRB0003287). Participants volunteered in the study and were not compensated. All individuals were provided with a written consent form. Participants' characteristics are displayed in Table 1.

Table 1. Participants' characteristics.

Features	avg | std	min	max	Units
Total number	20 (7 female)			
Age	43±15.4	19	62	years
SBP	133±18.5	113	174	mmHg
DBP	82.1±8.5	69	99	mmHg
HR	69.9±13.6	41	99	bpm
BMI	29.8±6.56	20.7	45.1	Kg/m^2
Arm circumference	32.51±4.4	25.4	43.2	cm

* 7 subjects with higher than average BP, SBP > 130 mmHg and/or DBP > 80 mmHg

Participants were instructed to sit in a comfortable desk chair with back support for five minutes while the consent form was explained. After five minutes, we measured BP using non-invasive techniques synchronously [66]. These techniques were: 1) a modified off-the-shelf BP meter (Omron BP710) with an appropriately sized arm cuff, 2) a contact microphone (CM-01B) with an amplifier (LM741), 3) and high-sensitivity pulse oximeter with its control electronics (MAX30105).

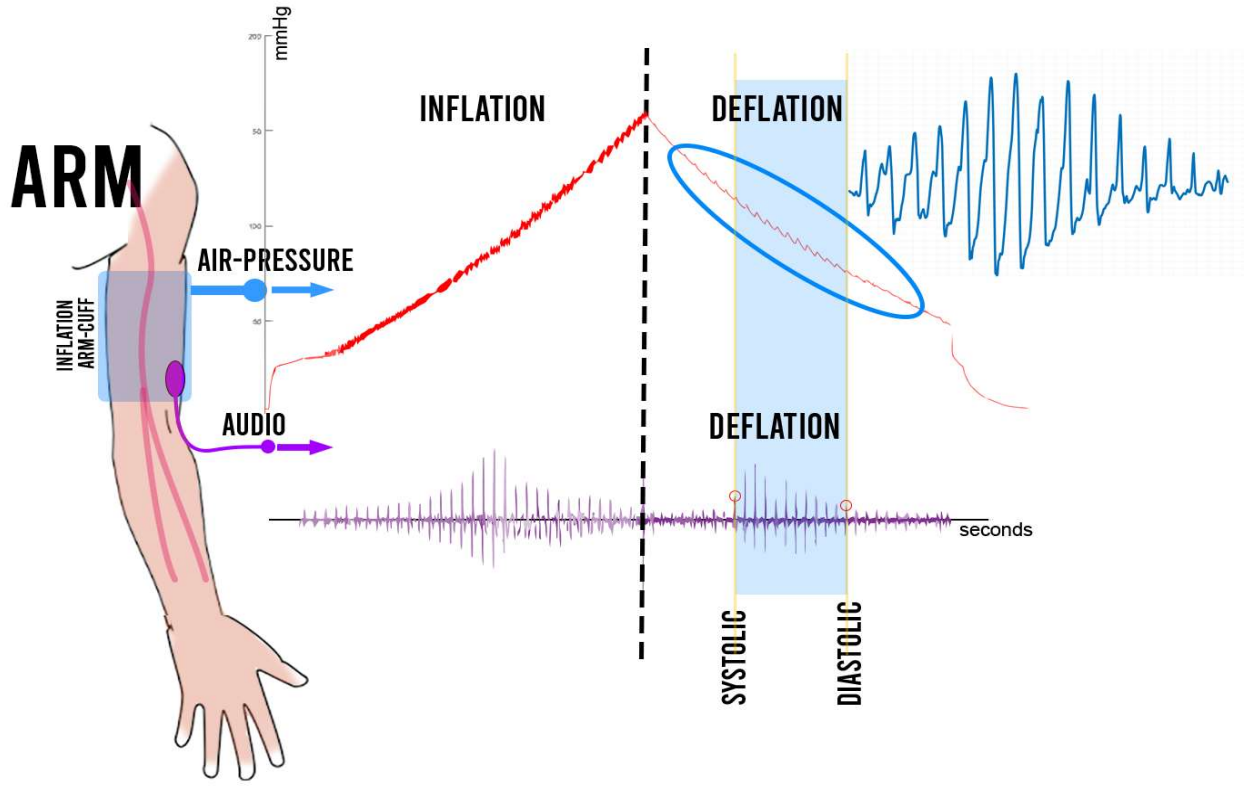


Figure 14. BP measurements were collected using an arm cuff and an inflation and deflation procedure. The system measures the Korotkoff sounds while the arm cuff deflates at a known fixed rate. The first audible sound corresponds to SBP. After SBP, DBP is determined when the specialist cannot hear any other sounds. The red top signal is the pressure wave. The top right corner blue signal is the oscillometric wave envelope. The purple wave is the audio signal from a contact microphone position over the brachial artery. The light blue rectangle shows the region of interest of Korotkoff sounds between SBP and DBP.

American Heart Association recommendations for measuring BP were followed when taking the measurement [68]. Participants were sitting with legs uncrossed, their back and arm supported, and their feet flat on the ground. The arm used to make the measurement had the hand pronated on the experiment table. The inflatable arm cuff was placed on their non-dominant arm and inflated to high pressure (between 160 mmHg and 180 mmHg and above SBP). After reaching peak pressure, the arm cuff was deflated at a constant rate (5 mmHg per second). Synchronous measurements of audio, and pressure were performed while deflating the arm cuff (deflationary phase).

We took two BP measurements separated by a five-minute rest period. After these two measurements, we also measured the participant's arterial BP and heart rate with a commercially available un-modified Omron BP710.

At the time of the sessions, because of ethical reasons, if the participant's systolic BP was between 140 and 180 mmHg, the participant was referred to their primary care provider. If the participant's systolic BP was above 180 mmHg, they were referred for urgent care.

Due to COVID19 policy, the experiment was highly optimized for time. The experiment room was limited to two people; all equipment was thoroughly disinfected, and the room was emptied for 30 minutes between participants.

3.4.3. Data analysis

We analyzed the samples derived from the Monte Carlo simulation plotting the histograms of the various sources of error for the single sample experiment. In addition to the individual sources, we also calculated E_{total} and plotted its histogram. Then, we estimated the probability density functions (PDF) [69] from all the sources of uncertainty and E_{total}. We normalized the PDFs so all probabilities would sum to one. With the normalized PDF calculated, we derived the 68% and 95% CIs for the distributions [70].

After calculating the single sample PDFs, we then studied the distribution of the difference between two consecutive samples of BP measurements. We computed the difference between the two samples generated with random initial conditions. We calculated the individual components of error in the difference and the total E_{diff}. After that, we plotted the PDFs for all sources of error and the total E_{diff}. We finally calculated the 68% and 95% CIs for E_{diff}.

Once the software model was characterized, we performed data analysis on the human subject data. Several features were extracted from the human experimental results. We recorded

pressure, and audio signals while deflating the arm cuff. Korotkoff sounds were calculated using a thresholding algorithm. The first Korotkoff sound, where the audio signal was over the threshold, would determine the value of SBP. Afterward, and while deflating the arm cuff, DBP was selected when the audio signal went under the threshold.

After calculating SBP and DBP, we evaluated the difference (Diff) between SBP/DBP from run #1 and the SBP/DBP from run #2 (which was conducted five minutes after run #1):

$$E_{diff_{SBP}} = SBP_{run\#2} - SBP_{run\#1}$$

$$E_{diff_{DBP}} = DBP_{run\#2} - DBP_{run\#1}$$

We calculated the PDFs of $E_{diff_{SBP}}$ and $E_{diff_{DBP}}$, and plotted a histogram with an x-axis in mmHg and a y-axis with the number of occurrences for that bin of mmHg. Plots were obtained using the statistical software JMP (from Statistical Discovery™) and Matlab.

Finally, we compared the software model and the human-subject results. We calculated the 68% CI and the 95% CI in both sets of data and we compared their ranges of uncertainty.

3.4.4. Limitations and challenges

Ideally, we would have used an intraarterial line to have a point of reference when comparing sequential values of BP with the gold standard of invasive measurements. That way, we could study the variation between intraarterial BP (IABP) values and the non-invasive measurements. At this time, it was impractical with our setup to experiment with invasive techniques.

We limited our experiment to two samples due to the following rationale. This was the minimum number of comparisons to measure variability between measurements. A multi-sample experiment's mean values and uncertainties may require 500 or more samples to determine the actual mean [51]. We also considered that numerous measurements obtained on the same arm

with the same setup could condition the tissue surrounding the brachial artery. We, therefore could bias the BP readings, thus affecting the range of uncertainty in our samples.

In addition, this human-subject study was run amid the COVID-19 pandemic, which made institutional review board (IRB) and safety precautions challenging.

3.5. Experimental results

Our results are divided into two groups: results from the software simulation and results from the human-subject study.

3.5.1. Simulation results | single-sample uncertainty

As expected, the 'measuring method' uncertainty has a significant negative behavior. This is because it correlates to the difference between the actual value of BP and the value of BP corresponding to the pulse immediately after the true value of BP. Because the recognition of the Korotkoff sound is always after the true value of BP, the calculated difference is less or equal to zero.

The final shape shown in Figure 15 for SBP and Figure 16 for DBP, is given by selecting, at random, values of heart rate from the normal distribution of HR.

Regarding the 'detection threshold' uncertainty, we observed that the error is zero in most cases, which means that in most cases we are selecting the correct pulse to determine SBP or DBP. In some instances, we measured small error values on the edges of the PDF, ranging from -5 mmHg to 5 mmHg. This un-balanced PDF shape results from the discrete nature of our uncertainty definition.

The 'moving target' uncertainty has a non-normal distribution. This uncertainty is based on a periodic sinusoidal wave. Therefore, the chances of error are higher in the sinusoid's peaks

than in the zero crossings [71], [72]. The calculated PDF has two distinctive local maxima on the edges (approximately -4 mmHg and 4 mmHg) and flattens around 0 mmHg.

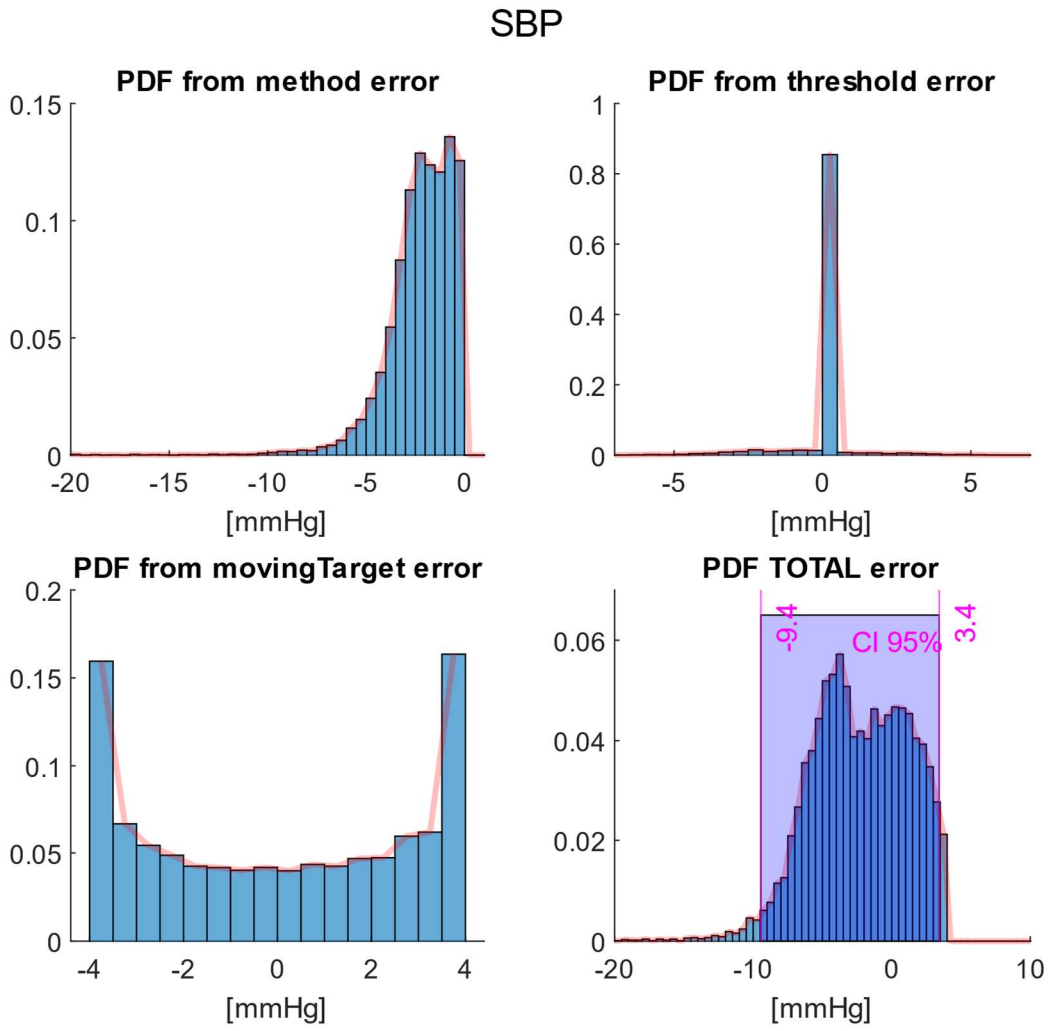


Figure 15. Normalized histogram of the simulated one-sample SBP. The uncertainty from the 'method', 'detection threshold', and 'moving target' sources are independently displayed. The bottom right corner shows the shape of the PDF for a single-sample SBP uncertainty using the auscultatory method.

