

## ABSTRACT

Title of Thesis: INVESTIGATING METHODS OF BLOOD PRESSURE MEASUREMENT: COMPARING CORRELATIONS OF MULTIPLE PULSE TRANSIT TIMES TO BLOOD PRESSURE

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Currently, one in three American adults suffer from high blood pressure, a condition known as hypertension, yet only half have their condition under control (CDC, 2016). Methods of continuous blood pressure measurement have been examined by the team over the past few years. Using five hemodynamic interventions to fluctuate blood pressure, blood pressure data was gathered from 35 healthy adult participants. This data was useful in measuring pulse transit time and determining optimal locations for biosensor placement. Participants were also surveyed to collect public opinion on potential health monitoring devices for future development. Furthermore, the potential of using mobile device applications was examined as an alternative method of retrieving signals and calculating blood pressure. The results from this project indicate that for a mobile device application, the best signals to use for estimating

blood pressure are PPG maximum to ECG R-wave, having an average correlation of  $r = 0.73$  for the systolic blood pressure and  $-r = 0.71$  for the diastolic blood pressure.

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by

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## List of Abbreviations

BCG: Ballistocardiogram  
BH: Breath Holding  
BP: Blood Pressure  
CP: Cold Pressor  
DBP: Diastolic Blood Pressure  
ECG: Electrocardiogram  
GUI: Graphic User Interface  
HBP: High Blood Pressure  
HST: Human Subjects Testing  
MA: Mental Arithmetic  
PAT: Pulse Arrival Time  
PPG: Photoplethysmography  
PTT: Pulse Transit Time  
SB: Slow Breathing  
SCG: Seismocardiogram  
SBP: Systolic Blood Pressure  
mmHG: Millimeters of Mercury  
RMSE: Root mean square error

## Chapter 1: Introduction

Due to the current rise in blood pressure (BP) related diagnoses, medical practitioners are searching for a more effective method of monitoring vital patient information (Marshall, 2004). Currently, one in three American adults suffer from high blood pressure (HBP), a condition known as hypertension (Center for Disease Control and Prevention [CDC], 2016). Astoundingly, only about half of the people who suffer from hypertension have their condition under control (CDC, 2016). Today, the predominant method of monitoring BP is achieved through visiting a doctor, which lacks the efficiency and convenience that could exist if there was a way for patients to continuously monitor their own BP. High blood pressure was a contributing cause of death for upwards of 400,000 Americans in 2014 (CDC, 2016). With proper preventive care, many of these deaths could have been avoided. Due to these alarming trends, frequent BP monitoring is necessary.

There are numerous logistical drawbacks to the current methods of obtaining BP measurements due to inconvenience, inconsistency, and inaccuracy. The time and money involved with periodically visiting a doctor is the root of America's problem with hypertension, contributing to overall patient noncompliance and thus trivializing the importance of consistent BP measurements. Even for those able to regularly visit healthcare facilities, an annual BP measurement from a doctor is simply insufficient, because BP is a constantly changing measurement that fluctuates according to the current condition of the body. For instance, excitement and exercise can create short-term levels of HBP, while relaxing or sleeping can produce an opposite pattern

(National Heart, Lung, and Blood Institute [NHLBI], 2015). Even the stress associated with seeing a doctor, medical trainee, or other healthcare professional has been shown to cause a sudden spike in blood pressure during readings, a phenomenon known as white coat hypertension (Handler, 2009; Matthys et al., 2004; NHLBI, 2015). Therefore, to precisely gauge an accurate and aggregate BP measurement, it must be measured constantly, underscoring the need to develop a method of continuous BP monitoring to promote preventive care within at-risk populations. Moreover, improper techniques of taking blood pressure, such as miscuffing, may lead to incorrect readings (NHLBI, 2015). Overestimating or underestimating blood pressure by 5 to 10 mm Hg can subsequently lead to incorrect diagnoses (Handler, 2009). One proposed alternative is to allow patients to take more frequent measurements from the comfort of their home (Marshall, 2004) which would increase practicality and decrease costs. Alternative methods of blood pressure estimation are warranted.

## Chapter 2: Literature Review

### 2.1: Background

Blood pressure is the force of blood pushing against arterial walls as it is pumped from the heart (NHLBI, 2015). There are two different types of pressure measurements that are jointly quantified to come up with a BP measurement. Systolic pressure (SBP) measures the pressure inside the arteries as the heart pumps blood, while diastolic pressure (DBP) conversely measures the pressure of the arteries when the heart is resting between beats (CDC, 2014). A normal, healthy BP for adults is conventionally defined as having an SP below 120 millimeters of Mercury (mmHg) and a DBP below 80 mmHg (see Figure 1). The measurement is displayed with the

SBP in the numerator and DP in the denominator of a fraction, as 120/80 mmHg (NHLBI, 2015). Fluctuations in BP are extremely common, and are often noticed when active, excited, or nervous, or between periods of sleep and consciousness (NHLBI, 2015). The most accurate measurement of resting BP would be taken during rest periods between activities that could contribute to these fluctuations.

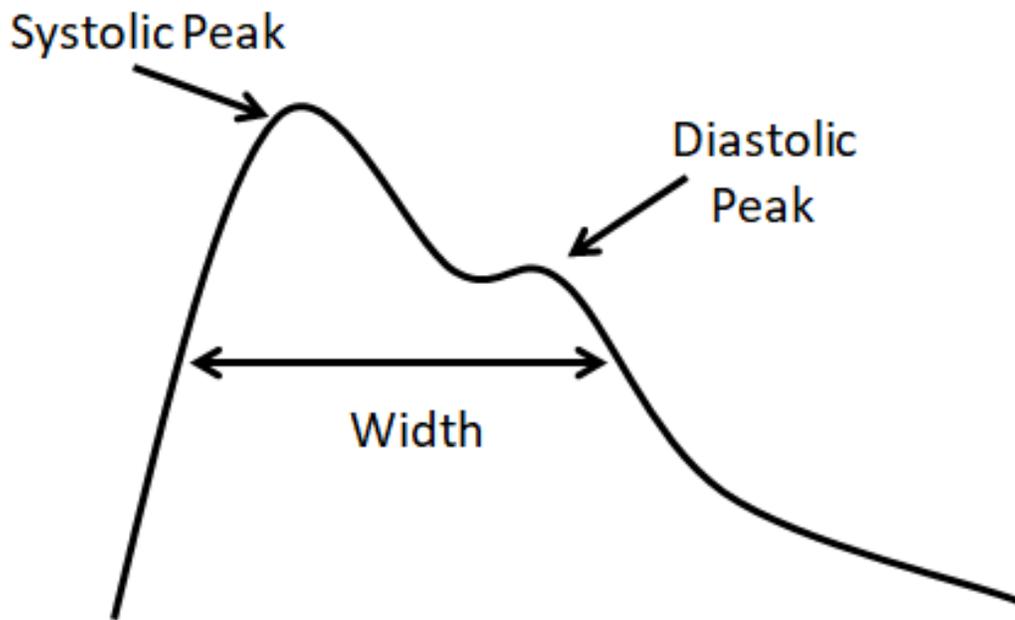


Figure 1. A typical PPG waveform depicting the difference in systolic and diastolic peak.

When the heart beats, blood is pumped into vessels that travel throughout the body (World Health Organization [WHO], 2013). Hypertension causes a greater force to be pushed against these vessels. In terms of systolic and diastolic blood pressure, hypertension is a common disease that occurs when blood flows through the arteries at a higher than normal pressure, resulting in blood pressure readings higher than the standard 120/80 mmHg. The more pressure there is in the vessel, the harder the heart

has to pump. Prehypertension, in which blood pressure numbers are slightly higher than normal—a warning sign of hypertension—ranges from SP readings from 120-139 or DP readings from 80-89 (NHLBI, 2015). Having either a systolic or diastolic pressure greater than these benchmarks, meaning greater than 140/90 mmHg, is categorized as hypertension.

Although anyone can develop high blood pressure (HBP), there are several factors that can increase the risk of developing this condition, such as age, weight, lifestyle habits, sex, race/ethnicity, family medical history, or pregnancy. Blood pressure often increases with age, as nearly two-thirds of Americans over the age of 60 have been diagnosed with hypertension (American Heart Association [AHA], 2016). As an individual ages, a layer of protein in the blood vessels that enhances flexibility, known as elastin, degenerates. Naturally, this causes the vessels to thicken and become stiff, resulting in higher systolic BP (NHLBI, 2015). Similarly, the risk for high blood pressure is much higher in individuals who are overweight and have poor diets, exercise, or lifestyle habits (AHA, 2016). This includes being physically inactive and consuming an excessive amount of sodium or alcohol (NHLBI, 2015).

In terms of sex, men under the age of 55 generally have a greater risk for developing cardiovascular diseases when compared to women. After this age, higher blood pressure is often found in menopausal women (Reckelhoff, 2001). Studies have confirmed this finding by identifying a higher prevalence of hypertension in women above the age of 60 years (Maranon & Reckelhoff, 2013). Regarding race/ethnicity, African Americans have higher average blood pressure and an earlier onset for developing high BP when compared to other racial or ethnic groups (NHLBI, 2015).