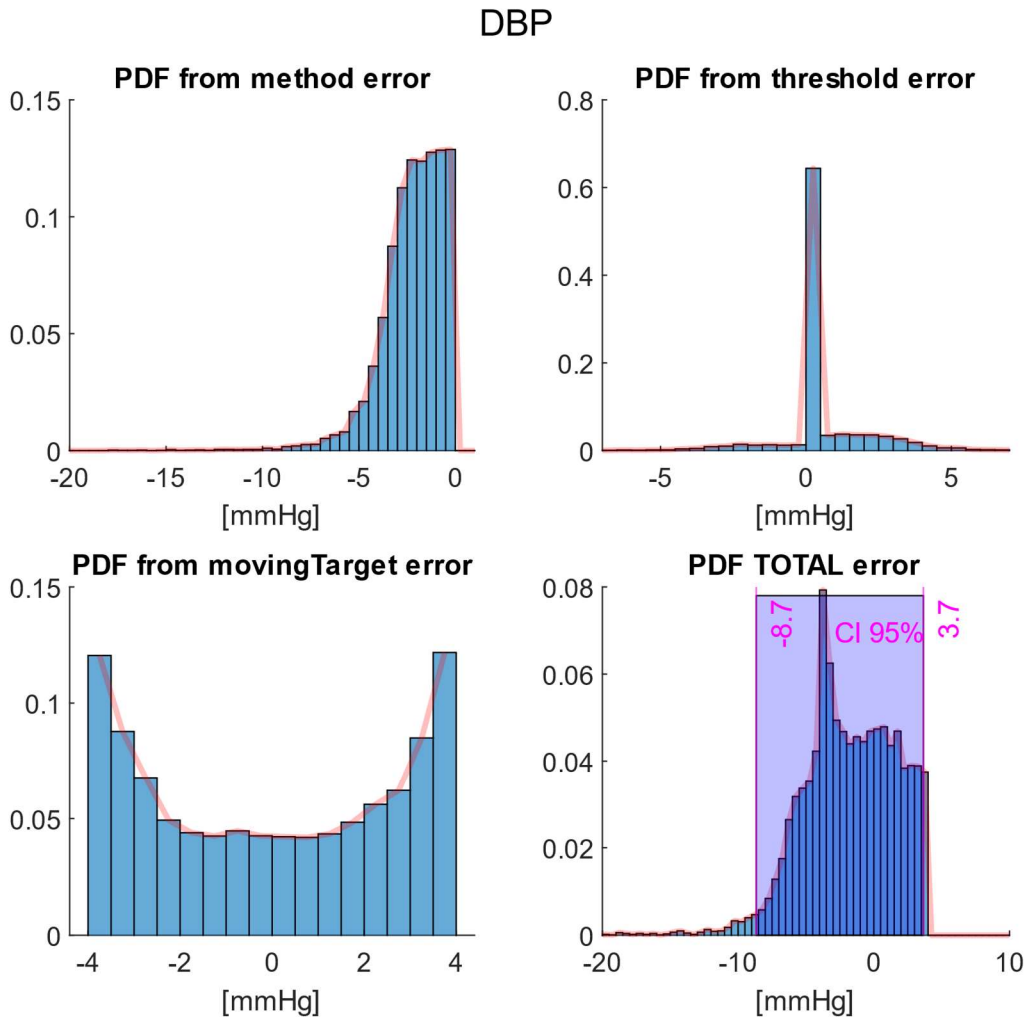


Figure 16. Normalized histogram of the simulated one sample DBP. The uncertainty from the 'method', 'detection threshold', and 'moving target' sources are independently displayed. The DBP threshold PDF differs from SBP because DBP was harder to threshold than SBP. The bottom right corner shows the PDF shape for a single-sample DBP uncertainty using the auscultatory method.

Our results show that U_{total} has a non-normal distribution with a CI of 95% between -9.4 mmHg and 3.4 mmHg for SBP and -8.7 mmHg and 3.7 mmHg for DBP.

3.5.2. Simulation results | two-sample difference uncertainty

The PDF of the two-sample difference is fairly symmetric centered on zero mmHg. The highest occurrence level also happens at the value of zero mmHg. The independent components

of uncertainty also show a symmetric behavior due to the nature that we are subtracting the value between two samples with the assumption that the underlying BP only changes within the parameters established by the 'moving target' uncertainty.

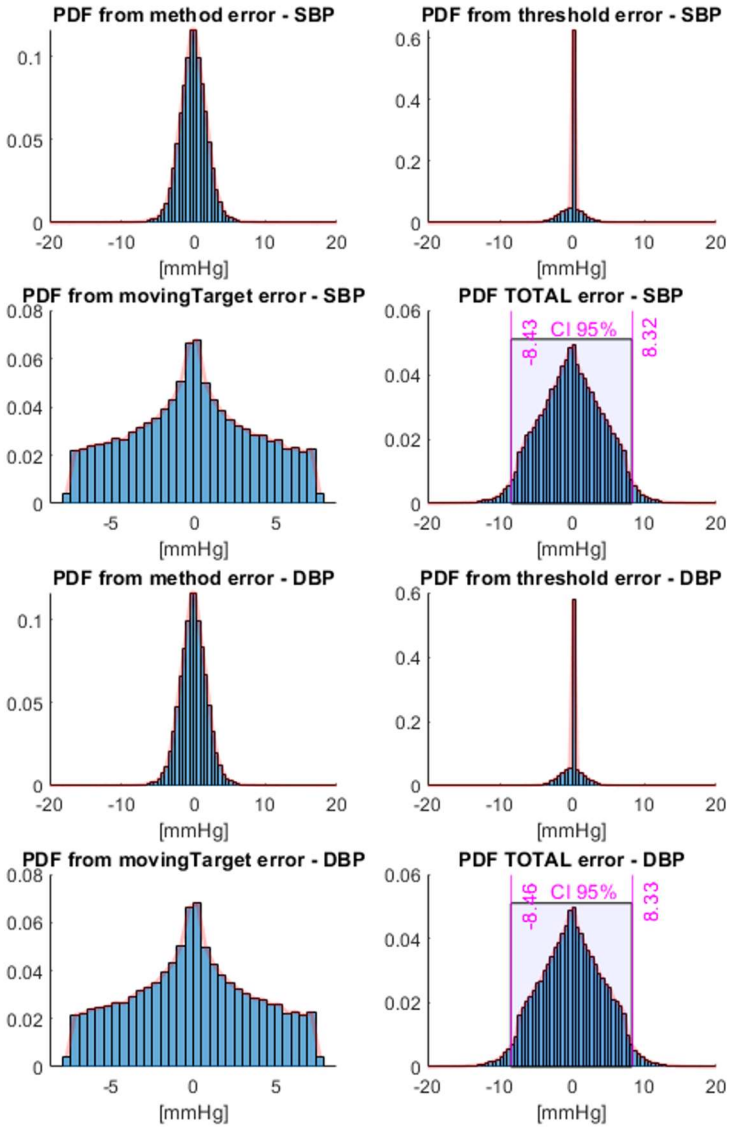


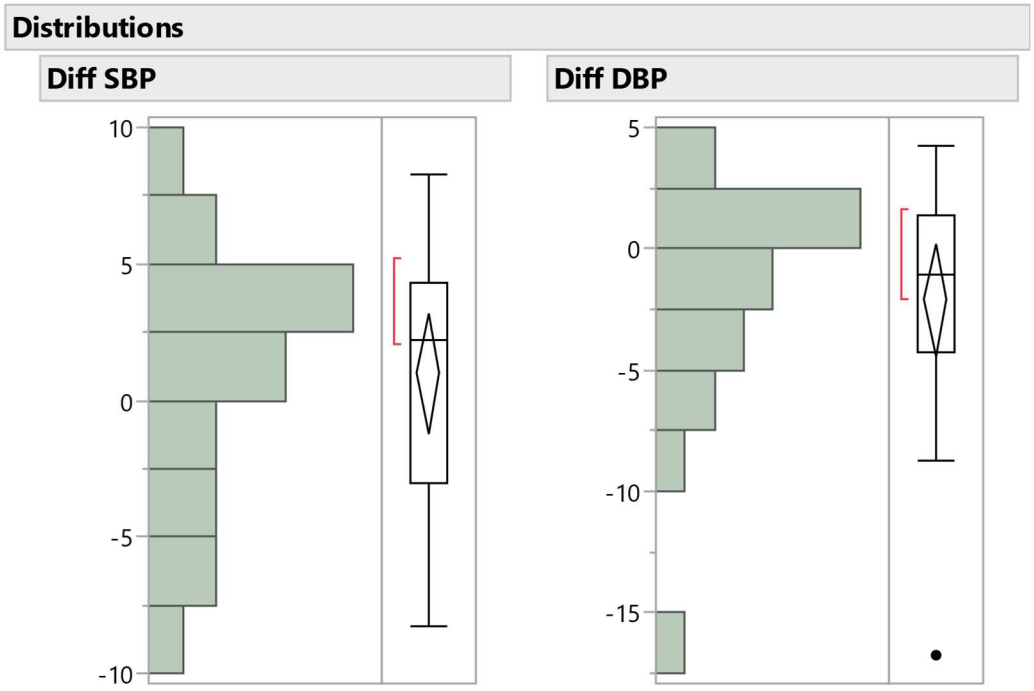
Figure 17. PDF of the two-sample difference between two samples of BP. SBP and DBP have similar characteristics under this model. SBP and DBP show a 95% CI of 16.7 mmHg.

Most samples at a CI of 95% land in between -8.4 and 8.3 mmHg both for SBP and DBP. The threshold PDF has very little influence on the final PDF. The most influential uncertainty in this model is the 'moving-target' uncertainty.

3.5.3. Human-subject experiment results

The human data (N=20) showed that the difference between measurement #1 and measurement #2 had a range in SBP of -10 mmHg to 10 mmHg. Similarly, DBP displayed a range of -5 mmHg to 10 mmHg (not considering outliers – Figure 18).

The individual points from the 'Diff' signal were plotted using a Bland diagram to show the distribution based on the mean of the SBP and DBP points (Figure 19). These plots are useful in identifying patterns that could correlate to the mean BP.



Quantiles

100.0%	maximum	8.28
99.5%		8.28
97.5%		8.28
90.0%		6.838
75.0%	quartile	4.32
50.0%	median	2.225
25.0%	quartile	-3.015
10.0%		-6.471
2.5%		-8.3
0.5%		-8.3
0.0%	minimum	-8.3

Summary Statistics

Mean	1.0075
Std Dev	4.7116137
Std Err Mean	1.0535489
Upper 95% Mean	3.2126031
Lower 95% Mean	-1.197603
N	20

Quantiles

100.0%	maximum	4.23
99.5%		4.23
97.5%		4.23
90.0%		3.33
75.0%	quartile	1.3475
50.0%	median	-1.035
25.0%	quartile	-4.2975
10.0%		-8.604
2.5%		-16.74
0.5%		-16.74
0.0%	minimum	-16.74

Summary Statistics

Mean	-2.112
Std Dev	4.9002541
Std Err Mean	1.0957301
Upper 95% Mean	0.1813895
Lower 95% Mean	-4.40539
N	20

Figure 18. Distribution of the human-data difference between two consecutive BP measurements five minutes apart. The difference in SBP is plotted on the left. The average was -1 mmHg with a standard deviation of 4.7 mmHg. The difference in DBP is plotted on the right. The average was 2.1 mmHg and the standard deviation was 4.9 mmHg.

In our case, we saw that our distributions of differences behave similarly within the range of the studied measurements (approximately 100 mmHg to 150 mmHg for SBP, and 65 mmHg to 100 mmHg for DBP).

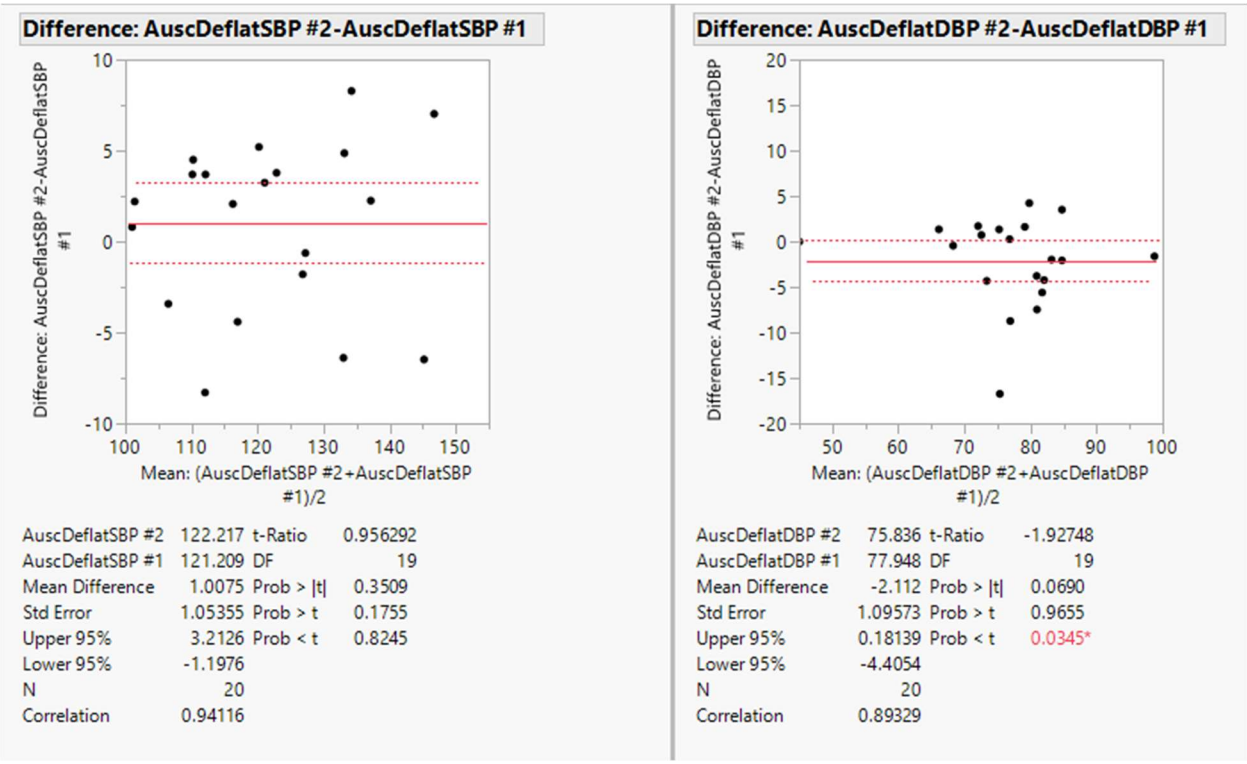


Figure 19. Bland-Altman plot displaying the difference between run #1 versus run #2 of SBP and DBP in human data. The y-axis corresponds to the difference value and the x-axis to the mean of the two samples.

The 95% CI calculated from the human data fell within the range of the simulations' 95% CI.

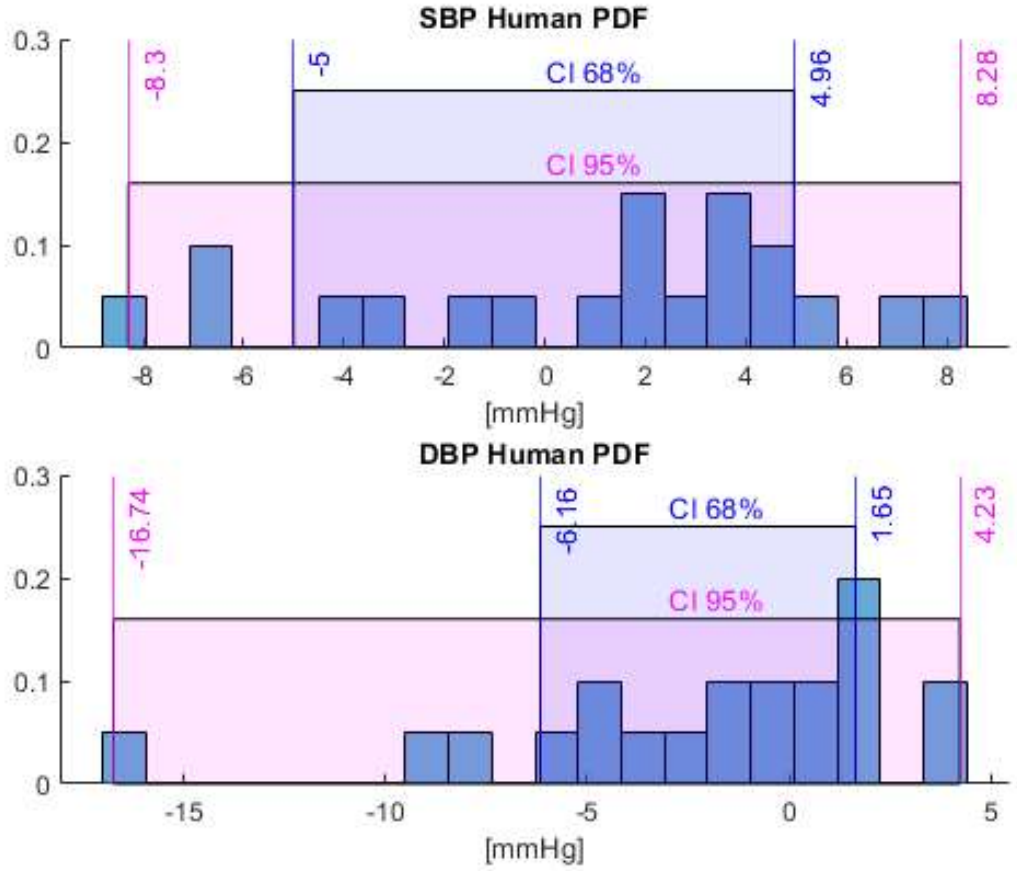


Figure 20. CI and normalized distribution of the human-data two-sample difference between two consecutive BP measurements five minutes apart. The top graph shows SBP and the bottom DBP. The magenta rectangle and magenta limits correspond to the 95% CI and the blue rectangle and blue limits to the 68% CI.

While not conclusive (N=20), our model of uncertainty fits the data observed in the human-based experiment (Figure 20). SBP fits fairly well in both 68% CI and 95% CI. For the 68% CI, the model fits 13 samples out of the 20 (65%), while 7 samples are placed outside the interval. In the case of 95% CI, 19 samples fit (95%) and 1 sample is outside the interval.

Table 2. CI comparison (Simulation and Human data)

	[Pressure in mmHg]			
Features	68% CI		95% CI	
	range min	range max	range min	range max
SBP sim	-4.6	4.6	-8.4	8.3
DBP sim	-4.6	4.6	-8.4	8.3
SBP human	-5.0	4.9	-8.3	8.3
DBP human	-6.2	1.6	-16.7	4.2

Table 3. Model fitting

	Simulation			Human			
	%	Simulation range min	Simulation range max	Samples fitting	Samples out of range	% fitting	% not fitting
SBP	68%	-4.63	4.61	13	7	65%	35%
DBP	68%	-4.62	4.63	16	4	80%	20%
SBP	95%	-8.39	8.31	19	1	95%	5%
DBP	95%	-8.41	8.35	18	2	90%	10%

The DBP had 16 occurrences (80%) within the simulation's 68% CI, and 18 occurrences (90%) in the 95% CI of the simulation prediction. Our DBP human-data samples are more clustered near zero and that may be the cause for these results.

These conclusions are derived under the assumption that the underlying true value range of blood pressure didn't change during the experiment beyond the boundaries set by the moving target uncertainty. We know BP could change because of numerous reasons (i.e., a participant had a stressful thought), so we need to keep this in mind when interpreting these results.

As an attempt to quantify the non-stationary state of the two samples we compared the HR of the participants while we sample BP. We measured that five participants' HR changed from 8% to 13% during the five minutes between the first and second measurement.

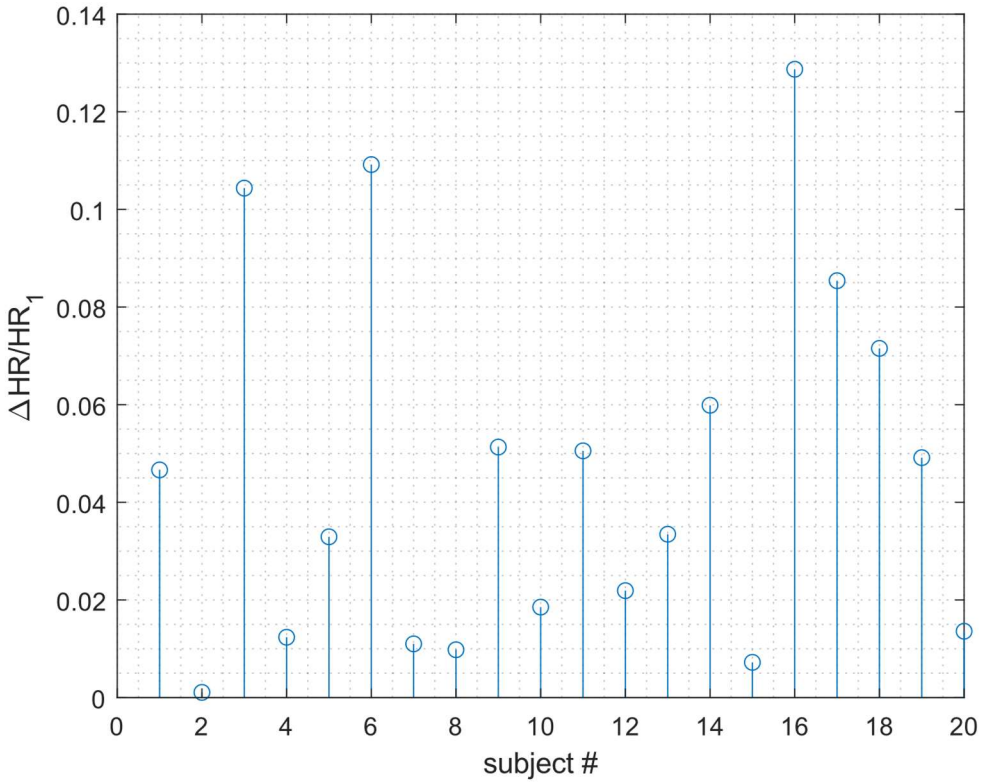


Figure 21. Difference of HR from run #1 and run #2. The x-axis denotes the subject id# and the y-axis corresponds to HR variability. In our case, we calculated HR from run #2 minus HR from run #1 divided by the HR from run #1.

While not conclusive we saw a change in HR in our participants even after following the recommended procedure for the auscultatory method [68]. We identified an outlier in DBP human data distribution with a -16 mmHg difference. This subject was later analyzed and found to be part of the group of the 7 subjects with higher-than-average BP, SBP > 130 mmHg, and/or DBP > 80 mmHg. It was also noted that the subject was under BP medication and that could explain the behavior in BP variability.

Table 4. Contributions of uncertainty to the auscultatory gold standard

Source of uncertainty	Impact	Nominal value (95% CI)
Method	Medium	-3.8 to 3.8 mmHg
Threshold	Low	-2.8 to 2.8 mmHg
Moving Target	High	-7 to 7 mmHg
Other (non-stationary system)	Unknown (depends on the nature of the change)	Unknown

As a summary of our results, we displayed the impact of the error sources when taking an auscultatory BP measurement. Table 4 shows the effect and the nominal value of the three sources of uncertainty identified in this paper. We see how the 'moving target' error is the most impactful of the three, with a nominal value between -7 mmHg and 7 mmHg. The total simulated 95% CI value from U_{Diff} was between -8.4 mmHg and 8.3 mmHg.

3.6. Conclusion

A BP measurement obtained by external methods is an estimation. The cardiovascular system is nonstationary and therefore is continuously changing. The uncertainty of the auscultatory method is greater than the +-1 mmHg (the expected error margins from the sphygmomanometer). There are other components in this method that add uncertainties to the observed value. The non-invasive gold standard used to measure BP is in itself a source of uncertainty. We need to understand these sources of uncertainty and keep them in consideration when making decisions based on a BP estimation.

Comprehending BP uncertainties is key to understanding the cardiovascular system. Within two consecutive measurements five minutes apart, we could expect uncertainties within a range of 16 mmHg (-8 mmHg to 8 mmHg in a 95% CI). This range is broad and highly variable from person to person. The 'moving-target' uncertainty has a high impact on the range of

uncertainty in an auscultatory measurement, in other words, the inter-personal BP variability is correlated to the person's BP cardiovascular system.

In this work, we developed a blood auscultatory BP measurement uncertainty model and verified it with a human study. We first defined a single sample auscultatory BP uncertainty, then we progressed to the uncertainty of two consecutive measurements, illustrating that the system under test is changing. Lee et al.'s work compared the uncertainty occurring between oscillometric and the auscultatory method. In this work, we have demonstrated that the auscultatory method (the gold standard in Lee et al.'s work) also contains several sources of uncertainty and that in most cases (95% CI), the value can range from -8 mmHg to 8 mmHg. With the potential interaction between the uncertainty of the auscultatory method and the uncertainty of the oscillometric method, we can predict that the uncertainty in oscillometric measurements is likely to be higher than previously published.

Knowing all these uncertainty ranges, we need to be careful when making decisions based on BP estimations. The difference between normal (<120/80 mmHg), elevated (120-129/<80 mmHg), stage 1 hypertension (130-139/80-89 mmHg), and stage 2 hypertension (≥140/≥90 mmHg) [8], [73] are classified using 10 mmHg increments, which is well within our range of uncertainty.

These results indicate that innovations are needed to better understand BP. One option is to capture the BP signal continuously over a long time to understand the moving-target error for that individual. Access to continuous BP measurements and precise individualistic models of BP may be the key to understanding the inter-personal range of arterial BP measurements and variability that provides a better personalized medical treatment.

4. GENERAL CONCLUSIONS AND FUTURE WORK

Non-invasive reliable and accurate BP measurements are challenging to measure. This exigent task gets even harder when trying to measure BP in certain populations (elderly, obese, hypertensive, etc.). We learned that BP is a signal on its own, with certain variability and oscillations. Targeting BP measurements is like trying to hit an always-moving target.

In addition to these challenges, we conducted the majority of our experimentation in the hardship of the COVID-19 pandemic. Human research in itself was quite the challenge in this period.

BP measuring techniques are a hot topic in research. Many novel BP measuring devices are designed every year, and many of them are innovative and complex. There is an immediate need for accurate and easy-to-use portable BP devices. The ultimate goal is to be able to measure continuous non-invasive BP in a non-intrusive way and in a wide range of population characteristics.

In our project, the main goals we aimed to accomplish were to:

- improve accuracy
- improve comfort

We developed a system with those goals in mind. Firstly, we wanted to measure BP by applying less air in the arm cuff, thus improving comfort. Additionally, we acquired simultaneous real-time bio-signals while inflating and deflating an arm cuff. We then studied our collected data to get a better estimation.

In our system we were able to:

- combine auscultatory, oscillometric, and PPG

- make two measurements of BP (SBP/DBP) per run: one measurement on the inflationary curve and one measurement on the deflationary curve.
- Control the cuff pumping rate
- Design custom digital processing capable of filtering the auscultatory signals in inflationary environments.
- Develop custom procedures to measure BP by controlling the pumping and release of air in the arm cuff.
- Create a dataset of data with 20 individuals with diverse highly-looked-for BP conditions (i.e., hypertension, obesity, etc.)
- Develop a model of uncertainty focusing on deflationary auscultatory.
- Validated the model with digitally synthesized samples and our 20 individual datasets.

In summary, we designed and implemented a custom BP device based on a readily available BP air-cuffed apparatus. We planned a study to test the device, and we analyzed the data from the study.

We believe the contributions presented in this work will be helpful to develop a future solution to acquire BP. When measuring BP, many factors have to be kept in consideration, this work furthers the understanding of these factors and how they can contribute to a BP estimation.

4.1. Future work

The present works aim to contribute to the body of knowledge in BP measurements.

We envision the future with continuous monitoring of BP using a comfortable and noninvasive device. Future work will focus on the idea of the immediate need for a personalized model to measure BP. Every human being is different and has various conditions that may need

specific personal adaptations. There is a need for an individualistic model in biomedical engineering. This is not a trivial problem to solve.

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APPENDIX A. EMBEDDED FIRMWARE FOR ADS1015

This appendix contains the firmware code used to acquire the bio-signals from the developed device.

```
#include <Wire.h>
#include <Adafruit_ADS1015.h>

 Adafruit_ADS1115 ads;  /* Use this for the 16-bit version */
//Adafruit_ADS1015 ads;     /* Use thi for the 12-bit version */

int state=0;
unsigned long time0;
int val = 0;       // variable to store the read value
int valS = 0;       // variable to store the read value
int oldVal = 0;       // variable to store the read value
int analogPin = A3;
int analogPinSound = A2;

void setup(void)
{
  Serial.begin(9600);

  //Serial.println("Hello!");
  //Serial.println("Getting differential reading from AIN0 (P) and AIN1
(N)");
  //Serial.println("ADC Range: 8x gain   +/- 0.512V  1 bit =
0.25mV   0.015625mV");

  //Serial.println("ADC Range: +/- 6.144V (1 bit = 3mV/ADS1015,
0.1875mV/ADS1115)");

  // The ADC input range (or gain) can be changed via the following
  // functions, but be careful never to exceed VDD +0.3V max, or to
  // exceed the upper and lower limits if you adjust the input range!
  // Setting these values incorrectly may destroy your ADC!
  // ADS1015  ADS1115
  //                                                                ------
-  -------
  // ads.setGain(GAIN_TWOTHIRDS);  // 2/3x gain +/- 6.144V  1 bit =
3mV      0.1875mV (default)
  // ads.setGain(GAIN_ONE);        // 1x gain   +/- 4.096V  1 bit =
2mV      0.125mV
  // ads.setGain(GAIN_TWO);        // 2x gain   +/- 2.048V  1 bit =
1mV      0.0625mV
  // ads.setGain(GAIN_FOUR);       // 4x gain   +/- 1.024V  1 bit =
0.5mV    0.03125mV
   ads.setGain(GAIN_EIGHT);      // 8x gain   +/- 0.512V  1 bit =
0.25mV   0.015625mV
  // ads.setGain(GAIN_SIXTEEN);    // 16x gain  +/- 0.256V  1 bit =
0.125mV  0.0078125mV

  ads.begin();
```

```
  pinMode(A3, INPUT);
  pinMode(A2, INPUT);
}

void loop(void)
{

  //state 0 - wait to receive start
  if (state==0) {
      //check serial to see if starts
      if (Serial.available()) {
        String inString = Serial.readString();
        if(inString=="start"){
            time0 = millis();
            state=1;
          }
      }
    }

  if(state==1){
    //ready to start
    //val = digitalRead(2);
    //while(val==0){val = digitalRead(2);} //do nothing

    int16_t results;

    /* Be sure to update this value based on the IC and the gain settings!
*/
    //float   multiplier = 3.0F;    /* ADS1015 @ +/- 6.144V gain (12-bit
results) */
    //float multiplier = 0.1875F; /* ADS1115  @ +/- 6.144V gain (16-bit
results) */
    float multiplier = 0.015625F;

    results = ads.readADC_Differential_0_1();

    val = analogRead(A3);   // read the input pin
    valS = analogRead(A2);   // read the input pin
    //Serial.print("Differential: "); Serial.print(results);
Serial.print("("); Serial.print(results * multiplier);
Serial.println("mV)");
    Serial.print(millis()-time0);
    Serial.print(" ");
    Serial.print(results * multiplier);
    Serial.print(" ");
    Serial.print(val);
    Serial.print(" ");
    Serial.print(valS);
    Serial.print(" ");  Serial.println("");

    //delay(10);
  }

  /*val = analogRead(A3);   // read the input pin
  //Serial.println(val);
  if (abs(val-oldVal)>=247){
```

```
    Serial.print(millis()-time0); Serial.print("
");  Serial.print(val);Serial.print(" ");  Serial.println("2");
    oldVal=val;
    }*/
}
```