Furthermore, a longitudinal study conducted over ten years found that children with a family history of hypertension also had higher average systolic BP when compared with children who did not have a family history of the disease (Munger, Prineas, & Gomez-Marin 1988). These patterns of persistently elevated blood pressure existed prior to adolescence in these children, suggesting that familial conditions may predict the likelihood of developing cardiovascular conditions. Interestingly, there was a greater correlation between a mother's BP and her child's when compared to the father's BP and his child's (Munger, Prineas, & Gomez-Marin 1988). Additionally, having a sensitivity to sodium, which increases the risk of developing high BP, may be a familial trait (NHLBI, 2015). These findings suggest that family history is a hereditary and non-modifiable risk factor associated with hypertension.

Moreover, hypertension was found in a sample of 5-7% of pregnancies and in about 8% of women of reproductive age (Lindheimer, Taler, & Cunningham, 2008; Bateman et al., 2012). A sudden increase in BP during the third trimester of pregnancy, known as preeclampsia, can cause serious complications to both the fetus and mother. For the fetus, high BP during pregnancy can decrease blood flow to the placenta, which leads to less oxygen, fewer nutrients, and lower birth weight. In some cases, it may result in preterm delivery to prevent lethal complications (Lindheimer, Taler, & Cunningham, 2008; NHLBI, 2015). For the mother, high BP may damage internal organs, such as the kidneys, or increase the likelihood of developing cardiovascular disease in the future (Mayo Clinic, 2018).

Many of the symptoms of hypertension, if not diagnosed or treated in due time, can lead to serious internal illnesses or even death. High blood pressure is often referred

to as “the silent killer”, because symptoms usually do not appear until the body has already been damaged from chronic HBP (AHA, 2016; WHO, 2013).

The most common and severe complications caused by chronic HBP include the increased risk of aneurysms and strokes, as well as kidney, heart, eye, and arterial damage (AHA, 2016). The arteries are the most adversely damaged from HBP, as the force exerted by blood onto the arteries causes microscopic tears in arterial walls that can lead to further damage (AHA, 2016). Damaged arteries accumulate cholesterol, fat, and plaque buildup, which increase the risk of peripheral or coronary artery disease. These life-threatening illnesses occur from the accumulation and hardening of plaque within the vessels, which clog and narrow the arteries.

Similarly, abnormal balloon-like bulges, called aneurysms, may also develop in the walls of the arteries as a result of blood pressure that is too forceful for arterial walls to withhold, further exacerbating arterial damage (AHA, 2016). Aneurysms grow for years before causing any noticeable symptoms, until they rupture, dissect, or grow large enough to block blood flow in the vessels. This blockage can cause strokes when the flow of oxygen-rich blood to the brain is restricted (AHA, 2016). A comparable situation arises when the heart is not receiving the oxygen-rich blood that it relies on, which can lead to a heart attack (NHLBI, 2015). In these circumstances, hypertension has the potential to cause severe physiological damage to the body through heart failure, long-term brain damage, or death.

## 2.2: Existing Technology

With an increase in health monitoring concerns, more and more people in the developed world are turning to devices that can effectively record physical activity and pertinent vital signs (Haghi, Thurow & Stoll, 2017). Since the mid-20th century, with the advent of the wearable pedometer (Haghi, Thurow & Stoll, 2017), it is clear that there is a growing desire for patients to monitor their own health, as it can assist their doctors in better serving them and allow for timely control over lifestyle changes when necessary. However, in order to achieve these goals, such devices must be improved to have the ability to measure one of the most widely monitored vital signs, blood pressure, in an accurate manner.

Improper techniques regarding blood pressure measurements can lead to severe and sometimes fatal consequences. Underestimating or overestimating true blood pressure measurements by just 5 mmHg would misdiagnose over 20 million Americans with prehypertension, or cause 30 million Americans to possibly receive erroneous treatment (Handler, 2009). The consequence underdiagnosing, which is largely attributed to inappropriate measuring techniques, has the capability of increasing the amount of strokes and myocardial infarctions by approximately 25% (Handler, 2009). On the other hand, overdiagnosing could increase medical costs or the potential for adverse drug effects. Therefore, it is imperative that the advantages and limitations of these devices are assessed in an objective manner to ensure that appropriate treatment is administered to patients with concerning blood pressure levels.

Existing methods of obtaining BP, such as catheterization, auscultation, and oscillometry also bring unique challenges. Catheterization is a process that obtains BP

measurements instantly by placing a gauge in direct contact with blood flow (Mukkamala et al., 2015). Although this method provides an instant and accurate reading, it is an invasive procedure that is simply not feasible for daily use. Perhaps the most commonly recognized clinical method of obtaining BP involves the process of auscultation. Using this method, systolic and diastolic BP are measured through an inflatable cuff. A medical professional then uses a stethoscope to find Korotkoff sounds, which are audible changes in the flow of blood, during cuff deflation. Systolic blood pressure is estimated using the first sound and diastolic blood pressure is estimated using the fifth (Mukkamala et al., 2015). The major benefit to this method is that it is noninvasive, but the drawback is that it usually requires the assistance of a trained medical personnel and can be quite time consuming. Lastly, oscillometry is another noninvasive option of measuring BP by using oscillated amplitudes from a sensor placed in a cuff. Although this is a popular method of obtaining blood pressure, this strategy of measurement is not sensitive enough for those with stiff arteries

The current gold standard method for measuring blood pressure is the sphygmomanometer (Ogedegbe & Pickering, 2010; Poon & Zhang, 2006), commonly known as the “blood pressure cuff” which is an auscultatory method. This method is ubiquitous in any healthcare facility and involves an inflatable cuff and a stethoscope to measure systolic and diastolic blood pressure. In order to measure these systolic and diastolic values, health care practitioners wrap the inflatable cuff around the brachial artery in the upper arm and use a stethoscope to calculate the respective values via Korotkoff sounds (Ogedegbe & Pickering, 2010). Despite being the most commonly

used and simplest form of blood pressure monitoring, there are several limitations that should be considered when implementing this method.

The biggest flaw associated with the sphygmomanometer method is that it lacks continuity, meaning patients are unable to continuously monitor their blood pressure at any given time. Instead, they must wait two minutes between measurements for the cuff to inflate if they need a more accurate reading, often making the process quite time consuming (Gesche, Grosskurth, Kuchler, & Patzak, 2012). This lapse in measurements prevents patients with short-term blood pressure fluctuations from precisely monitoring their health in an uninterrupted manner, thus complicating the task of taking blood pressure measurements.

In addition to these limitations, there are common mistakes that can be made when using the sphygmomanometer that result in physiological and psychological spikes in blood pressure values. For example, “miscuffing” refers to an improper practice when health care professionals accidentally use the wrong size cuff or place the cuff on an incorrect area of the arm (Handler, 2009). The size of the cuff must be proportional to the diameter of the arm to prevent overestimating blood pressure (Ogedegbe & Pickering, 2010). Furthermore, proper sphygmomanometer procedures require the cuff to be wrapped around a bare upper arm while the forearm is positioned at heart level and supported on a table (Handler, 2009). Cuffing over clothing, wrapping the cuff around the forearm, or using a cuff that is too small will result in false positives that are much higher than normal (see Table 1 for factors affecting BP readings). Thus, practitioners who are calculating blood pressure must be cognizant of these factors as well as the potential to overestimate blood pressure measurements.

Equally important to consider is the psychological stress that may arise and produce incorrect measurements if the patient experiences white coat hypertension. Copious studies have revealed that people tend to become more nervous, and thus have a higher record of systolic blood pressure, in the presence of a medical professional or medical environment (Handler, 2009; Matthys et al., 2004). Because of this, multiple measurements should be taken in a variety of settings over time to ensure the accuracy of the diagnosis. White coat hypertension further emphasizes the need for patients to have the freedom of monitoring their health in the comfort of their home (Marshall, 2004; Ogedegbe & Pickering, 2010).

Table 1. Factors influencing the accuracy of blood pressure measurements. (Handler, 2009).

<b>Factor</b>	<b>Magnitude of systolic/ diastolic blood pressure discrepancy (mm Hg)</b>
Talking or active listening	10/10
Distended bladder	15/10
Cuff over clothing	5–50/
Cuff too small	10/2–8
Smoking within 30 minutes of measurement	6–20/
Paralyzed arm	2–5/
Back unsupported	6–10/
Arm unsupported, sitting	1–7/5–11
Arm unsupported, standing	6–8/

**2.2.1 Dinamap.** Another technique used to measure blood pressure was the Dinamap (Device for Indirect non-invasive Automatic Mean Arterial Pressure). This device was introduced to the medical field during the 1970's and relies on the

oscillometric principle, which expresses pressure measurements using both the maximum (systolic) and minimum (diastolic) blood pressure (Flaherty, Sher, & Caro, 2000). In its most basic form, the Dinamap uses a cuff to place pressure onto an artery while the pressure of the cuff is raised in increments to points above the systolic BP and points below the diastolic BP (Flaherty et al., 2000). This allows the device to compute a mean arterial pressure by using both the maximum and minimum blood pressures. Usually, the cuff begins at an inflation of 160 mmHg and then increases incrementally until the inflation of the cuff reaches a level 35 mmHg higher than the patient's previous systolic reading (Flaherty et al., 2000). From there, the cuff deflates at a rate of 3-6 mmHg per second and the arterial pressures are recorded by the device as the cuff deflates by each increment. A pressure transducer, which is attached to the cuff, indicates the volume of the artery. When the artery has a larger volume, the pressure of the cuff will be higher (Flaherty et al., 2000).