APPENDIX B. EMBEDDED FIRMWARE FOR CONTROLLER

This appendix contains the firmware code used to control the Omron BP710.

```
/* Pro Micro
*/

int RXLED = 17;  // The RX LED has a defined Arduino pin
// Note: The TX LED was not so lucky, we'll need to use pre-defined
// macros (TXLED1, TXLED0) to control that.
// (We could use the same macros for the RX LED too -- RXLED1,
//  and RXLED0.)
int incomingByte = 0;
String incomingString="";
unsigned long previousMillis = 0;        // will store last time LED was
updated
unsigned long previousMillisTag = 0;        // will store last time LED was
updated
long period = 500;           // interval at which to blink (milliseconds)
long width=5;
int solenoidEnable=0;
int solState = LOW;
int state=0;
int stateTag=0;

void setup()
{
  pinMode(RXLED, OUTPUT);  // Set RX LED as an output
  // TX LED is set as an output behind the scenes

  Serial.begin(9600); //This pipes to the serial monitor
  Serial.println("Initialize Serial Monitor");

  //Serial1.begin(9600); //This is the UART, pipes to sensors attached to
board
  //Serial1.println("Initialize Serial Hardware UART Pins");

  //TXLED0;digitalWrite(RXLED, LOW);
}

void loop()
{
  unsigned long currentMillis = millis();
  unsigned long currentMillisTag = millis();

  if(state==0 && currentMillis - previousMillis <= width){
    state=1;
    solState=LOW;
  }
  if(state==1 && currentMillis - previousMillis >= width){
    state=2;
    solState=HIGH;
  }
  if(state==2 && currentMillis - previousMillis >= period){
    state=0;
    previousMillis=currentMillis;
```

```
  }

  if(solenoidEnable==1){
    digitalWrite(6, solState);
  }

  // TAG signal
  if(stateTag==0 && currentMillisTag - previousMillisTag <= 5000){
    stateTag=1;
    digitalWrite(8, LOW);
  }
  if(stateTag==1 && currentMillisTag - previousMillisTag >= 5000){
    stateTag=2;
    digitalWrite(8, HIGH);
  }
  if(stateTag==2 && currentMillisTag - previousMillisTag >= 5050){
    stateTag=0;
    previousMillisTag=currentMillisTag;
  }



  //Serial.println("Hello world!");  // Print "Hello World" to the Serial
Monitor
  //Serial1.println("Hello! Can anybody hear me?");  // Print "Hello!" over
hardware UART

  //digitalWrite(RXLED, LOW);   // set the RX LED ON
  //TXLED0; //TX LED is not tied to a normally controlled pin so a macro is
needed, turn LED OFF
  //delay(1000);              // wait for a second

  //digitalWrite(RXLED, HIGH);    // set the RX LED OFF
  //TXLED1; //TX LED macro to turn LED ON
  //delay(1000);              // wait for a second

  //analogWrite(5, 125);

  if (Serial.available() > 0) {
      digitalWrite(RXLED, HIGH);
      //delay(500);
      incomingString = Serial.readStringUntil('\n'); //read incoming data
      String command=incomingString.substring(0,1);
      int
PWM1=(incomingString.substring(1,incomingString.length())).toInt();
      if(PWM1>=255) PWM1=255; //limit the max


      if(command=="M"){
        Serial.print(command); //print data
        Serial.println(PWM1); //print data
        analogWrite(5, PWM1);
      }
      else if(command=="S"){
        Serial.print(command); //print data
        Serial.println(PWM1); //print data
        //analogWrite(6, PWM1);
```

```
          if(PWM1==0){
            solenoidEnable=0;
          }
          else{
            solenoidEnable=1;
            //interval=PWM1;
          }
        }
        else if(command=="X"){
          Serial.print(command); //print data
          Serial.println(PWM1); //print data
          analogWrite(6, PWM1);
        }
        else if(command=="W"){
          Serial.print(command); //print data
          Serial.println(PWM1); //print data
          width=PWM1;
        }
        else if(command=="P"){
          Serial.print(command); //print data
          Serial.println(PWM1); //print data
          period=PWM1;
        }
        else{
          Serial.print("command not recognized - ");
          Serial.println(incomingString);
          }
        digitalWrite(RXLED, LOW);
 }

}
```

APPENDIX C. CONTROL AND ANALYSIS SOFTWARE CODE

This appendix includes a summary of the key Matlab routines to extract and analyze the BP signals.

Measuring Protocol - BPprotocol1_4_21.m

```
clear all;
close all;
global handles;
handles.stop=0;
handles.data1=0;
handles.data3=0;
handles.count1=0;
handles.count2=0;
handles.count3=0;
handles.exitF=0;

%user ID
prompt= 'ID#:';
id=input(prompt,'s');

% PRESSURE SENSOR - arduino
handles.s_s = serialport ("COM4",9600);
configureCallback(handles.s_s,"terminator",@readSerialData1);
pause(3);%required to work with Arduino - check if this one can be removed

% CONTROLLER - Pro Mini
handles.s_c = serialport ("COM18",9600);
configureCallback(handles.s_c,"terminator",@readSerialData2);
pause(3);%required to work with Arduino

% PPG - Nano with PPG
handles.s_p = serialport ("COM16",9600);
configureCallback(handles.s_p,"terminator",@readSerialData3);
pause(3);%required to work with Arduino

% CONTINUOUS PLOT
handles.time=0;
handles.data=0;
handles.h_fig=figure2;
set(handles.h_fig,'KeyPressFcn',@myfun);
handles.plotGraph = plot(handles.time,handles.data,'-r' );  % every
AnalogRead needs to be on its own Plotgraph
plotGrid = 'on';                    % 'off' to turn off grid
grid(plotGrid);
tic
handles.count=0;

% AUDIO setup
recObj1=audiorecorder(8000,8,1,1);

%start geting samples from the BP sensor
write(handles.s_s, 'start', 'string');  % sensor START
```

```
write(handles.s_p, 'start', 'string');  % PPG    START
record(recObj1);                        % AUDIO  START

% while(~isfield(handles, 'data1'))
%     %do nothing and wait
% end
pause(1);

% TIMER to plot every x milliseconds the samples stored in the buffer
handles.t = timer('StartDelay', 3, 'Period', 0.01, ...
          'ExecutionMode', 'fixedRate', 'TimerFcn',@my_callback_fcn);
start(handles.t);


% PROCEDURE START ---------------------------------

%power the motor
writeline(handles.s_c, "M255");
%close the solenoid
writeline(handles.s_c, "X255");


%wait until certain value of built up pressure
pause(0.02);
tic
while(handles.data1(end,2)<30 && toc<5)
    %do nothing and wait | timeout can get you out
    pause(0.02);
end

% %release - solenoid
%
% writeline(handles.s_c, "W50");      %width of PWM
% writeline(handles.s_c, "P4000");    %period of PWM
% %enables solenoid control custom PWM
% writeline(handles.s_c, "S1");
% % ------ end release solenoid ----------
%
% writeline(handles.s_c, "M0");
% tic
% while(handles.data1(end,2)>3 && toc<3)
%     %do nothing and wait | timeout can get you out
%     pause(0.01);
% end
%
% % close solenoid
% writeline(handles.s_c, "S0");
% writeline(handles.s_c, "X255");
% % ----- end of release of solenoid

%ramp
tic
speedx=[];
initSpeed=70;
speedFactor=1;
topPressureStop=160;
stateTime=0;
```

```
%was 60
while(toc<45 && handles.data1(end,2)<topPressureStop && handles.exitF==0)
    f=50;
    speed=initSpeed+toc*speedFactor;

    %timing going up
    if (stateTime==0 && handles.data1(end,2)>40)
        stateTime=1;
        t60up=toc;
    end
    %disp(['speed=' num2str(ceil(speed))]);
    %speedx=[ speedx ; num2str(ceil(speed))];
    %do nothing and wait | timeout can get you out
    writeline(handles.s_c, strcat("M",num2str(ceil(speed))));
    pause(0.01);
end

t160up=toc;

% release at fixed slope
writeline(handles.s_c, "M0");
tic
while(handles.data1(end,2)>40 && toc<30 && handles.exitF==0)

    %timing going up
    if (stateTime==1 && handles.data1(end,2)<40)
        stateTime=1;
        t60down=toc;
    end

    %do nothing and wait | timeout can get you out
    pause(0.01);
end
t60down2=toc;

% solenoid full release
writeline(handles.s_c, "X0");

% ------ end OF PROTOCOL -
% ---   record the tail in the plot
tic
while(toc<5 && handles.exitF==0)
    %do nothing and wait | timeout can get you out
    pause(0.01);
end

% END of PROCEDURE --------------------------------



disp("done ..");
%stop motor and open solenoid
writeline(handles.s_c, "M0");
writeline(handles.s_c, "X0");
% stop sensing built up pressure
handles.stop=1;     % STOP sensors
```

```
stop(recObj1);      % STOP AUDIO
stop(handles.t);    % STOP plotting

delete(handles.t);

audioSignal1 = getaudiodata(recObj1);
sensor1= handles.data1(:, 1:2);

% FIGURES -------------------------------

% FIGURE 1
figure2
subplot(311)
hold on
yyaxis left
plot(handles.data1(:,1), handles.data1(:,2), 'r');
yyaxis right
plot(handles.data1(:,1), handles.data1(:,3), 'k');
subplot(312)
plot(audioSignal1);
subplot(313)
hold on
yyaxis left
plot(handles.data3(:,1), -1*handles.data3(:,2), 'b');
yyaxis right
plot(handles.data3(:,1), handles.data3(:,3), 'k');

% FIGURE 2
t2=max(handles.data1(:,1));
t1=0;
shift=-20;
t=linspace(t1-shift, t2-shift, length(audioSignal1));

tPPG=linspace(t1,max(handles.data1(:,1)) , length(handles.data3(:,1)));
figure2
hold on
plot(handles.data1(:,1), handles.data1(:,2), 'r');
plot(t,audioSignal1*100, 'Color', '#7E2F8E');
yyaxis right
%plot(handles.data3(:,1), -1*handles.data3(:,2), 'b');
plot(tPPG, -1*handles.data3(:,2), 'b');
legend('pressure','audio', 'ppg');
grid minor



figure2
plot(handles.data3(:,1), -1*handles.data3(:,2), 'b');

figure2
hold on
yyaxis left
plot(handles.data1(:,1), handles.data1(:,2), 'r');
yyaxis right
plot(handles.data3(:,1), -1*handles.data3(:,2), 'b');
hold off
```

```
save (['workspaceBPSensor ' datestr(now,'mm-dd-yyyy HH-MM') 'ID#' id
'.mat']);

% figure
% hold on
% plot(handles.data1(:,1), handles.data1(:,2));
% ylabel('OhmronP')
% xlabel("Time [ms]");
% hold off

%% callback functions %%%%%%%%%%%%%%%%%%%%%%%%%%%%

function readSerialData1(src,~)
   global handles

   if handles.count1==0
       handles.count1=1;
       handles.data1 = str2num(readline(src));
   else
       handles.count1=handles.count1+1;
       %yt=slope*xt+29;
       handles.data1 = [handles.data1;str2num(readline(src))*9+29];
   end

   if handles.stop==1
       configureCallback(handles.s_s,"off");
   end
end

function readSerialData2(src,~)
   global handles

   if handles.count2==0
       handles.count2=1;
       %handles.data2 = str2num(readline(src));
   else
       handles.count2=handles.count2+1;
       %handles.data2 = [handles.data2;str2num(readline(src))];
   end

   if handles.stop==1
       configureCallback(handles.s_c,"off");
   end
end

function readSerialData3(src,~)
   global handles

   if handles.count3==0
       handles.count3=1;
       handles.data3 = str2num(readline(src));
   else
       handles.count3=handles.count3+1;
       handles.data3 = [handles.data3;str2num(readline(src))];
   end

   if handles.stop==1
```

```
        configureCallback(handles.s_p,"off");
    end
end

function my_callback_fcn(obj, event)
    global handles

    %handles.dat = 30*rand(); %Data from the arduino
    handles.count = handles.count + 1;
%     handles.time(handles.count) = handles.data1(handles.count);
%     handles.data(handles.count) = handles.data1(handles.count, 2);
%     set(handles.plotGraph,'XData',handles.time,'YData',handles.data);

set(handles.plotGraph,'XData',handles.data1(:,1),'YData',handles.data1(:,2))
;
    axis([0 handles.data1(end,1) 0 200]);
end

function myfun(src,event)
    global handles
    keyPressed = event.Key;
    disp(keyPressed);

    if strcmpi(keyPressed,'escape')
        handles.exitF=1;
    end
end
```

Signal processing routine

```
close all
clear all

% load workspace
%[filename,path] = uigetfile('*.mat');

filename='workspaceBPSensor 01-13-2021 10-53ID#1.mat';
load(filename)

%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%% DEFLATIONARY %%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

pressure=handles.data1(:,2);

t_p=handles.data1(:,1);

figure
hold on
%plot(t_p, pressure, 'r');
grid minor

[ymax,xmax]=max(pressure);
ip1=250;
```

```
ip2=xmax;    %index sample of the presssure

%temp=find(t_p>P2);  ip2=temp(1);
t_p_section=t_p(ip1:ip2);
plot(t_p_section,pressure(ip1:ip2));

pressureSection=pressure(ip1:ip2);
pressure2=detrend(pressureSection);
pressure3=highpass(pressure2,1, 111);

%polyfit for detrending
p = polyfit(t_p_section,pressureSection,7);
linearTrend = polyval(p,t_p_section);

pressure2=pressureSection-linearTrend;

figure
plot(t_p_section, pressure2)

figure
plot(t_p_section,pressure3)


%FFT for P wave

signal=pressure2;

%plot and select bin
S = fftshift(fft(signal));
plot(abs(S));
%zoom xon
%zoom(5);
title('input spectrum - select cutoff');

%[x,y] = ginput(1);
%N_clear=x(1);

N_clear=321.4286;

% Remove the calls to fftshift, if you want to delete the lower frequency
components
S = fftshift(fft(signal));
S_cleared = S;
S_cleared(1:N_clear) = 0;
S_cleared(end-N_clear+2:end) = 0;
S_cleared = fftshift(S_cleared);

signal_cleared = ifft(S_cleared,'symmetric');

%%AUDIO FFT

figure
hold on
xline(t_p(ip2))     %max of pressure
plot(t_p, pressure)
t_a=linspace(t1-8250, max(handles.data1(:,1)), length(audioSignal1));
%plot(t_a, audioSignal1*100-50)
```

```
%[xz,yz]=ginput(1)
%xline(xz)
temp=find(t_a>t_p(ip2));  ia2=temp(1);
temp=find(t_a>t_p(ip1));  ia1=temp(1);
plot(t_a(ia1:ia2), audioSignal1(ia1:ia2)*100-50)

%FFT for A wave

signal=audioSignal1(ia1:ia2)*100;
figure
%plot and select bin
S = fftshift(fft(signal));
plot(abs(S));
zoom xon
zoom(5);
title('input spectrum - select cutoff');

%[x,y] = ginput(1);
%N_clear=x(1);
N_clear=64290.3225806452;

% Remove the calls to fftshift, if you want to delete the lower frequency
components
S = fftshift(fft(signal));
S_cleared = S;
S_cleared(1:N_clear) = 0;
S_cleared(end-N_clear+2:end) = 0;
S_cleared = fftshift(S_cleared);

[pk_p_inflat,ik_p_inflat] = findpeaks(signal_cleared, 'MinPeakDistance',30);
[pk_p_inflat_inv,ik_p_inflat_inv] = findpeaks(-signal_cleared,
'MinPeakDistance',30);
h=figure;
subplot(221)
hold on
diff=pk_p_inflat+pk_p_inflat_inv;
%t=linspace(1, length(signal_cleared), length(ik_p_inflat));
%t_trend=linearTrend(round(t));
t_trend=linearTrend(ik_p_inflat);   % more correct

plot(linearTrend, signal_cleared);
plot(linearTrend(ik_p_inflat), pk_p_inflat)
plot(linearTrend(ik_p_inflat_inv), -pk_p_inflat_inv)
plot(t_trend, diff, 'LineWidth', 3);
[ymax, xmax]=max(diff);
plot(t_trend(xmax), ymax, 'xr','LineWidth', 3);

%polyfit difference between upper envelope and lower envelope
pT = polyfit(ik_p_inflat,pk_p_inflat,7);
lineTOP = polyval(pT,ik_p_inflat);
plot(t_trend,lineTOP,'LineWidth', 3);

pB = polyfit(ik_p_inflat_inv,pk_p_inflat_inv,7);
lineBTTM = polyval(pB,ik_p_inflat_inv);
plot(t_trend,-lineBTTM,'LineWidth', 3);

diffPolyFit=lineTOP+lineBTTM;
```

```
plot(t_trend, diffPolyFit, 'LineWidth', 3);
[ymax, xmax]=max(diffPolyFit);
plot(t_trend(xmax), ymax, 'xr','LineWidth', 3);
grid minor
xlabel('DC[mmHg]');
title('Pressure Inflationary');

%% AUDIO

signal_cleared = ifft(S_cleared,'symmetric');
audioSection=detrend(signal_cleared, 10);
%plot(audioSection);

%polyfit for detrending and oversampling to match audio sampling
stepOverSample=(max(t_p_section)-min(t_p_section))/length(audioSection);
t_p_sectionOverSampled=min(t_p_section):stepOverSample:max(t_p_section)-
stepOverSample;
linearTrendOverSampled = polyval(p,t_p_sectionOverSampled);

[pk_a_inflat,ik_a_inflat] = findpeaks(audioSection, 'MinPeakDistance',5000);
[pk_a_inflat_inv,ik_a_inflat_inv] = findpeaks(-audioSection,
'MinPeakDistance',5000);
%figure
%hold on
diff=pk_a_inflat+pk_a_inflat_inv;
t_a_trend=linearTrendOverSampled(ik_a_inflat);   % more correct

subplot(223)
hold on
plot(linearTrendOverSampled, audioSection);
plot(linearTrendOverSampled(ik_a_inflat), pk_a_inflat)
plot(linearTrendOverSampled(ik_a_inflat_inv), -pk_a_inflat_inv)
plot(t_a_trend, diff, 'LineWidth', 3);
[ymax, xmax]=max(diff);
plot(t_a_trend(xmax), ymax, 'xr','LineWidth', 3);

%polytfit
aT = polyfit(ik_a_inflat,pk_a_inflat,7);
lineTOP_a = polyval(aT,ik_a_inflat);
plot(t_a_trend,lineTOP_a,'LineWidth', 3);

aB = polyfit(ik_a_inflat_inv,pk_a_inflat_inv,7);
lineBTTM_a = polyval(aB,ik_a_inflat_inv);
plot(t_a_trend,-lineBTTM_a,'LineWidth', 3);

diffPolyFit_a=lineTOP_a+lineBTTM_a;
plot(t_a_trend, diffPolyFit_a, 'LineWidth', 3);
[ymax, xmax]=max(diffPolyFit_a);
plot(t_a_trend(xmax), ymax, 'xr','LineWidth', 3);
grid minor
xlabel('DC[mmHg]');
title('Audio Inflationary');

%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%% DEFLATIONARY %%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

```
pressure=handles.data1(:,2);

t_p=handles.data1(:,1);

figure
hold on
%plot(t_p, pressure, 'r');
grid minor

[ymax,xmax]=max(pressure);
ip1=xmax+2;
ip2=length(pressure)-380;    %index sample of the presssure

%temp=find(t_p>P2);  ip2=temp(1);
t_p_section=t_p(ip1:ip2);
plot(t_p_section,pressure(ip1:ip2));

pressureSection=pressure(ip1:ip2);
pressure2=detrend(pressureSection);
pressure3=highpass(pressure2,1, 111);

%polyfit for detrending
p = polyfit(t_p_section,pressureSection,7);
linearTrend = polyval(p,t_p_section);

pressure2=pressureSection-linearTrend;

figure
plot(t_p_section, pressure2)

%not so good results
% figure
% plot(t_p_section,pressure3)

%FFT for P wave ----------------------------------------
% not needed on the deflationary

signal_cleared_p = pressure2

figure
plot(signal_cleared_p)

%%AUDIO FFT

figure
hold on
xline(t_p(ip2))     %max of pressure
plot(t_p, pressure)
t_a=linspace(t1-8250, max(handles.data1(:,1)), length(audioSignal1));
%plot(t_a, audioSignal1*100-50)
%[xz,yz]=ginput(1)
%xline(xz)
temp=find(t_a>t_p(ip2));  ia2=temp(1);
temp=find(t_a>t_p(ip1));  ia1=temp(1);
plot(t_a(ia1:ia2), audioSignal1(ia1:ia2)*100-50)
```

```
%FFT for A wave
%not neeeded in the deflationary

signal_cleared_a=audioSignal1(ia1:ia2)*100;

%END of FFT AUDIO ----------------------------------

%%% PLOT P subplot DEFLATIONARY

[pk_p_inflat,ik_p_inflat] = findpeaks(signal_cleared_p,
'MinPeakDistance',30);
[pk_p_inflat_inv,ik_p_inflat_inv] = findpeaks(-signal_cleared_p,
'MinPeakDistance',30);
set(0,'CurrentFigure',h)
subplot(222)
hold on
diff=pk_p_inflat+pk_p_inflat_inv;
%t=linspace(1, length(signal_cleared), length(ik_p_inflat));
%t_trend=linearTrend(round(t));
t_trend=linearTrend(ik_p_inflat);   % more correct

plot(linearTrend, signal_cleared_p);
plot(linearTrend(ik_p_inflat), pk_p_inflat)
plot(linearTrend(ik_p_inflat_inv), -pk_p_inflat_inv)
plot(t_trend, diff, 'LineWidth', 3);
[ymax, xmax]=max(diff);
plot(t_trend(xmax), ymax, 'xr','LineWidth', 3);

%polyfit difference between upper envelope and lower envelope
pT = polyfit(ik_p_inflat,pk_p_inflat,7);
lineTOP = polyval(pT,ik_p_inflat);
plot(t_trend,lineTOP,'LineWidth', 3);

pB = polyfit(ik_p_inflat_inv,pk_p_inflat_inv,7);
lineBTTM = polyval(pB,ik_p_inflat_inv);
plot(t_trend,-lineBTTM,'LineWidth', 3);

diffPolyFit=lineTOP+lineBTTM;
plot(t_trend, diffPolyFit, 'LineWidth', 3);
[ymax, xmax]=max(diffPolyFit);
plot(t_trend(xmax), ymax, 'xr','LineWidth', 3);
grid minor
xlabel('DC[mmHg]');
title('Pressure deflationary');

%% AUDIO

audioSection=detrend(signal_cleared_a, 10);
%plot(audioSection);

%polyfit for detrending and oversampling to match audio sampling
stepOverSample=(max(t_p_section)-min(t_p_section))/length(audioSection);
t_p_sectionOverSampled=min(t_p_section):stepOverSample:max(t_p_section)-
stepOverSample;
linearTrendOverSampled = polyval(p,t_p_sectionOverSampled);
```

```
[pk_a_inflat,ik_a_inflat] = findpeaks(audioSection, 'MinPeakDistance',5000);
[pk_a_inflat_inv,ik_a_inflat_inv] = findpeaks(-audioSection,
'MinPeakDistance',5000);
%figure
%hold on
diff=pk_a_inflat+pk_a_inflat_inv;
t_a_trend=linearTrendOverSampled(ik_a_inflat);    % more correct

subplot(224)
hold on
plot(linearTrendOverSampled, audioSection);
plot(linearTrendOverSampled(ik_a_inflat), pk_a_inflat)
plot(linearTrendOverSampled(ik_a_inflat_inv), -pk_a_inflat_inv)
plot(t_a_trend, diff, 'LineWidth', 3);
[ymax, xmax]=max(diff);
plot(t_a_trend(xmax), ymax, 'xr','LineWidth', 3);

%polytfit
aT = polyfit(ik_a_inflat,pk_a_inflat,7);
lineTOP_a = polyval(aT,ik_a_inflat);
plot(t_a_trend,lineTOP_a,'LineWidth', 3);

aB = polyfit(ik_a_inflat_inv,pk_a_inflat_inv,7);
lineBTTM_a = polyval(aB,ik_a_inflat_inv);
plot(t_a_trend,-lineBTTM_a,'LineWidth', 3);

diffPolyFit_a=lineTOP_a+lineBTTM_a;
plot(t_a_trend, diffPolyFit_a, 'LineWidth', 3);
[ymax, xmax]=max(diffPolyFit_a);
plot(t_a_trend(xmax), ymax, 'xr','LineWidth', 3);
grid minor
xlabel('DC[mmHg]');
title('Audio deflationary');
```

Auscultatory analysis –

selectPwaveAndAudioSubplotComboDeflationaryAndInflationaryGen.m

```
close all
clear all

% load workspace
[filename,path] = uigetfile('*.mat');

%filename='workspaceBPSensor 01-13-2021 10-53ID#1.mat';

filex = fullfile(path, filename);
load(filex)

%global variables

pPeakDist=35;
audioPeakDist=6000;     %6000
minProm=0.5;
```

```
minPromA=5;
minPromA_deflat=8;

%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%% INFLATIONARY %%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

pressure=handles.data1(:,2);

t_p=handles.data1(:,1);

figure
hold on
%plot(t_p, pressure, 'r');
grid minor

[ymax,xmax]=max(pressure);
ip1=250;
ip2=xmax;    %index sample of the presssure

%temp=find(t_p>P2);  ip2=temp(1);
t_p_section=t_p(ip1:ip2);
plot(t_p_section,pressure(ip1:ip2));

pressureSection=pressure(ip1:ip2);
pressure2=detrend(pressureSection);
pressure3=highpass(pressure2,1, 111);

%polyfit for detrending
p = polyfit(t_p_section,pressureSection,7);
linearTrend = polyval(p,t_p_section);

pressure2=pressureSection-linearTrend;

figure
plot(t_p_section, pressure2)

figure
plot(t_p_section,pressure3)


%FFT for P wave

signal=pressure2;

%plot and select bin
S = fftshift(fft(signal));
plot(abs(S));
%zoom xon
%zoom(5);
title('input spectrum - select cutoff');

[x,y] = ginput(1);
N_clear=x(1);

%N_clear=321.4286;
```

```
% Remove the calls to fftshift, if you want to delete the lower frequency
components
S = fftshift(fft(signal));
S_cleared = S;
S_cleared(1:N_clear) = 0;
S_cleared(end-N_clear+2:end) = 0;
S_cleared = fftshift(S_cleared);

signal_cleared = ifft(S_cleared,'symmetric');
signal_cleared=highpass(signal_cleared, 0.045); %eliminate the trend

%%AUDIO FFT

h1=figure
hold on
xline(t_p(ip2))     %max of pressure
plot(t_p, pressure)
t_a=linspace(t1-8250, max(handles.data1(:,1)), length(audioSignal1));
%plot(t_a, audioSignal1*100-50)
%[xz,yz]=ginput(1)
%xline(xz)
temp=find(t_a>t_p(ip2));  ia2=temp(1);
temp=find(t_a>t_p(ip1));  ia1=temp(1);
plot(t_a(ia1:ia2), audioSignal1(ia1:ia2)*100-50)

%FFT for A wave

signal=audioSignal1(ia1:ia2)*100;
figure
%plot and select bin
S = fftshift(fft(signal));
plot(abs(S));
zoom xon
zoom(5);
title('input spectrum - select cutoff');

[x,y] = ginput(1);
N_clear=x(1);
%N_clear=64290.3225806452;

% Remove the calls to fftshift, if you want to delete the lower frequency
components
S = fftshift(fft(signal));
S_cleared = S;
S_cleared(1:N_clear) = 0;
S_cleared(end-N_clear+2:end) = 0;
S_cleared = fftshift(S_cleared);

%pressure inflationary

[pk_p_inflat,ik_p_inflat] = findpeaks(signal_cleared,
'MinPeakDistance',pPeakDist, 'MinPeakProminence',minProm);    %30
[pk_p_inflat_inv,ik_p_inflat_inv] = findpeaks(-signal_cleared,
'MinPeakDistance',pPeakDist,'MinPeakProminence',minProm);
while(length(pk_p_inflat)>length(pk_p_inflat_inv))
    pk_p_inflat_inv=[pk_p_inflat_inv;pk_p_inflat_inv(end)];
```