Although this method has been in use for a considerable amount of time, it is often extremely time consuming as it relies on multiple cardiac cycles in order for it to finally produce a reading (Hutton, Dye, & Prys-Roberts, 1984). Furthermore, the cost of the device makes it less than ideal for a home device, especially for patients with low socioeconomic backgrounds. A functional Dinamap device ranges from \$500-\$2,400, excluding maintenance costs, which makes it a less accessible form of measuring blood pressure for some demographics (Hutton et al., 1984).

**2.2.2 Finapres.** The Finapres is a device that uses the Penaz principle to determine blood pressure. The Penaz principle states, "a force exerted by a body can be determined by measuring an opposing force that prevents physical disruption (Ward

& Langton, 2007).” The Finapres incorporates this notion through their device by utilizing a small, ring-sized cuff that is wrapped around or slipped over a finger to record systolic and diastolic measurements (Imholz et al., 1988). The cuff itself is connected to a machine that interprets the waveform and displays the blood pressure reading. When the Finapres was first developed, readings had an average +/-7 mmHg error, making it a reasonable method to record blood pressure (Imholz et al, 1988).

The company responsible for the Finapres technology has since improved upon their design and now offers four different devices that utilize the same method of blood pressure recording. Some of the models are even designed to connect with laptop computers to make data access and management more convenient. However, the flaws with this device are rather evident: it is large, cumbersome, and has several components that must be carried in a waistband in order to serve its desired purpose of being “portable.” According to Finapres, another issue with this device is its price point: at \$40,000 per unit, it is essentially inaccessible and unnecessary for most people outside of the medical profession. Therefore, this device has largely been restricted to users in a clinical setting. This provides sufficient evidence to support the necessity of developing a more cost effective and truly portable method of blood pressure measurement that is convenient for patient use.

**2.2.3 ccNexfin.** A more recent development using noninvasive technology continuous blood pressure measurements is the ccNexfin. This device is a blood pressure cuff that fits on the finger and automatically inflates and deflates in order to capture the blood pressure waveform in the subject’s index finger artery (Trinkmann et al., 2013). An extension to the technology of the Finapres, the device provides beat-to-

beat information on cardiac output and blood pressure (Schattenkerk, 2009). The Nexfin clamps the pulsating finger artery in order to apply pressure and generate a pressure waveform (Sipkens et al., 2011). The non-invasiveness of this latest development is an attractive innovation in the realm of surgical procedures, in which only a small percentage of patients can receive the standard, invasive intra-arterial line for continuous BP measurement due to the many associated complications (Sipkens et al., 2011).

**2.2.4 Apple Watch.** A more recent breakthrough in the realm of health monitoring devices is Apple's 2018 release of information on their Apple Watch 4. The Apple Watch, which already measures the most common health data and vital signs such as steps taken, distance moved, heart rate, and sleep quality will now reportedly have the capability to conduct electrocardiogram (ECG) testing. A traditional EKG requires several electrodes to give a reading of the heart's electrical activity, but the Apple Watch 4 creates a more accessible method to give these readings, which can lead to a quicker diagnosis of conditions such as atrial fibrillation (AFib), an irregular or rapid heart rate that can increase the risk of a stroke, heart failure, and many other cardiac conditions. Conditions like AFib can be intermittent and often asymptomatic, but dangerous to an individual's health, as it can double the risk of heart-related death if left untreated (American Heart Association [AHA] News, 2018).

Apple is able to achieve these EKG readings by having the user place their finger on the screen for 30 seconds. The watch face contains electrodes, and, combined with the heart-rate sensor on the back of the watch, the app will determine if the heart is beating normally or if it detects signs of AFib. All of the recordings are then stored

within the device, and a PDF can be generated to share with healthcare professionals for further evaluation and/or testing. Despite creating cutting-edge technology and leading the field of health-monitoring smart watches, Apple still has not developed a device capable of continuous blood pressure measurements (AHA News, 2018). The company has proven, though, that health monitoring technology can be taken to the level of the individual, and is both possible and necessary for individuals to have consistent access to this information. As heart disease remains a prominent illness in American adults, and one of the most substantial medical issues worldwide, research to improve accuracies and capabilities of portable health-monitoring devices will continue to evolve.

### 2.3 Cardiovascular Sensing

There is a clear and present public health need for the development of a cuffless, non-invasive blood pressure measurement system. Existing biometric sensing technologies can be adapted and combined in order to help improve blood pressure estimation. In this section, the physical properties of acceleration, electricity, and light using readily available sensors will be discussed.

**2.3.1 Electrocardiogram.** With each heartbeat, the heart generates electrical activity that can be sensed with a device known as an electrocardiogram (ECG; Ashley & Niebauer, 2004). The ECG uses leads which are electrical sensors placed on specific locations of the body. One lead is attached to the right arm and one lead is attached to the left arm, one lead is attached to the left leg, and one grounding lead is attached to the right leg. The ECG then graphs the data from these sensors on a plot, generating an electrocardiograph that is used by medical professionals to diagnose cardiac

abnormalities and pathologies. The R-peak represents the point in the ECG complex where the ventricles, depolarize and contract (Ashley & Niebauer, 2004). The ventricles are the largest chambers of the heart, creating the largest amount of depolarization, and thus create a sharp peak that is easy to detect using an automated computer analysis of the waveform. The R-peak (shown in Figure 2 below), while having no direct correlation to blood pressure, can be used as a reference for the moment when blood is being ejected from the heart and a pulse wave is generated. The applications of the R-peak as a proximal timing reference will be discussed later as a component of pulse transit time.

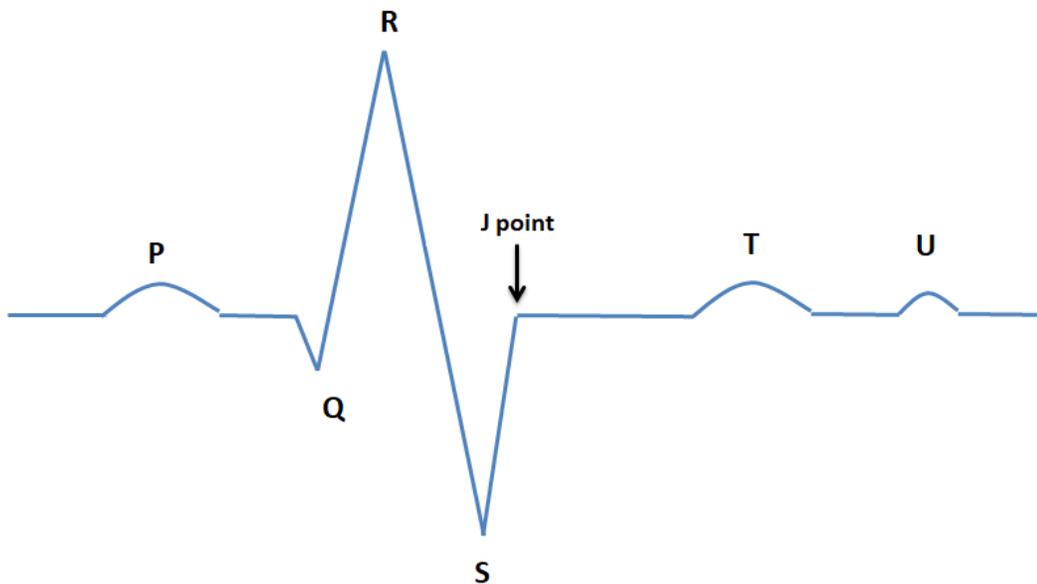


Figure 2 The electrocardiogram interval for one heartbeat.

**2.3.2 Photoplethysmography.** Photoplethysmography (PPG) is a simple, non-invasive technique that is used to detect changes in blood volume in the arteries (Allen, 2007). It is typically collected using a fingertip sensor, called a pulse oximeter, which

shines a light-emitting diode (LED) at a typical wavelength of 640 nm (Jeong, Ko, Hwang, & Yoon, 2006). A photodiode, a semiconductor device that converts light into current, is used to sense this light (Jeong et al., 2006). The photodiode measures the light reflected back on the device, as the rest of the light is absorbed into the arterial blood, venous blood, and tissue (Elgendi, 2012). When the light is emitted onto an extremity, the blood vessels in the skin reflect and absorb a measurable amount of light. As long as the photodiode response to the light is linear, the output voltage is proportional to the light falling on the photodiode (Held, 2016). The amount of blood coursing through the arteries changes the amount of light that is reflected back. More blood in the arteries will allow for less light to reflect back to the photodiode, while less blood will allow for more light to reach the photodiode (Elgendi, 2012). The light that the photodiode reads changes the voltage created by the diode, with a higher voltage corresponding to a larger amount of light sensed by the photodiode (Jeong et al., 2006). By recording and calculating the difference in the amount of light absorbed over time, it is able to determine the changes in blood volume (Jeong et al., 2006).