```
    ik_p_inflat_inv=[ik_p_inflat_inv;ik_p_inflat_inv(end)];
end
while (length(pk_p_inflat)<length(pk_p_inflat_inv))
    pk_p_inflat=[pk_p_inflat; pk_p_inflat(end)];
    ik_p_inflat=[ik_p_inflat; ik_p_inflat(end)];
end

h=figure;
subplot(221)
hold on
diff_inflat=pk_p_inflat+pk_p_inflat_inv;
%t=linspace(1, length(signal_cleared), length(ik_p_inflat));
%t_trend=linearTrend(round(t));
t_trend=linearTrend(ik_p_inflat);   % more correct

plot(linearTrend, signal_cleared);
plot(linearTrend(ik_p_inflat), pk_p_inflat)
plot(linearTrend(ik_p_inflat_inv), -pk_p_inflat_inv)
plot(t_trend, diff_inflat, 'LineWidth', 3);
[ymax_p_inflat, xmax_p_inflat]=max(diff_inflat);
plot(t_trend(xmax_p_inflat), ymax_p_inflat, 'xr','LineWidth', 3);

%polyfit difference between upper envelope and lower envelope
pT_inflat = polyfit(ik_p_inflat,pk_p_inflat,7);
lineTOP_pinf = polyval(pT_inflat,ik_p_inflat);
plot(t_trend,lineTOP_pinf,'LineWidth', 3);

pB_inflat = polyfit(ik_p_inflat_inv,pk_p_inflat_inv,7);
lineBTTM_pinf = polyval(pB_inflat,ik_p_inflat_inv);
plot(t_trend,-lineBTTM_pinf,'LineWidth', 3);

diffPolyFit_pinf=lineTOP_pinf+lineBTTM_pinf;
plot(t_trend, diffPolyFit_pinf, 'LineWidth', 3);
[ymax_p_inflat, xmax_p_inflat]=max(diffPolyFit_pinf);
plot(t_trend(xmax_p_inflat), ymax_p_inflat, 'xr','LineWidth', 3);
grid minor
xlabel('DC[mmHg]');
title('Pressure Inflationary');


%super titel figure
outPath=regexp(path,'\','split');
sgtitle(outPath{end-1})

%% AUDIO INFLATIONARY

signal_cleared = ifft(S_cleared,'symmetric');
audioSection=detrend(signal_cleared, 10);
set(0,'CurrentFigure',h1)
plot(t_a(ia1:ia2),audioSection*10)
set(0,'CurrentFigure',h)
%plot(audioSection);

%polyfit for detrending and oversampling to match audio sampling
stepOverSample=(max(t_p_section)-min(t_p_section))/length(audioSection);
t_p_sectionOverSampled=min(t_p_section):stepOverSample:max(t_p_section)-
stepOverSample;
```

```
linearTrendOverSampled = polyval(p,t_p_sectionOverSampled);


[pk_a_inflat,ik_a_inflat] = findpeaks(audioSection,
'MinPeakDistance',audioPeakDist,'MinPeakProminence',minPromA);     %5000
[pk_a_inflat_inv,ik_a_inflat_inv] = findpeaks(-audioSection,
'MinPeakDistance',audioPeakDist,'MinPeakProminence',minPromA);

%reshape vectors with peaks if they have different size
while(length(pk_a_inflat)>length(pk_a_inflat_inv))
    pk_a_inflat_inv=[pk_a_inflat_inv;pk_a_inflat_inv(end)];
    ik_a_inflat_inv=[ik_a_inflat_inv;ik_a_inflat_inv(end)];
end
while (length(pk_a_inflat)<length(pk_a_inflat_inv))
    pk_a_inflat=[pk_a_inflat; pk_a_inflat(end)];
    ik_a_inflat=[ik_a_inflat; ik_a_inflat(end)];
end
%do nothing if they are the same size
%pause(1);
diff_a_inflat=pk_a_inflat+pk_a_inflat_inv;
t_a_trend_inflat=linearTrendOverSampled(ik_a_inflat);   % more correct

subplot(223)
hold on
plot(linearTrendOverSampled, audioSection);
plot(linearTrendOverSampled(ik_a_inflat), pk_a_inflat)
plot(linearTrendOverSampled(ik_a_inflat_inv), -pk_a_inflat_inv)
plot(t_a_trend_inflat, diff_a_inflat, 'LineWidth', 3);
[ymax_a_inflat, xmax_a_inflat]=max(diff_a_inflat);
plot(t_a_trend_inflat(xmax_a_inflat), ymax_a_inflat, 'xr','LineWidth', 3);

%polytfit
aT_inflat = polyfit(ik_a_inflat,pk_a_inflat,7);
lineTOP_ainf = polyval(aT_inflat,ik_a_inflat);
plot(t_a_trend_inflat,lineTOP_ainf,'LineWidth', 3);

aB_inflat = polyfit(ik_a_inflat_inv,pk_a_inflat_inv,7);
lineBTTM_ainf = polyval(aB_inflat,ik_a_inflat_inv);
plot(t_a_trend_inflat,-lineBTTM_ainf,'LineWidth', 3);

diffPolyFit_ainf=lineTOP_ainf+lineBTTM_ainf;
plot(t_a_trend_inflat, diffPolyFit_ainf, 'LineWidth', 3);
[ymax_a_inflat, xmax_a_inflat]=max(diffPolyFit_ainf);
plot(t_a_trend_inflat(xmax_a_inflat), ymax_a_inflat, 'xr','LineWidth', 3);
grid minor
xlabel('DC[mmHg]');
title('Audio Inflationary');

AWEinf=polyfit(t_a_trend_inflat,diffPolyFit_ainf',7);
PPWEinf=polyfit(t_trend,diffPolyFit_pinf,7);

%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%% DEFLATIONARY %%%%%%%%%%%%%%%%%%%%%%%%
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%
```

```
pressure=handles.data1(:,2);

t_p=handles.data1(:,1);

figure
hold on
%plot(t_p, pressure, 'r');
grid minor

[ymax,xmax]=max(pressure);
ip1=xmax+2;
ip2=length(pressure)-265;    %index sample of the presssure

%temp=find(t_p>P2);  ip2=temp(1);
t_p_section=t_p(ip1:ip2);
plot(t_p_section,pressure(ip1:ip2));

pressureSection=pressure(ip1:ip2);
pressure2=detrend(pressureSection);
pressure3=highpass(pressure2,1, 111);

%polyfit for detrending
p = polyfit(t_p_section,pressureSection,7);
linearTrend = polyval(p,t_p_section);

pressure2=pressureSection-linearTrend;

figure
plot(t_p_section, pressure2)

%not so good results
% figure
% plot(t_p_section,pressure3)

%FFT for P wave ----------------------------------------
% not needed on the deflationary

signal_cleared_p = pressure2;
%signal_cleared_p=highpass(signal_cleared_p, 0.045); %eliminate the trend

figure
plot(signal_cleared_p)

%%AUDIO FFT

%plot signals in time WITHOUT much processing -----
set(0,'CurrentFigure',h1)
hold on
xline(t_p(ip2))     %end of pressure
plot(t_p, pressure)
t_a=linspace(t1-8250, max(handles.data1(:,1)), length(audioSignal1));
%plot(t_a, audioSignal1*100-50)
%[xz,yz]=ginput(1)
%xline(xz)
temp=find(t_a>t_p(ip2));  ia2=temp(1);
temp=find(t_a>t_p(ip1));  ia1=temp(1);
plot(t_a(ia1:ia2), audioSignal1(ia1:ia2)*200)
```

```
grid minor
tPPG=linspace(t1,max(handles.data1(:,1)) , length(handles.data3(:,1)));
yyaxis right
plot(tPPG, -1*handles.data3(:,2), 'b');

%FFT for A wave
%not neeeded in the deflationary

signal_cleared_a=audioSignal1(ia1:ia2)*100;

%END of FFT AUDIO ----------------------------------

%%% PLOT P subplot DEFLATIONARY

[pk_p_inflat,ik_p_inflat] = findpeaks(signal_cleared_p,
'MinPeakDistance',pPeakDist,'MinPeakProminence',minProm); %30
[pk_p_inflat_inv,ik_p_inflat_inv] = findpeaks(-signal_cleared_p,
'MinPeakDistance',pPeakDist, 'MinPeakProminence',minProm);
while(length(pk_p_inflat)>length(pk_p_inflat_inv))
    pk_p_inflat_inv=[pk_p_inflat_inv;-pk_p_inflat(end)];
    ik_p_inflat_inv=[ik_p_inflat_inv;ik_p_inflat(end)];
end
while (length(pk_p_inflat)<length(pk_p_inflat_inv))
    pk_p_inflat=[pk_p_inflat; -pk_p_inflat_inv(end)];
    ik_p_inflat=[ik_p_inflat; ik_p_inflat_inv(end)];
end

set(0,'CurrentFigure',h)
subplot(222)
hold on
diff=pk_p_inflat+pk_p_inflat_inv;
%t=linspace(1, length(signal_cleared), length(ik_p_inflat));
%t_trend=linearTrend(round(t));
t_trend=linearTrend(ik_p_inflat);   % more correct

plot(linearTrend, signal_cleared_p);
plot(linearTrend(ik_p_inflat), pk_p_inflat)
plot(linearTrend(ik_p_inflat_inv), -pk_p_inflat_inv)
plot(t_trend, diff, 'LineWidth', 3);
[ymax_p_inflat, xmax_p_inflat]=max(diff);
plot(t_trend(xmax_p_inflat), ymax_p_inflat, 'xr','LineWidth', 3);

%polyfit difference between upper envelope and lower envelope
pT = polyfit(ik_p_inflat,pk_p_inflat,7);
lineTOP_pdef = polyval(pT,ik_p_inflat);
plot(t_trend,lineTOP_pdef,'LineWidth', 3);

pB = polyfit(ik_p_inflat_inv,pk_p_inflat_inv,7);
lineBTTM_pdef = polyval(pB,ik_p_inflat_inv);
plot(t_trend,-lineBTTM_pdef,'LineWidth', 3);

diffPolyFit_pdef=lineTOP_pdef+lineBTTM_pdef;
plot(t_trend, diffPolyFit_pdef, 'LineWidth', 3);
[ymax, xmax]=max(diffPolyFit_pdef);
plot(t_trend(xmax), ymax, 'xr','LineWidth', 3);
grid minor
xlabel('DC[mmHg]');
```

```
title('Pressure deflationary');

%% AUDIO DEFLATIONARY

audioSection=detrend(signal_cleared_a, 10);
%plot(audioSection);

%polyfit for detrending and oversampling to match audio sampling
stepOverSample=(max(t_p_section)-min(t_p_section))/length(audioSection);
t_p_sectionOverSampled=min(t_p_section):stepOverSample:max(t_p_section)-
stepOverSample;
linearTrendOverSampled = polyval(p,t_p_sectionOverSampled);

[pk_a_deflat,ik_a_deflat] = findpeaks(audioSection,
'MinPeakDistance',audioPeakDist,'MinPeakProminence',minPromA_deflat); %5000
[pk_a_deflat_inv,ik_a_deflat_inv] = findpeaks(-audioSection,
'MinPeakDistance',audioPeakDist,'MinPeakProminence',minPromA_deflat);
%figure
%hold on
while(length(pk_a_deflat)>length(pk_a_deflat_inv))
    pk_a_deflat_inv=[pk_a_deflat_inv;pk_a_deflat_inv(end)];
    ik_a_deflat_inv=[ik_a_deflat_inv;ik_a_deflat_inv(end)];
end
while (length(pk_a_deflat)<length(pk_a_deflat_inv))
    pk_a_deflat=[pk_a_deflat; pk_a_deflat(end)];
    ik_a_deflat=[ik_a_deflat; ik_a_deflat(end)];
end
diff_deflat=pk_a_deflat+pk_a_deflat_inv;
t_a_trend_deflat=linearTrendOverSampled(ik_a_deflat);   % more correct

subplot(224)
hold on
plot(linearTrendOverSampled, audioSection);
plot(linearTrendOverSampled(ik_a_deflat), pk_a_deflat)
plot(linearTrendOverSampled(ik_a_deflat_inv), -pk_a_deflat_inv)
plot(t_a_trend_deflat, diff_deflat, 'LineWidth', 3);
[ymax_deflat, xmax_deflat]=max(diff_deflat);
plot(t_a_trend_deflat(xmax_deflat), ymax_deflat, 'xr','LineWidth', 3);

%polytfit TOP
aT_deflat = polyfit(ik_a_deflat,pk_a_deflat,7);
lineTOP_adef = polyval(aT_deflat,ik_a_deflat);
plot(t_a_trend_deflat,lineTOP_adef,'LineWidth', 3);

%polyfit BOTTOM
aB_deflat = polyfit(ik_a_deflat_inv,pk_a_deflat_inv,7);
lineBTTM_adef = polyval(aB_deflat,ik_a_deflat_inv);
plot(t_a_trend_deflat,-lineBTTM_adef,'LineWidth', 3);

diffPolyFit_adef=lineTOP_adef+lineBTTM_adef;
plot(t_a_trend_deflat, diffPolyFit_adef, 'LineWidth', 3);
[ymax_deflat, xmax_deflat]=max(diffPolyFit_adef);
plot(t_a_trend_deflat(xmax_deflat), ymax_deflat, 'xr','LineWidth', 3);
grid minor
xlabel('DC[mmHg]');
title('Audio deflationary');
```

```
AWEdef=polyfit(t_a_trend_deflat,diffPolyFit_adef',7);
PPWEdef=polyfit(t_trend,diffPolyFit_pdef,7);
%polyval(PPinf, 109.8)

save (['workspaceAnalysis ' datestr(now,'mm-dd-yyyy HH-MM') '_' filename]);
```

Uncertainty simulation and analysis

```
clear all
close all

n_sim=100000;
n_simThreshold=100;

mu=75.8;
sigma=(99.6-53.7)/2;

slope=(160-60)/20;
Perror=[];
error_sampling=[];
error_threshold_SBP=[];
error_threshold_DBP=[];
error_movingTarget=[];
Total_e_SBP=[];
Total_e_DBP=[];

for i=1:n_sim

    % E1 | error sampling | UNIFORM [0, max) | max is due to HR and slope
    HR=normrnd(mu,sigma);       % simulated from paper with 4,018,679 HR
measurements
    %error_sampling(end+1)=slope/(HR/60)*rand()*-1;
    error_sampling(end+1)=slope/(HR/60)*rand()*-1-slope/(HR/60)*rand()*-1;

    % E2 | error threshold | NON-UNIFORM [0.75, 0.20, 0.05]
    p=[.70, 0.15, 0.15];
    errorTemp=0;
        pt=rand();
        if(pt<p(1))
            errorTemp=errorTemp+0;
        elseif(pt>=p(1) && pt<(p(1)+p(2)))
            errorTemp=errorTemp+error_sampling(end);    %4.33 becomes
error_sampling
        elseif(pt>=(p(1)+p(2)))
            errorTemp=errorTemp+error_sampling(end);
        end

    errorTemp2=0;
    pt=rand();
    if(pt<p(1))
       errorTemp2=errorTemp2+0;
    elseif(pt>=p(1) && pt<(p(1)+p(2)))
       errorTemp2=errorTemp2+error_sampling(end);    %4.33 becomes
error_sampling
    elseif(pt>=(p(1)+p(2)))
```

```
       errorTemp2=errorTemp2+error_sampling(end);
    end
    error_threshold_SBP(end+1)=errorTemp-errorTemp2;

    p=[.60, 0.1, 0.3];
    errorTemp=0;
        pt=rand();
        if(pt<p(1))
            errorTemp=errorTemp+0;
        elseif(pt>=p(1) && pt<(p(1)+p(2)))
            errorTemp=errorTemp+error_sampling(end);    %4.33 becomes
error_sampling
        elseif(pt>=(p(1)+p(2)))
            errorTemp=errorTemp+error_sampling(end);
        end
        errorTemp2=0;
    pt=rand();
    if(pt<p(1))
       errorTemp2=errorTemp2+0;
    elseif(pt>=p(1) && pt<(p(1)+p(2)))
       errorTemp2=errorTemp2+error_sampling(end);    %4.33 becomes
error_sampling
    elseif(pt>=(p(1)+p(2)))
       errorTemp2=errorTemp2+error_sampling(end);
    end
    error_threshold_DBP(end+1)=errorTemp-errorTemp2;

    % E3 | error moving-target | NON-UNIFORM since is mainly influenced by
sinosoidal wave of
    %f=0.01;
    A=3.8;
    %A= 3 + (6-3).*rand(1,1);
    %time=(1/f)*rand()-1/(2*f);
    %time2=(1/f)*rand()-1/(2*f);
    time=rand()*2*pi;    % [0..2*pi]
    time2=rand()*2*pi;   % [0..2*pi]
    %time=(1/(2*f))*rand();
    error_movingTarget(end+1)=A*sin(time)-A*sin(time2);
    %error_movingTarget(end+1)=A*sin(2*pi*f*time)+A/3*rand();

    fprintf('Error in HR=%d sim#=%d nsim=%d es= %d eh= %d em= %d\n',HR, i,
n_sim,error_sampling(end), error_threshold_SBP(end),
error_movingTarget(end));

    Total_e_SBP(end+1)=
error_sampling(end)+error_threshold_SBP(end)+error_movingTarget(end);
    Total_e_DBP(end+1)=
error_sampling(end)+error_threshold_DBP(end)+error_movingTarget(end);
end

subplot(4,2,1)
hold on
%option='pdf';
option='probability';
histogram(error_sampling,'BinWidth',0.5, 'Normalization', option)
[values, edges] = histcounts(error_sampling,'BinWidth',0.5, 'Normalization',
option);
```

```
centers = (edges(1:end-1)+edges(2:end))/2;
p=plot(centers, values, 'r-', 'LineWidth',2)
p.Color(4) = 0.25;
title('PDF from method error - SBP')
xlabel('[mmHg]')
xlim([-20 20])

subplot(4,2,2)
hold on
histogram(error_threshold_SBP,'BinWidth',0.5, 'Normalization', option)
[values, edges] = histcounts(error_threshold_SBP,'BinWidth',0.5,
'Normalization', option);
centers = (edges(1:end-1)+edges(2:end))/2;
p=plot(centers, values, 'r-', 'LineWidth',2)
p.Color(4) = 0.25;
title('PDF from threshold error - SBP')
xlabel('[mmHg]')
xlim([-20 20])

subplot(4,2,3)
hold on
histogram(error_movingTarget,'BinWidth',0.5, 'Normalization', option)
[values, edges] = histcounts(error_movingTarget,'BinWidth',0.5,
'Normalization', option);
centers = (edges(1:end-1)+edges(2:end))/2;
p=plot(centers, values, 'r-', 'LineWidth',2)
p.Color(4) = 0.25;
title('PDF from movingTarget error - SBP')
xlabel('[mmHg]')

subplot(4,2,4)
hold on
histogram(Total_e_SBP,'BinWidth',0.5, 'Normalization', option)
[values, edges] = histcounts(Total_e_SBP,'BinWidth',0.5, 'Normalization',
option);
centers = (edges(1:end-1)+edges(2:end))/2;
p=plot(centers, values, 'r-', 'LineWidth',2)
p.Color(4) = 0.25;
title('PDF TOTAL error - SBP')
xlabel('[mmHg]')
xlim([-20 20])

CIFcn = @(x,p)prctile(x,abs([0,100]-(100-p)/2));
CI = CIFcn(Total_e_SBP,95);
xline(CI(1), '-m', round(CI(1),2))
xline(CI(2), '-m', round(CI(2),2))

rectangle('Position', [CI(1) 0 CI(2)-CI(1) 0.051], 'FaceColor', [0 0 1
0.06])
text(-2.9, 0.055, 'CI 95%', 'Color','magenta');


% DBP

subplot(4,2,5)
%option='pdf';
option='probability';
```

```
hold on
histogram(error_sampling,'BinWidth',0.5, 'Normalization', option)
[values, edges] = histcounts(error_sampling,'BinWidth',0.5, 'Normalization',
option);
centers = (edges(1:end-1)+edges(2:end))/2;
p=plot(centers, values, 'r-', 'LineWidth',2)
p.Color(4) = 0.25;
title('PDF from method error - DBP')
xlabel('[mmHg]')
xlim([-20 20])

subplot(4,2,6)
hold on
histogram(error_threshold_DBP,'BinWidth',0.5, 'Normalization', option)
[values, edges] = histcounts(error_threshold_DBP,'BinWidth',0.5,
'Normalization', option);
centers = (edges(1:end-1)+edges(2:end))/2;
p=plot(centers, values, 'r-', 'LineWidth',2)
p.Color(4) = 0.25;
title('PDF from threshold error - DBP')
xlabel('[mmHg]')
xlim([-20 20])

subplot(4,2,7)
hold on
histogram(error_movingTarget,'BinWidth',0.5, 'Normalization', option)
[values, edges] = histcounts(error_movingTarget,'BinWidth',0.5,
'Normalization', option);
centers = (edges(1:end-1)+edges(2:end))/2;
p=plot(centers, values, 'r-', 'LineWidth',2)
p.Color(4) = 0.25;
title('PDF from movingTarget error - DBP')
xlabel('[mmHg]')

subplot(4,2,8)
hold on
histogram(Total_e_DBP,'BinWidth',0.5, 'Normalization', option)
[values, edges] = histcounts(Total_e_DBP,'BinWidth',0.5, 'Normalization',
option);
centers = (edges(1:end-1)+edges(2:end))/2;
p=plot(centers, values, 'r-', 'LineWidth',2)
p.Color(4) = 0.25;
title('PDF TOTAL error - DBP')
xlabel('[mmHg]')
xlim([-20 20])

CIFcn = @(x,p)prctile(x,abs([0,100]-(100-p)/2));
CI = CIFcn(Total_e_DBP,95);
xline(CI(1), '-m', round(CI(1),2))
xline(CI(2), '-m', round(CI(2),2))

rectangle('Position', [CI(1) 0 CI(2)-CI(1) 0.051], 'FaceColor', [0 0 1
0.06])
text(-2.9, 0.055, 'CI 95%', 'Color','magenta');

%END of DBP
```

```
%end of simulation %%%%%%%%%%%%%%%%%%%


%human results
T = readtable('resultsTable.xlsx');
SBP1= table2array(T(:,31));
SBP2= table2array(T(:,39));
Diff_SBP=SBP2-SBP1;

DBP1= table2array(T(:,32));
DBP2= table2array(T(:,40));
Diff_DBP=DBP2-DBP1;
%%%%%%%%%%%%%%%%%%

range_SBP_68=CIFcn(Total_e_SBP,68)
range_SBP_95=CIFcn(Total_e_SBP,95)
range_DBP_68=CIFcn(Total_e_DBP,68)
range_DBP_95=CIFcn(Total_e_DBP,95)

%calculate performance of my model
SBP_68=[ sum(Diff_SBP>=range_SBP_68(1) & Diff_SBP<=range_SBP_68(2))
sum(Diff_SBP<range_SBP_68(1) | Diff_SBP>range_SBP_68(2)) ...
    round(sum(Diff_SBP>=range_SBP_68(1) & Diff_SBP<=range_SBP_68(2))/20,2)
round(sum(Diff_SBP<range_SBP_68(1) | Diff_SBP>range_SBP_68(2))/20,2)]
SBP_95=[ sum(Diff_SBP>=range_SBP_95(1) & Diff_SBP<=range_SBP_95(2))
sum(Diff_SBP<range_SBP_95(1) | Diff_SBP>range_SBP_95(2))...
    round(sum(Diff_SBP>=range_SBP_95(1) & Diff_SBP<=range_SBP_95(2))/20,2)
round(sum(Diff_SBP<range_SBP_95(1) | Diff_SBP>range_SBP_95(2))/20,2)]

DBP_68=[ sum(Diff_DBP>=range_DBP_68(1) & Diff_DBP<=range_DBP_68(2))
sum(Diff_DBP<range_DBP_68(1) | Diff_DBP>range_DBP_68(2)) ...
    round(sum(Diff_DBP>=range_DBP_68(1) & Diff_DBP<=range_DBP_68(2))/20,2)
round(sum(Diff_DBP<range_DBP_68(1) | Diff_DBP>range_DBP_68(2))/20,2)]
DBP_95=[ sum(Diff_DBP>=range_DBP_95(1) & Diff_DBP<=range_DBP_95(2))
sum(Diff_DBP<range_DBP_95(1) | Diff_DBP>range_DBP_95(2))...
    round(sum(Diff_DBP>=range_DBP_95(1) & Diff_DBP<=range_DBP_95(2))/20,2)
round(sum(Diff_DBP<range_DBP_95(1) | Diff_DBP>range_DBP_95(2))/20,2)]
```

HR model

```
close all
clear all

n_sim=10000;
n_simThreshold=1000;

HRs=[69,89,73,77,73,41,58,56,60,99,69,64,68,78,81,80,64,85,51,63];
slope=(160-60)/20;
Perror=[];
error_sampling=[];
error_threshold=[];
error_movingTarget=[];

%probabilities to make the right selection of the beat
p1=.75;
```

```
p2=0.2;
p3=0.05;


for i=1:n_sim

    % E1 | error sampling
    % UNIFORM [0, max) | max is due to HR and slope
    HR=randsample(HRs,1);
    error_sampling(end+1)=slope/(HR/60)*rand();


    % E2 | error threshold
    % NON-UNIFORM [0.75, 0.20, 0.05]
    errorTemp=0;
    for j=1:n_simThreshold
        pt=rand();
        if(pt<p1)
            errorTemp=errorTemp+0;
        elseif(pt>=p1 && pt<p1+p2)
            errorTemp=errorTemp+error_sampling(end);    %4.33 becomes
error_sampling
        elseif(pt>=p1+p2)
            errorTemp=errorTemp+abs(-error_sampling(end));
        end
    end
    error_threshold(end+1)=errorTemp/n_simThreshold;

    % E3 | error moving-target
    % NON-UNIFORM since is mainly influenced by sinosoidal wave of
    f=0.01;
    A=4;
    %time=(1/f)*rand()-1/(2*f);
    time=(1/(2*f))*rand();
    %error_movingTarget(end+1)=A*sin(2*pi*f*time);
    error_movingTarget(end+1)=A*sin(2*pi*f*time)+A/3*rand();

    fprintf('Error in HR=%d sim#=%d nsim=%d = %d \n',HR, i,
n_sim,error_sampling(end)+error_threshold(end));
end
Perror=error_sampling+error_threshold+error_movingTarget;

subplot(2,2,1)
histogram(error_sampling)
title('#1 error sampling')

subplot(2,2,2)
histogram(error_threshold)
title('#2 error threshold')

subplot(2,2,3)
histogram(error_movingTarget)
title('#3 error movingTarget')

subplot(2,2,4)
histogram(Perror)
title('TOTAL')
```

Oscillometric analysis

```
close all
clear all

filename='workspaceBPSensorOmron 09-17-2020 15-19_EAV'; %151/79
filename='workspaceBPSensorOmron 09-17-2020 14-56_EAV';  %126/76


load(filename);    %151/79
%load('workspaceBPSensorOmron 09-17-2020 15-18_EAV');   %157/84 *
%load('workspaceBPSensorOmron 09-17-2020 15-00_EAV');    %147/79
% load('workspaceBPSensorOmron 09-17-2020 14-59_EAV');   %164/70 *
%load('workspaceBPSensorOmron 09-17-2020 14-56_EAV');    %126/76
% load('workspaceBPSensorOmron 09-17-2020 14-44_EAV');  %NA
% load('workspaceBPSensorOmron 09-17-2020 14-37_EAV');   %127/68
%load('workspaceBPSensorOmron 09-17-2020 14-35_EAV');    %129/72
%load('workspaceBPSensorOmron 09-17-2020 14-33_EAV');   %error in K-index
close all

pressure=handles.data1(:,2);
shift1=8000;
shift2=550;
t2=max(handles.data1(:,1))+900;
t1=0;
t_a=linspace(t1-shift1, t2-shift2, length(audioSignal1));
t_p=handles.data1(:,1);

tPPG=linspace(t1,max(handles.data1(:,1)) , length(handles.data3(:,1)));
figure
hold on
plot(handles.data1(:,1), handles.data1(:,2), 'r');
%plot(t_a,audioSignal1*80+2, 'Color', '#7E2F8E');
%[Ypmax Xpmax]=max(handles.data1(:,2));
%xline(handles.data1(Xpmax,1));
%yyaxis right
%plot(tPPG, -1*handles.data3(:,2), 'b');
%legend('pressure','audio', 'ppg');
%legend('pressure','audio');
xlabel('time');
ylabel('mmHg');
%title(['Omron= [ ' bpFromOmron{1} ' | ' bpFromOmron{2} ' | ' bpFromOmron{3}
' ]'])
grid minor

%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

% 1st WAY DOWN --------------------------------------------
%max diff
offset=500;
t1_WD= handles.data1(Xpmax,1)+offset;

%limits in time axis
```

```
ip1_WD=find(t_p>t1_WD,1);
[YDiff XDiff]=max( abs(diff(pressure(ip1_WD:end))));
t2_WD= handles.data1(Xpmax+XDiff,1)-offset;
%xline(t2_WD);

Yt1=Ypmax;
Yt2=YDiff;
figure

ip2_WD=find(t_p>t2_WD,1);
ia1_WD=find(t_a>t1_WD,1);   ia2_WD=find(t_a>t2_WD,1);

%presssure signal
dt_WD=detrend(pressure(ip1_WD:ip2_WD), 20);
filteredDt_WD=highpass(dt_WD,1, 111);       %111 Hz sampling?
pressureFiltered_WD = wdenoise(filteredDt_WD,3);

hold on
%plot(audioSignal1)
audioSignal1Mod=(audioSignal1*20).^3;
medfiltAudio_WD = medfilt1(audioSignal1Mod(ia1_WD:ia2_WD),100);
t_pressureFiltered_WD=t_p(ip1_WD:ip2_WD);
t_medfiltAudio_WD=t_a(ia1_WD:ia2_WD);
yyaxis left
hold on
plot(t_medfiltAudio_WD, medfiltAudio_WD, 'k');
plot(t_medfiltAudio_WD, audioSignal1(ia1_WD:ia2_WD), 'g');
yyaxis right
plot(t_pressureFiltered_WD, pressureFiltered_WD);