These changes in blood volume caused by the beating of the heart are often graphed over time in order to produce a waveform called a photoplethysmogram. Photoplethysmograms contain valuable information about an individual's cardiovascular system, which can be used to measure blood pressure (Allen, 2007). The graph in Figure 3 provides a representation of the light measured by the photodiode, represented in volts, over time with the peaks right before the contracting of the heart and the troughs right after the contracting of the heart (Jeong et al., 2006). As seen in Figure 3, the distance from the trough to the peak is the systolic time ( $t_s$ ) and the

distance from the peak to the next trough is the diastolic time ( $t_2$ ) (Teng & Zhang, 2003). The peaks on the Figure 3 are called the systolic peaks and the smaller bump afterwards is called the diastolic peak (Elgendi, 2012).

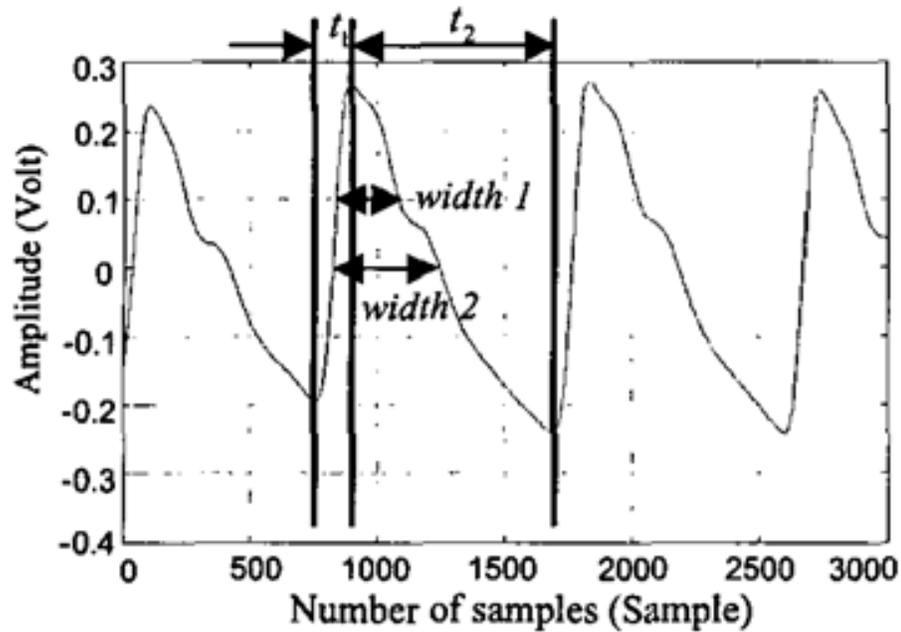


Figure 3. Systolic time shown as  $t_1$  and diastolic time shown as  $t_2$ .

(Teng & Zhang, 2003)

Features found in a single PPG wave such as the systolic and diastolic time (Figure 3) have been shown to correlate to blood pressure with varying degrees of success (Kurylyak, Lamonaca, Grimaldi, 2013). In one case, PPG was shown to have some power in predicting BP within a relatively small group of 15 healthy subjects (Teng & Zhang, 2003). A simple linear regression from this study was able to obtain a

standard error of 0.02 mmHg in the diastolic pressure and 0.21 mmHg in the systolic pressure with standard deviations of 4.39 mmHg and 7.32 mmHg respectively (Teng & Zhang, 2003). Although these results appear promising, the limited sample size included test subjects that were all young, healthy males meaning that many confounding variables did not apply. These findings may not hold true when applied to a different demographic, such as an older population, because of confounding factors such as stiffer arterial walls that tend to be present in older populations (Shaltis, Reisner, & Asada, 2006). Therefore, it is important to consider additional factors such as age, sex, and weight when determining an alternative method of BP measurement.

One significant confounding factor is arterial stiffness, which changes with age and can cause the PPG wave to change shape when compared to people with more flexible arterial walls (Shaltis et al., 2006). This can change the shape of the PPG waveform by smoothing it out and making it difficult to measure features such as the diastolic peak of the waveform (Allen, 2007). Arterial stiffness can also change with ambient temperature of the measurement site, affecting the amplitude of the wave and obscuring the measurement (Allen, 2007). People with heart conditions that cause irregular heartbeats, called arrhythmias, can change the shape of the PPG waveform and make it difficult to measure systolic peaks and diastolic troughs as well (Allen, 2007).

Furthermore, there is a significant difference in blood pressure between the blood flowing in the heart and the blood flowing in the finger that will also make BP difficult to measure using a single PPG wave. To combat this issue, one study used a single PPG sensor with two accelerometers to measure the approximate height and

distance from the heart to the base of the finger (Shaltis et al., 2006). This method required inconvenient equipment that the average person would typically not wear, while disregarding the possible changes in arterial stiffness that could result from changes in temperature or age (Allen, 2007). Although this study found success in using PPG to measure blood pressure, it is important to consider the implications of other factors such as practicality and efficiency when developing a BP measurement device.

A similar study by Kurylyak and colleagues (2013) was conducted using a single PPG signal and a neural network to determine blood pressure using the systolic and diastolic width of the PPG wave at various points along the PPG signal. This method was very effective in predicting the blood pressure from a large number of subjects with a mean error of  $3.80 \pm 3.46$  mmHg in the systolic and  $2.21 \pm 2.09$  mmHg in the diastolic (Kurylyak et al., 2013). These values are within the acceptable range denoted by the American National Standards of the Association for the Advancement of Medical Instrumentation of a mean absolute difference of 5 mmHg and a standard deviation of less than  $\pm 8$  mmHg. (Kurylyak et al., 2013). However, accessibility serves as the main flaw with this method since the use of a neural network requires a significant amount of processing, which may make it incompatible with a phone or other device with limited processing power. Neural networks also require significant amounts of training for each individual, which will require retraining as an individual ages because of the changes in arterial wall stiffness (Kurylyak et al., 2013). This highlights the need for a simpler and more convenient alternative to continuously measure blood pressure.

Overall, these studies do not show very promising results in relying solely on a single PPG signal to predict BP because there lacks an appropriate theory to explain why a correlation may exist. It also requires the control of confounding variables since the standard error in these measurements tends to be large when dealing with subjects with stiffer arterial walls or other confounding factors. Since PPG is shown to measure heart rate very well and can be used on multiple locations on the body such as the ear, toe, and finger, it is probably best to use this method for precise heart rate monitoring alone (Allen, 2007). Thus, it may be beneficial to consider using PPG in conjunction with another tool of measurement to gain more accuracy in BP readings.

### **2.3.3 Accelerometer (Seismocardiogram/ Ballistocardiography).**

Ballistocardiography (BCG) waveforms are measurements of the movements of the body directly caused by the heartbeat of a subject (Giovannardi et al., 2014). These subtle movements are measured by an accelerometer that is either attached to the subject or placed underneath the subject. BCG waveforms can be measured by a scale that the subject stands on. This scale measures the body's longitudinal motion generated by the ejection of the blood at each cardiac cycle (Giovannardi et al., 2014). This waveform is typically less reliable to measure than other forms due to the fact that subjects can throw off the measurements by not remaining completely still. The movements of subjects shifting their balance can cause significant noise in the resulting data.

A sample BCG wave can be seen in figure 4 below, as well as labels for each peak and trough of the waveform. For this study we were focusing on the IJK part of the wave and more specifically the I trough and the J peak. The IJK part of the wave is caused by the ejection of the blood from the heart to the aorta (Kim et al. 2016). The J

peak is the easiest part of the IJK part of the wave to detect with data containing significant noise, which was expected in this experiment. The I trough and J peak, while having no direct correlation to blood pressure, can be used as references for the moment when blood is being ejected from the heart as a proximal timing reference that will be discussed later.

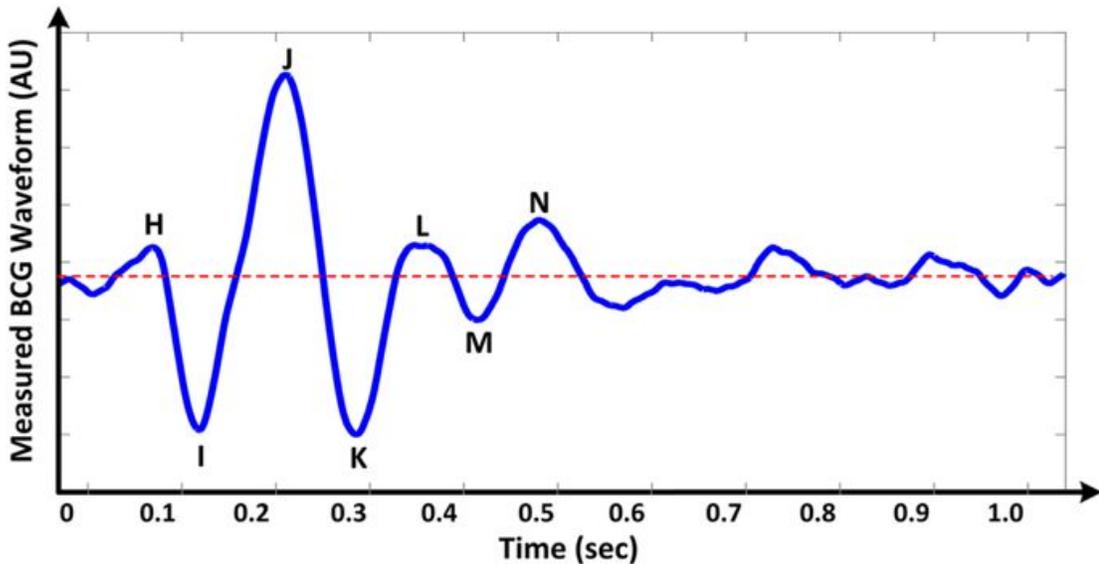


Figure 4. Sample BCG waveform (Kim et al. 2016)

Seismocardiogram (SCG) is the recording of the micro-scale precordial vibrations resulting from beating heart and blood flow into the vascular tree. These vibrations can be acquired by small and cost-effective accelerometers, which makes acquisition of SCG in wearable configuration feasible (Shafiq et al. 2016). It is common for the accelerometer to be placed on the chest of the subject during testing to more accurately measure their heart motions. The SCG waveform is typically unreliable due to the ease at which noise can overwhelm the data due to excessive

shifting and/or heavy breathing of the subject. A typical SCG signal is shown in Figure 5. The peaks in the SCG signal correspond to opening and closing of aortic (AO/AC) and mitral (MO/MC) valve while the IM point occurs during the period of rapid change in ventricular pressure (Shafiq et al. 2016). For this study we will be focusing on the AO peak of the wave. The AO peak of the wave, while having no direct correlation to blood pressure, can be used as a reference for the moment when blood is being ejected from the heart as a proximal timing reference that will be discussed later in this section.

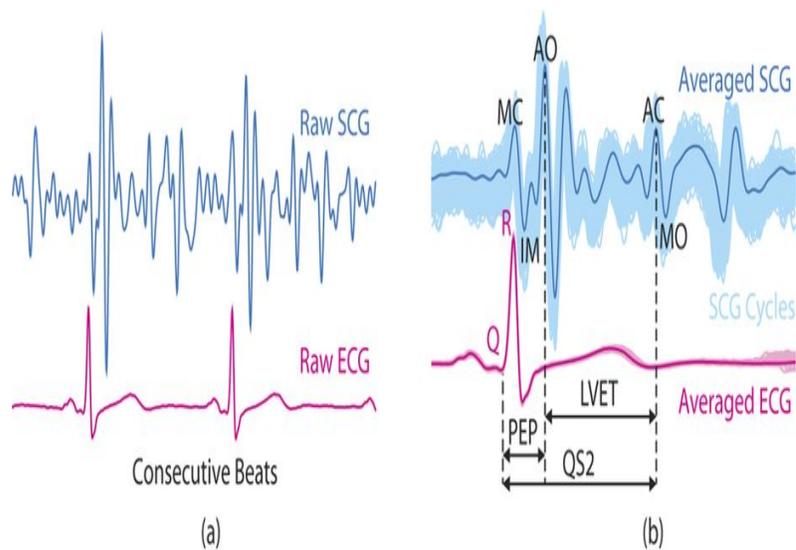


Figure 5. Average SCG waveform (Shafiq et al. 2016)

**2.3.4 Pulse Transit Time.** Pulse transit time (PTT) is the time that it takes for a single pulse wave to travel between two reference points down an arterial pathway (Smith, Argod, Pépin, & Lévy, 1999). A combination of a proximal and distal sensors are used to create timing references for pulse waves to calculate PTT. Once PTT is obtained, it is possible to use it to determine the blood pressure. Pulse velocity has

shown to be positively correlated with systolic blood pressure, therefore PTT would decrease with increasing blood pressure (Kim et al., 2015).

PTT can be measured using several different methods, one of which entails measuring an individual's pulse from one point on their body to another through the use of PPG sensors attached to two different locations on a person's body (McCombie, Reisner, & Asada, 2006). The method of measuring PTT using two PPG sensors are described in this paper as "pulse-to-pulse" transit time in order to differentiate it from other methods of obtaining PTT. Pulse-to-pulse transit time should be gathered through the use of two inline PPG sensors, a known distance apart, on the same appendage (McCombie et al., 2006). For example, sensors can be placed along the ulnar artery at the wrist and the base of the pinky finger (McCombie et al., 2006). Different sensor locations, such as the finger and toe, can also be used (Tsai et al., 2005). Points on the waveforms generated by the PPG sensors are identified and the time between the two are recorded. For example, the onset of the pulse waveform of proximal wrist sensor is timed to the onset of the pulse waveform of the distal index finger PPG sensor. The PTT data gathered from the dual PPG sensors can be used to determine one's blood pressure after a calibration is conducted (McCombie et al., 2006).

PTT can be written as a function of a thinly walled vessel elasticity according to the Moens-Korteweg equation (McCombie et al., 2006). Vessel elasticity can then be written as a function of pressure. A combination of both provides an equation for the relationship between PTT and blood pressure (McCombie et al., 2006). In order to calibrate a device that uses dual PPG sensors for accurate blood pressure monitoring, one must compare the PTT data with a known change in arterial pressure and a known

blood pressure taken using a standardized and clinically used device such as a sphygmomanometer (McCombie et al., 2006). Algorithms need to be written that consider changes in arm height as hydrostatic pressure at one's extremities changes as the extremity is raised above or below the heart (Beevers, Lip, & O'Brien, 2001).

Another technique involves an electrocardiogram (ECG; Chen, Kobayashi, Ichikawa, Takeuchi, & Togawa, 2000). An ECG can measure biological rhythms; therefore, it is capable of measuring blood pressure through PTT. The ECG to pulse technique is an accurate way to track blood pressure consistently because there appears to be a clear linear relationship with systolic blood pressure and pulse transit time (Chen et al., 2000). For the most accurate reading, a previous study states that the second finger of the hand is the most optimal location for the distal PPG sensor (Chen et al., 2000). An accelerometer will also be tested in our study as a proximal timing reference in lieu of ECG. It can be strapped to the individual's chest or be incorporated into a scale that then senses the contraction of the heart during systole which references the point at which blood is ejected from the heart and a pulse wave is generated.

This method of measuring blood pressure by utilizing pulse transit time is not perfect, since there are multiple variables that could confound the data and lead to inaccurate results. A root cause of this complication stems from the fact that the measurement is taken over two points in the body. Abnormal local changes of the peripheral arterial wall can create an issue with the accuracy of the measurements (Foo, 2007). Another common factor is arterial wall stiffness, also known as arteriosclerosis, which is caused by the buildup of plaque on the arterial walls and can be associated with various diseases (Poon & Zhang, 2006). An issue found in literature noticed that

subjects with hypertension have stiffer arterial walls and therefore are more likely to confound transit time related parameters (Foo, 2007). Therefore, this method will be less useful for individuals who have hypertension.

#### 2.4 Interventions and Blood Pressure Fluctuations

Blood pressure is highly variable and is able to react to various forms of external stimulation. Researchers have measured fluctuations in BP using interventions in a controlled lab setting that mimic natural changes in BP occurring within the body. When conducting interventions to measure BP, a baseline BP level is determined through a rest period (Martin et al., 2016). This is typically done before the start of the intervention and between each intervention. This rest period prevents the effects of one intervention from interfering with the next, which is known as carryover effects (see Figure 6 for common hemodynamic interventions).

The cold pressor test is a common procedure done to cause a rapid increase in the BP of the participant. It involves a procedure which requires the local extremity of a participant, such as an arm, to be quickly immersed into ice water (Hines & Brown, 1936). This produces a profound thermosensory stimulus that causes a physiological response in the body. Studies that have repeated this procedure have also found a similar pattern in BP response to this stimulus, which validates the procedure's consistency. A major advantage to this intervention is that it is noninvasive and minimally harmful to the participant.

Another intervention done to increase BP involves mental arithmetic (Al'Absi et al., 1997). Research has shown that mental arithmetic is a publicly salient task, much like public speaking, and can be a source of stress for an individual. Stressors have been

shown to increase cardiovascular activity including heart rate and systolic and diastolic BP (Steptoe, 2000). An intervention involving mental arithmetic requires a participant to complete timed mental mathematical problems in front of the researchers. Prior research has suggested that mental arithmetic results in substantial cardiovascular, endocrine, and cortisol responses in subjects and negative overall mood following the intervention. Psychologically, the mental arithmetic and public speaking tasks invoke anxiety and stress. Although public speaking tasks often produce more profound physiological activity (higher SBP, DBP, and heart rate), mental arithmetic is a viable alternative that produces similar effects to a lesser degree.

Furthermore, breath holding can also be used to temporarily increase the BP of an individual. The process of breath holding involves a vasomotor stimulus that is related to physiological changes. Studies using a sample of females have found that holding your breath increases heart rate and arterial blood pressure (Grunovas et al., 2016). The BP returned back to normal during a five minute break. The findings from this study suggest the temporary nature of BP fluctuations. Similar results were found in men doing resistance training (Linsenhardt, Thomas, & Madsen, 1992) who experienced higher systolic and diastolic BP when holding their breath compared to other breathing exercises.