[vmax_WD, i_max_WD]=max(pressureFiltered_WD);
[vmax1_WD, i_max1_WD]=max(medfiltAudio_WD);
yyaxis left
plot(t_medfiltAudio_WD(i_max1_WD), vmax1_WD, 'o','LineWidth',3);
yyaxis right
plot(t_pressureFiltered_WD(i_max_WD), vmax_WD, 'o','LineWidth',3);
%[yupper,ylower]=envelope(abs(audioSignal1(ia1_WD:ia2_WD)), 1000, 'peak');
%plot(t_medfiltAudio_WD,yupper);

%envelope
[pk_p_WD,ik_p_WD] = findpeaks(pressureFiltered_WD, 'MinPeakDistance',30);
%findpeaks(pressureFiltered, 'MinPeakDistance',30);
[pk_a_WD,ik_a_WD] = findpeaks(medfiltAudio_WD, 'MinPeakDistance',6000);
%findpeaks(medfiltAudio, 'MinPeakDistance',6000);
yyaxis left
plot(t_medfiltAudio_WD(ik_a_WD), pk_a_WD);
%plot(t_medfiltAudio(lk_a(5)), pk_a(5), 'o');    %k threshold sounds
k1_WD=[ ik_a_WD(4)      pk_a_WD(4)  ];
k2_WD=[ ik_a_WD(12)     pk_a_WD(12) ];
text(t_medfiltAudio_WD(k1_WD(1)),k1_WD(2),'\leftarrow K1')
text(t_medfiltAudio_WD(k2_WD(1)),k2_WD(2),'\leftarrow K2')
yyaxis right
plot(t_pressureFiltered_WD(ik_p_WD), pk_p_WD);

legend('audio', 'pressure osc', 'max_P', 'max_K', 'env_P', 'env_A');
title('on the way down - 1st');
grid minor
```

```
f=figure;
figure(f);
hold on
t_pressureFiltered_WDx=linspace(Ypmax, YDiff, length( pressureFiltered_WD));
plot(t_pressureFiltered_WDx, pressureFiltered_WD);
xlabel('mean BP');
grid minor;

%% Audio WAV file

%audiowrite([filename '.wav'], audioSignal1, 8000)
```

APPENDIX D. IRB STUDY CONSENT

Electrical and Computer Engineering Department
134E20 Minard Hall NDSU
Fargo, ND 58108-6050
7012315129

New method to measure blood pressure on your upper arm using different sensors

This study is being conducted by Dr. Daniel Ewert, Emeritus Professor in the Department of Electrical and Computer Engineering at NDSU (dan.ewert@ndsu.edu) and Enrique Alvarez Vazquez (enrique.vazquez@ndsu.edu)

Why am I being asked to take part in this study?

You are invited to take part in this research study because you are between the ages of 18 and 70 and your participation could help the researchers learn more about a new method to measure blood pressure.

Your participation is entirely your choice, and you may change your mind or quit taking part at any time, with no penalty to you.

What will I be asked to do?

In this experiment, we will ask you to provide the following information:

- COVID screening questions
- Full name
- Email
- Age
- Sex
- Weight
- Height

We will measure and record your:

- arm circumference
- number of heart beats per minute
- blood pressure
- the sounds recorded by a small microphone placed in your arm
- the pressure variations got from an arm cuff
- the light changes from your finger tip

We will use a combination of **three** sensors:

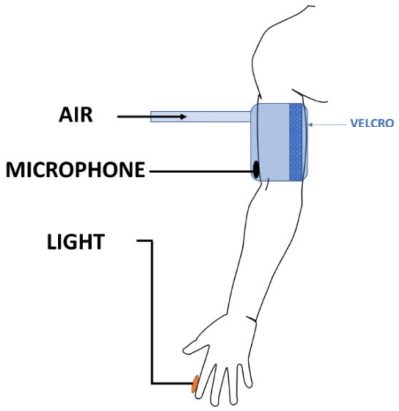
- one arm blood pressure cuff that wraps around your arm above your elbow,
- one microphone in the shape of a coin that is placed underneath the arm cuff
- one flat sensor that uses light to measure the amount of oxygen in your blood

We have developed a device that measures blood pressure by combining three different sensors.

We will place an inflatable cuff over your arm, just like the ones used in a doctor's office. We will also listen to the sounds produced inside your arm, and we can record the amount of oxygen in your finger by shining a harmless light and recording the reflection of that light.

These three sensors have no sharp edges, and they all lay flat on top of your skin.

The experience while using this prototype is very similar to when you get your blood pressure measured in a routine medical checkup. You will feel a squeeze on your arm just as in a routine medical checkup.



Where is the study going to take place, and how long will it take?

The experiment will take place in Minard 134E20. The experiment will take about 15 minutes to complete.

What are the risks and discomforts?

The risks and discomforts involved in this study are the possible loss of confidentiality. In addition, there is a risk of a minor level of discomfort because of the pressure applied in the arm cuff.

The risk of electrical shock is exceedingly low. The sensors are powered by current limited USB ports from the desktop computer (5V).

It is not possible to identify all potential risks in research; however, reasonable safeguards have been taken to minimize known risks. If new findings develop during the research which may change your willingness to participate, we will tell you about these findings.

What are the expected benefits of this research?

Individual Benefits: By participating in this study, you may benefit by learning more about how biomedical research relates to engineering. However, you may not get any benefit from being in this study.

Societal Benefits: Correct blood pressure measurements are important to prevent and treat illnesses. You will help researchers learn more about a new way to measure blood pressure.

Do I have to take part in this study?

Your participation in this research is your choice. If you decide to participate in the study, you may change your mind and stop participating at any time without penalty or loss of benefits to which you are already entitled.

Will it cost me anything to participate?

No

What are the alternatives to being in this study?

Instead of being in this research, you may choose not to participate.

Who will have access to my information?

The principal investigators will have access to your written consent form, your biometric data, and your computerized stored information. We will assign you a number and we will use that number to analyze your information without having to know from whom it comes.
We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is. For example, your name and email will be kept separate from your research records and these two things will be stored in different places under lock and key.

How will my [information/biospecimens] be used?

Your information will be coded with unidentifiable numbers and combined with information from other people taking part in the study. When we write about the study, we will write about the combined information that we have gathered. We may publish the results of the study; however, we will keep your name and other identifying information private. The study results will be combined with no names.

Collected samples/data may be given to another investigator for future research without additional consent. In that case, we will keep your name and other identifying information private.

Documentation of Informed Consent:

You are freely making a decision whether to be in this research study. Signing this form means that

1. you have read and understood this consent form
2. you have had your questions answered, and
3. you have decided to be in the study.

You will be given a copy of this consent form to keep.

_____ _____

Your signature Date

_____ _____

Your printed name Date

_____ _____

Signature of researcher explaining study Date

_____

Printed name of researcher explaining study

You are automatically entered in a secured database and we may contact you for future studies. If you don't want to get contacted in the future please write an 'x' in the following checkbox.

☐ I don't give permission to be re-contacted again for future experiments

APPENDIX E. IRB PROTOCOL

NDSU NORTH DAKOTA STATE UNIVERSITY

PROTOCOL

New method to measure blood pressure on your upper arm using different sensors

Materials:

1. COVID screening questions
2. Consent form
3. Biometric data page 1
4. Biometric data page 2
5. Labeled investigational device
6. Desktop computer
7. Disinfecting wipes
8. Masks
9. Hand sanitizer

Personnel involved: experimenter (1) participant (1)

AT LEAST 24 HOURS BEFORE EXPERIMENT SESSION

Contact participant to remind them they have an experiment session at _____ o'clock the next day in Room 134E20 Minard Hall (give directions if necessary). Inform the participant that the experiment will consist of measuring blood pressure with a new method by reading different harmless sensors in the non-dominant arm, so they should wear a loose fitting short-sleeve shirt.
Ask the questions included in the COVID questionnaire.

Ask if the participant understands and wait for a verbal agreement.

Answer questions.

INTRO / WELCOME

EXPERIMENTER Before the arrival of the participant, have the equipment ready. Make sure you are wearing a mask. Disinfect your hands with hand sanitizer.

When the participant arrives, greet him/her, check if they are wearing a mask. If they don't, please give them one from the lab. Provide hand sanitizer for them to disinfect their hands.

Ask again the questions included in the COVID questionnaire. Anyone responding "yes" to any of the questions is excluded from participating in the study. STOP the session.

Ask if he/she needs to use the restroom or to spit out any gum. Remind the participant to switch off their cellphone and keep it away for the duration of the experiment. Show the participant where to sit and explain:

"Hi, I'm the experimenter for this study. Thank you for coming in to do our experiment. In this experiment, we are interested in studying a better method to measure blood pressure. Therefore, I am going to take a series of measurements with this investigational device.

We have developed a device that measures blood pressure by combining three different sensors.

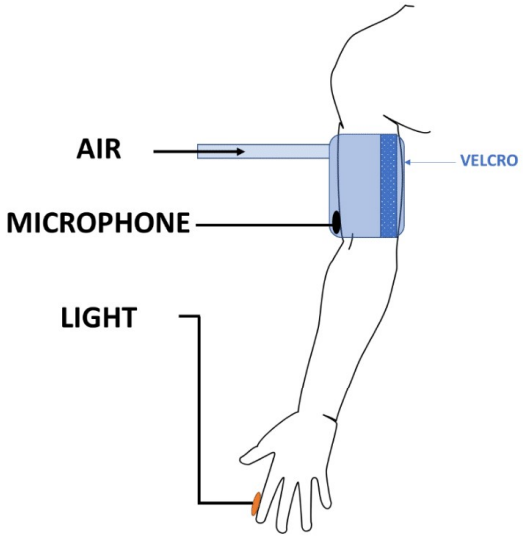
We will place an inflatable cuff over your arm, just like the ones used in a doctor's office. We will also listen to the sounds produced inside your arm, and we can record the amount of oxygen in your finger by shining a harmless light and recording the reflection of that light.

These three sensors have no sharp edges, and they all lay flat on top of your skin.

The experience while using this prototype is very similar to when you get your blood pressure measured in a routine medical checkup. You will feel a squeeze on your arm just as in a routine medical checkup.

The setup will automatically take readings and will feel a little snug when it does, but it is not painful.
This is how it looks"

[Show diagram of the device and physical device] →



"Do you have questions about anything I've said so far?"

CONSENT FORM

EXPERIMENTER: *"All the data gathered here today including physiological measures and any questions you answer will be kept strictly confidential. No one outside this lab will ever be able to match up your name with the data. Also, I must inform you that you can discontinue the experiment at any time without penalty. This consent form basically says everything I just explained. Please read it over carefully and let me know if you have questions."*

ANSWER QUESTIONS TO THE BEST OF YOUR ABILITY.

"Are you ready to begin?"

AFTER THE PARTICIPANT SAYS YES

Write the biometric data page #1 and #2. Weight and height are both self-reported.
Take the tape measure and measure arm circumference in the non-dominant arm.

After the BIOMETRIC FORM is WRITTEN DOWN

NON-INVASIVE HARDWARE PLACEMENT AND EXPERIMENT

EXPERIMENTER: *"Alright. First, please sit down in this chair, place your legs uncrossed and have your feet flat on the ground. Now, I am going to place the arm cuff. Which hand do you write with? Alright, can I please have you put your other arm on the table so I can fit the arm cuff? It's very important that you don't move this arm while we are taking your blood pressure. So please keep it on the table and still for the duration of the experiment. Now I will place the contact microphone underneath the arm cuff. Then we are going to place your and on top of this table and your index finger fingertip on top of this sensor".*

Make sure the microphone is placed near the brachial artery (marked with a black dot in the arm cuff). Rest participants' arm on the table and place their index finger on top of the MAX30105 sensor. Make sure the participant does not have her/his legs crossed, feet lay down flat and is in a comfortable position.

"Ok, now I am going to start the experiment. We are going to make an initial measurement wait 5 min and take a second one, after that we are done."

Sit down at least 6 feet away and run the Matlab script. The script will ask you for the ID number, type down the ID number that was assigned from the biometric data pages. The computer will start taking measurements.

When the script is done. Write the readings from the Omron BP710 in the biometric data page #2, under 'read#1'. After that, wait 5 min.

After 5 minutes, the script will prompt you to repeat the measurement.

"Ok, are you ready for the second measurement?"

If the answer is yes, continue the script. The computer will start again taking measurements. Write the readings from the Omron BP710 in the biometric data page #2, under 'read#2'.

At the end of the experiment we will measure the blood pressure and heart rate of the participant with an Omron BP710. At the time of the session, if the participant's systolic BP is between 140 and 180, please refer the participant to their primary care provider. If the participant's systolic BP is above 180, please refer the participant to urgent care.
Also, offer the participant a printed copy of American Heart Association 'Small changes make a big difference'. [https://www.heart.org/-/media/files/health-topics/high-blood-pressure/tylenol-hbp/aha19_tylenolbroch_web2.pdf?la=en].

After the computer script is done continue to debrief.

DEBRIEF

Thank you for participating in our study.

Blood pressure measurements take time and may not be accurate, we are trying to get blood pressure measurements using a more intelligent approach. Your participation today will help us understand the cardiovascular system.

We highly appreciate your collaboration.

Are there any questions?

ANSWER QUESTIONS TO THE BEST OF YOUR ABILITY OR REFER THE PARTICIPANT TO CONTACT DR. EWERT or ENRIQUE ALVAREZ.

Thanks for your participation.

THANK, AND EXCUSE THE PARTICIPANT. Encourage to use hand sanitizer.

CLEANING

Wipe the arm cuff, the microphone, and the oximeter with disinfecting wipes.
Clean the table and chair with disinfecting wipes.
Clean your hands with hand sanitizer.
Leave the room empty until the next appointment is ready (approximately 45 minutes buffer time).

COVID Screening Questions:

1. Do you have any of the following symptoms, or pending COVID-19 test because you were having any of the below symptoms?

- Fever
- Chills
- Body aches
- Cough
- Shortness of breath
- Sore throat
- New onset loss of smell or taste
- New onset of vomiting or diarrhea

2. Do you have a pending COVID-19 test without any of the symptoms previously mentioned?

3. In the last 14 days, have you been exposed to anyone with a lab confirmed COVID-19 test or have you had a COVID-19 positive test result?

Anyone responding “yes” to any of the three questions should be excluded.

Biometric data [Page 1 of 2]

Experiment ID # *(experimenter assigns one)*	
Full name	
Email	

Biometric data [Page 2 of 2]

Experiment ID # *(experimenter assigns one)*	
Age	
Sex	
Weight	
Height	
Arm circumference	
#1 Systolic read in Omron BP710	
#1 Diastolic read in Omron BP710	
#1 Heart Rate read in Omron BP710	
#2 Systolic read in Omron BP710	
#2 Diastolic read in Omron BP710	
#2 Heart Rate read in Omron BP710	