Finally, slow breathing has the opposite effect on blood pressure. Deep and slow breathing has been shown to temporarily dilate blood vessels, causing them to reach a relaxed state (Canadian Association of Retired Persons, 2006). A study comparing an intervention and control group found that using interactive music or devices to regulate slow breathing was associated with lower levels of BP (Grossman,

2001; Elliott et al., 2007). Deep abdominal breathing is also a common practice in relaxation and meditation techniques that have been linked with reduced levels of BP (Elliott et al., 2004). Like the aforementioned interventions, slow breathing is a temporary and noninvasive methods of fluctuating BP.

Figure 6 below shows the changes in BP and HR that would be observed with the introduction of each intervention. The abbreviations in Figure 6 are labeled as follows: R1 is rest period 1, CP is cold pressor test, R2 is rest period 2, MA is mental arithmetic, R3 is rest period 3, SB is slow breathing, R4 is rest period 4, BH is breath holding, R5 is rest period 5.

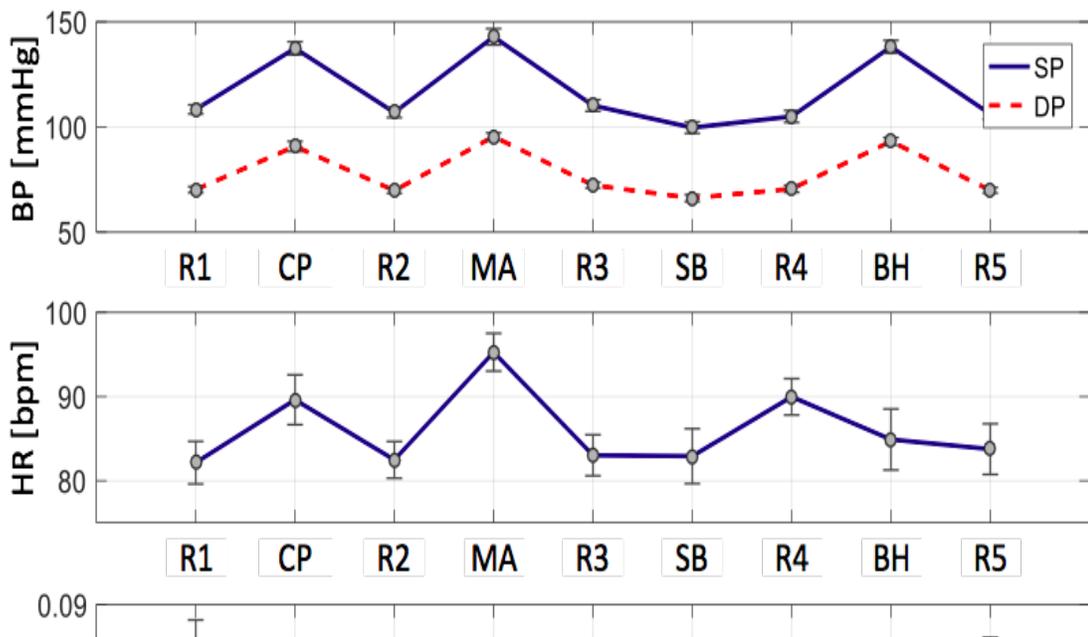


Figure 6. Average BP and heart rate changes during human subject study. R1-5= Rest periods 1-5, CP= Cold pressor, MA= Mental arithmetic, SB= Slow breathing, BH= breath holding (Yousefian et al., 2018).

### 2.5 Research Objectives

The primary objective of this research project was to identify signal pairs for measuring pulse transit time that correlate closely with blood pressure. This would allow researchers to identify proximal and distal sensor location pairs that could be used in the calculation of pulse transit time. A human subject study was designed using previously validated hemodynamic interventions in order to achieve this goal. The second objective was to examine the feasibility of using integrated sensors on a mobile device in the measurement of blood pressure.

### 2.6: Summary

The purpose of this project was to advance knowledge regarding the calculation of pulse transit time and its relation to obtaining a blood pressure measurement. Specifically, it was hypothesized that pulse transit time could be obtained using biometric sensors located in various positions of the human body. Furthermore, it was hypothesized that existing sensors on a mobile device could be used in order to obtain a blood pressure measurement. This study was important because many people are vulnerable to the adverse effects of elevated blood pressure, which leads to long term medical complications. Addressing these risks early is an essential component to enhancing preventative care. If blood pressure could be measured conveniently at a low cost, more individuals could become aware of potentially lethal cardiovascular conditions. The findings from this study could inform the development of future interventions to reduce the adverse effects of hypertension. Moreover, these results could offer alternate methods of investigating blood pressure using biometric sensors.

## Chapter 3: Methodology

### 3.1 Human Subject Study

In order to test the accuracy of various sensor placements against the Nexfin, the human subject subteam decided to obtain blood pressure measurements from a group of participants. Once approval was received from the Institutional Review Board, participants who met the inclusion criteria were recruited via word of mouth to participate in the study. Team members recruited students from the University of Maryland, College Park. Participants between the ages of 18-70 who were not pregnant and had no previous history of cardiovascular concerns were encouraged to participate in the study. An oral overview of the study was provided prior to the beginning of the study. They had to sign papers including a consent form and a form acknowledging understanding of these aforementioned criteria. They were informed that they could withdraw from the study if they experienced discomfort at any time.

For the study, participants completed a one-hour long series of interventions to fluctuate and measure BP. A ten question survey was briefly administered to participants at the conclusion of their participation to obtain their feedback on the process and opinions on the sensors. Survey data was collected from 28 participants. Some participants chose not to complete the survey. As compensation, participants received \$20 in cash for the hour long study and survey. Participants then signed a form acknowledging the receipt of this payment. Participation was voluntary and subjects had the opportunity to conclude the study earlier or take breaks as needed. Sensitive data including height, age, weight, sex, and ethnicity was voluntarily self-reported by

the participants. All other personally identifying information were removed from analysis. Data were collected during the fall of 2017 and spring of 2018.

**3.1.1 Participants.** The participants in this study were 35 University of Maryland, College Park students aged 18 to 23. All participants were above the age of 18, had no prior history of cardiovascular conditions, and were not pregnant. During analysis, data from 15 participants were not viable and subsequently excluded due to errors in data collection or due to logistical difficulties in the analysis. One of the 15 participants was unable to complete the interventions and withdrew from the study. Thus, the final sample for analysis included data collected from 20 participants.

Participants varied in terms of academic major, race/ethnicity, exercise routine, and demographic background. In total, participants ranged in age from 18-23 years, with a mean age of 20. Regarding sex, 14 participants (40%) identified as female, 20 identified as male (57.14%), and one was not reported (2.86%). The weight of the participants ranged from 107 lbs to 205 lbs with the average weight being 154.54 lbs (see Table 2 for demographics). Height ranged from 157.5 cm to 193 cm with the average being 173.56 cm. In terms of race/ethnicity, participants were predominantly White/Caucasian (62.86%) followed by Asian (20.0%), Black/African American (14.29%), Hispanic/Latino (5.71%).

Table 2. Participant Demographics

Demographic Variable (n=35)	
<b>Male</b>	20 participants (60%)
<b>Female</b>	14 participants (40%)
<b>Average Weight</b>	154.54 lbs
<b>Weight Range</b>	107-200 lbs
<b>Average Height</b>	173.56 cm
<b>Height Range</b>	157.5-193 cm
<b>Average Age</b>	20 years
<b>Age Range</b>	18-22 years
<b>Average Body Mass Index (BMI)</b>	22.59
<b>BMI Range</b>	17.6-28.1
<b>White/Caucasian</b>	22 participants (62.86%)
<b>Asian</b>	7 participants (20.0%)
<b>Black/African American</b>	5 participants (14.29%)
<b>Hispanic/Latino</b>	2 participants (5.71%)

**3.1.2 Instrumentation.** Subject information including age, height, weight, and sex was entered into the Nexfin machine. A BioPac MP150 machine was also used to collect data using the BioPac AcqKnowledge Software. Subjects stood on a predesigned BCG scale (Martin et al., 2016) that resembled a traditional bathroom weighing scale for the duration of the experiment. Waveforms produced from the

sensor signals were recorded on this software. Signals from the ECG, BCG (scale), BCG (accelerometer), and BP from the Nexfin were all collected and recorded in the AcqKnowledge software (see Figure 7 for an illustration /of the signal recordings). Prior to the initiation of the interventions, lab team members examined the waveforms to ensure R-waves were identifiable in the ECG signals, I, J, and K waves were identifiable in the BCG signal, and systolic and diastolic peaks were identifiable in the Nexfin signal.

On the right side of the participant's body, one electrode was placed on their upper chest (see Figure 8 for a diagram of sensor placement). A Nexfin was placed on their wrist and middle finger. Various sized finger cuffs (extra small, small, medium, large) were used to ensure participant comfort and detection of signals. The cuff was wrapped around the middle phalanx of the right hand middle finger. An accelerometer was placed on their upper arm. The left side of the body had two more electrodes, one placed on the upper chest and another placed near the waistline. All three electrode leads were attached to the ECG input of the BioNomadix Transmitter. This transmitter was wrapped and fastened around the subject's waist.

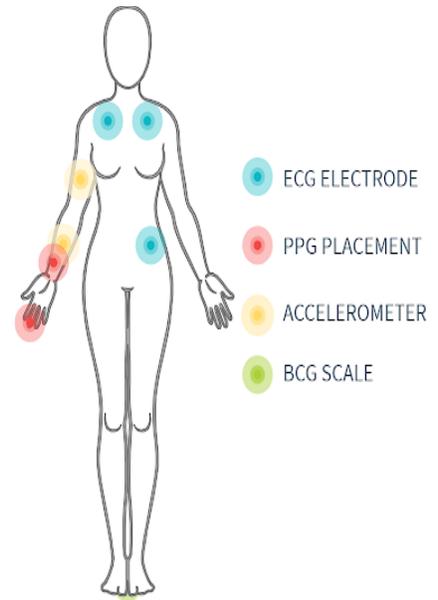


Figure 7. Photo and diagram depicting location of sensor placements

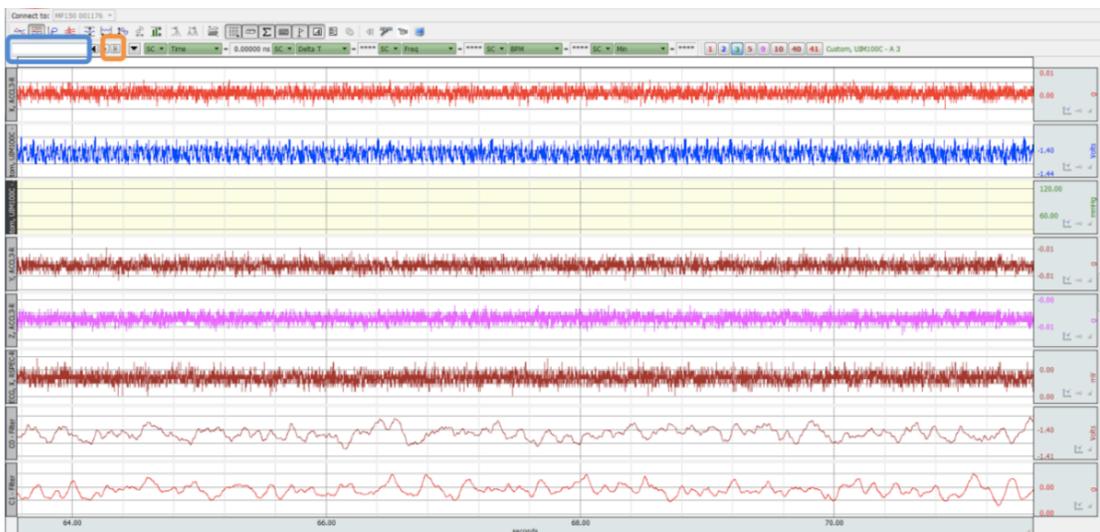


Figure 8. Waveforms recorded in the AcqKnowledge Software.

**3.1.3 Study design: Interventions.** Using aforementioned literature, the study was designed to consist of five physiological interventions to alter BP including cold pressor, mental arithmetic, breath holding, slow breathing, and hand raising and lowering. Due to logistical issues with data collection, the hand raising and lowering intervention was removed from analysis. The cold pressor, mental arithmetic, and breath holding procedures were intended to increase the BP of the participants temporarily, as noted in prior literature. On the other hand, the slow breathing intervention was implemented to temporarily reduce BP levels in the participant. Between each intervention, there was a 90 second rest period that allowed the physiological responses of the participant to return to baseline (see Figure 9 for a depiction of all interventions). This also prevented effects from one intervention from carrying over into the subsequent intervention.

Prior to the start of interventions, a baseline BP level was obtained by allowing the participant to stand still on the BCG scale for 60 seconds. This was considered Rest Period 1 (R1) (see Figure 9 for schematic on study procedures) . Following this rest period, the first intervention, cold pressor (CP), began which lasted for 180 seconds. This intervention required the left arm of the participant to be submerged in ice water for the duration of the intervention. If this intervention caused excessive discomfort for the participant, they were permitted to remove their hand from the bucket of ice water and proceed with the rest of the study. Previous literature has shown that immersing an extremity in ice water can lead to a sudden and noticeable spike in BP levels (Hines & Brown, 1936).

After this intervention, the participant had a second rest period (R2) that lasted 90 seconds. Then, the next intervention, mental arithmetic (MA), began for a total of 120 seconds. This intervention required the researcher to provide the participant with a mathematical problem that they had to mentally solve as quickly as possible. Subjects were given a three-digit number (e.g., 123) and asked to sum the individual digits in the number (e.g.,  $1+2+3=6$ ). Then, the subject was instructed to add this value to the original number (e.g.,  $123+6=129$ ) and to provide the final answer back to the researcher. Incorrect responses resulted in the researcher repeating the same problem and asking the participant to redo the mathematical problem in an effort to add stress and tension to the situation.

Upon completion of the mental arithmetic task, a third rest period (R3) lasting 90 seconds was done to allow BP levels to return to baseline. The next intervention required participants to slow breathe (SB). As mentioned in previous studies, slow breathing has been shown to low BP levels due to the dilation of arteries (Grossman, 2001; Elliott et al., 2007). Subjects were instructed to breathe in for a few seconds and then breathe out for the same length of time. After the slow breathing exercise, another rest period (Rest Period 4 (R4)) allowed the BP levels to return to normal before the next intervention. This subsequent intervention required the the subject to hold their breath for as long as possible, to a healthy and comfortable extent. Responses to the breath holding exercise lasted anywhere from a few seconds to over a minute. This intervention was intended to once again, increase the BP level.

Finally, after a fifth rest period (R5), the participants completed a hand raising and lowering exercise intended to alter the local BP in their hand. They were instructed

to maneuver their hand in 5 different positions (HAL) (first position was 10 cm above subject's height and the next four positions went down in 20 centimeter increments). However, due to technological errors resulting from this intervention and difficulty analyzing this data, this intervention was not included in the final analysis. The study concluded with a sixth, and final, rest period.



Figure 9. Procedure for human subject study. Each intervention was coupled with a 90 second rest period to return vitals to baseline levels. CP= Cold pressor, MA= Mental arithmetic, SB= Slow breathing, BH= Breath holding, HAL= Hand raising and lowering

**3.1.4 Survey.** A ten question survey was administered to the participants upon completion of the study. This was known as the “Post Test Survey” (see Appendix X for full survey). The survey included the following questions: *How comfortable was the [Nexfin, ECG sensor, brachial accelerator, wristband, and PPG sensor]?, What location was it most comfortable to wear a sensor for long periods of time?, Have you owned a fitness tracker before?, Do you own an ambulatory blood pressure monitor at home?, and How much would you pay for a device that could continuously measure Blood Pressure?* Participants rated their responses for the first question on a Likert scale ranging from 1 (least comfortable) to 5 (most comfortable). The purpose of this study was to gauge public opinion on measuring blood pressure as a basis for future research to explore those options. It also helped reveal what qualities and locations are preferred by the college-aged demographic.

### 3.2 Data Analysis Methodology

It was necessary that the team understood and processed the information gathered by the human subject study in order to analyze trends, draw correlations between key signal features, and produce meaningful conclusions to support this thesis. With the help of Yang Yao (a visiting student of the team's principal investigator, Dr. Jin-Oh Hahn), the team was able to use filtering techniques and a graphical user interface (GUI) to process the data collected by multiple sensors. This data, as described by the human subject methodology, was collected by sensors placed in multiple location on the subjects' bodies. A MATLAB script was written to filter out signal noise using several methods. These methods included frequency domain analysis of the collected signals for filtering out DC components of measured data (such as instrument bias) as well as high frequency components not important to the slow moving signals of PPG or BCG. This meant bandpassing the signal based on characteristics of the signals in the frequency domain. Figure 10 shows the process by which these signals were collected, filtered, and what was additionally required to ensure usability.



Figure 10. Signal filtering flow chart

**3.2.1 Feature Identification.** Error in the collection process was evident after processing the subjects data. Each sensor had its own inherent error and the collection process itself included some human error that varied from subject to subject. Some possible sources of error were incorrect documentation of intervention start and end time, sensor noise associated with placement on the human body, changes in signal power over time, and interruption in the data collection process. Sensor noise was often associated with accelerometer noise due to subject moving during the study, PPG noise due to sliding of sensor over the finger, or other random noise. Error in peak detection due to changes in signal power had to be corrected manually by changing thresholds for feature detection. Interruption in the collection process was encountered when some subjects became fatigued or lightheaded during interventions, requiring the team to pause briefly or end the session entirely.

It was important that the team identify which subjects' data was usable for further analysis. Of the 35 subjects monitored, 20 were usable and consistent while the remaining 15 were not for the reasons described above. In some cases, sensors were improperly placed or timing references were not properly recorded. Each signal received from the sensors had associated characteristic features that can be identified. Some subjects were found to have resting systolic blood pressure of over 160, who were excluded due to having blood pressure much higher than what was expected for the study. Using this method, the team was able to differentiate what signals were consistent and where any error may have occurred.

The first metric that the team used to determine the usability of a subject's data was whether or not an appropriate frequency domain could be selected. Frequency

domains were filtered based on the second and third peaks in the scale BCG spectrum for all interventions. In some cases the signal noise was too erratic and inconsistent, making the identification of the second and third peaks impossible. This meant that the domain for that subject's intervention could not be determined since the start, midpoint, and end of the domain could not be selected.

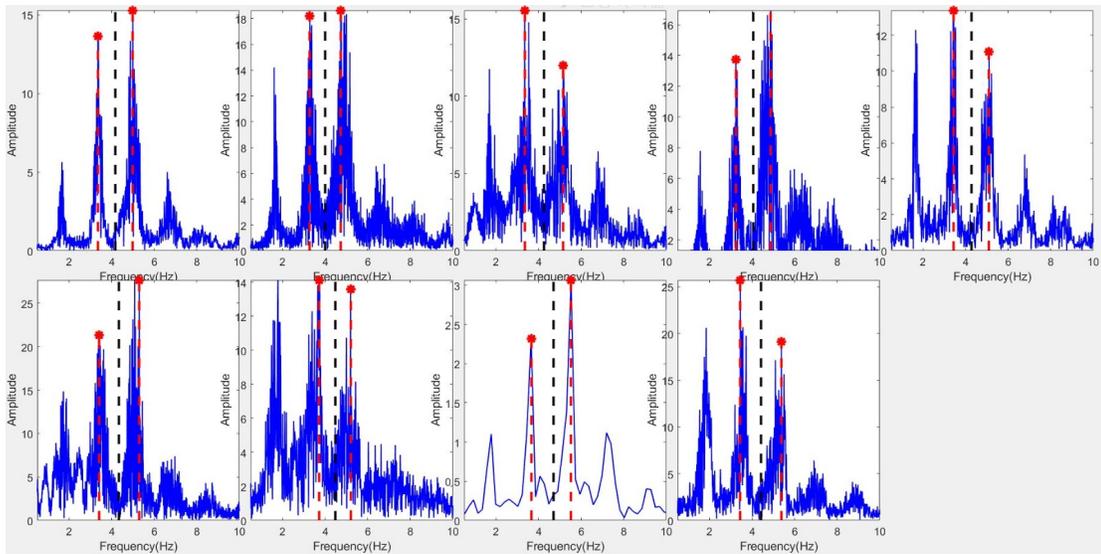


Figure 11. Frequency domains of a subject for each intervention (In order, rest 1, cold pressor, rest 2, mental arithmetic, rest 3, slow breathing, rest 4, breath holding, rest 5).



**3.2.2 PTT Computation and Correlation Analysis.** Upon feature extraction, the different metrics PAT1, PAT2, and the PTT1-PTT4 needed to be calculated. A separate program was given the data from the preprocessing. The preprocessing provided values of systolic blood pressure (SBP), diastolic blood pressure (DBP) as well as the times that these pressures occurred. It also provided time locations of the R-wave in the ECG waveform, peaks and troughs in the PPG waveform, as well as I-wave and J-wave in the arm BCG waveform. The post processing program is meant to take these time references and measure PAT and PTT for specific beats.

The program sets out to find the correlation between each separate PAT/PTT and BP. To do this, we utilize each intervention as a data point, where an average value of PAT/PTT within that intervention would be plotted against the average SBP/DBP during that intervention. Assuming each of the interventions worked properly, there would be a good range of blood pressures and PTT/PAT present to show a clear relationship between these two variables. Below in Figure 13 is an example output of the correlation program showing results for an arbitrarily generated subject.

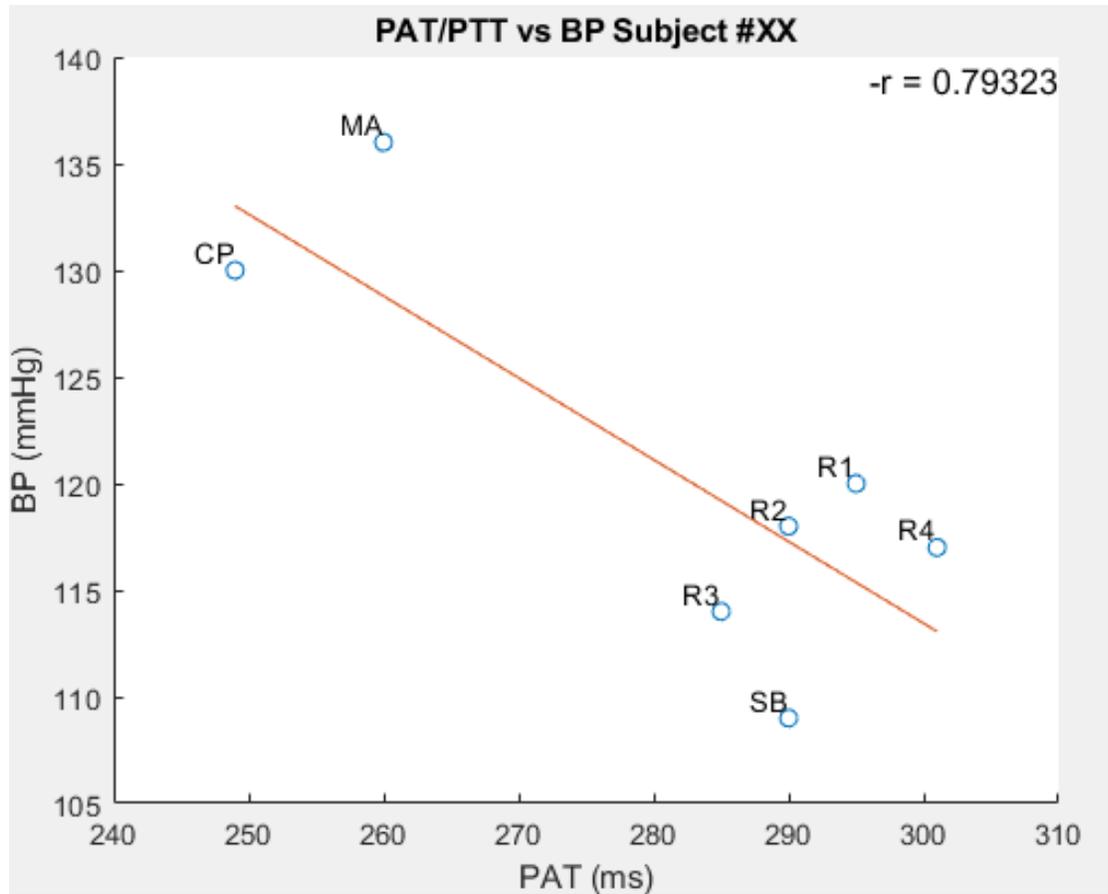


Figure 13. Correlation Output

There was found to be much variation in heart rate over the course of each intervention. Since this can introduce variability in PTT and PAT measurements, we selected only seven adjacent beats to remove some of the variability associated with changing heart rate over time. Seven was chosen to be small enough that there would not be much variation in heart rate or BP over this interval, but large enough to contain a larger sampling of points. To select the seven beats, the program first found the global minimum or maximum value of SBP depending on whether the intervention was meant to increase or decrease SBP with rest periods taken as minimums. Then the program moved 3 beats behind this point to declare a starting point for PAT/PTT will be taken

and correlated with BP. Thus an array of 7 beats with their corresponding values of PAT/PTT could be stored with corresponding values of SBP/DBP at those points centered around a maximum/minimum point considered characteristic of the intervention.

With a starting beat, the program is now able to begin finding PAT/PTT. To achieve this, the program first retrieves the nearest time location of an R-wave before the time of the SBP maximum occurring. Then the program stores the next R-wave occurring after the max in SBP. To evaluate if these two R-waves are appropriately spaced, the program evaluates the difference in time between them (the beat period) and decides to skip the beat if the heart rate is above 180bpm or below 30bpm (considered unacceptable limits). If the program chooses to skip a beat, it will move to the next SBP value available and continue storing beats until 7 acceptable beats are found. So skipping a beat does not make the sample size within an intervention smaller, it just makes the time window over the sample larger to include 7 usable beats. Seven was chosen because it was a short enough period of time to have a relatively constant heart rate, but large enough to sample a characteristic number of points.

After finding acceptable ECG R-waves, the program next evaluates the PPG waveform. It checks for the first PPG max occurring after the initial R-wave. It then checks that this PPG max occurred before the second R-wave. If it did not, it skips this beat. This skip means that there is no PPG max available for this beat and therefore it must be skipped. After finding an appropriate PPG max, the program finds the first PPG foot available before the stored PPG max. The program then finds the amount of time lapsed between the PPG foot and max. If the time lapsed is greater than the heart

period, it means that the PPG foot does not correspond to this max, and therefore this beat does not have a foot available. Thus this beat must be skipped for another with a foot that is available.

Upon finding appropriate PPG references, the program next finds the first J-wave in the BCG waveform to occur within the period defined by the 2 ECG R-waves. If a J-wave does not exist in this interval, the beat is skipped. If the J-wave does exist, the I-wave before this J-wave is found. The time lapsed between I-wave and J-wave is then evaluated. If this time is greater than the heart period, the beat is skipped, meaning that the available I-wave did not correspond to the current beat.

With all timing references available, the values of SBP and DBP for each beat is stored in an array. Then the values of PAT/PTT are calculated using the timing references. The metrics are defined as follows:

PAT1: ECG R wave - PPG foot

PAT2: ECG R wave - PPG maximum

PTT1 and PTT2: BCG I wave - PPG foot and maximum

PTT3 and PTT4: BCG J wave - PPG foot and maximum

Figures 14 and 15 show where on the waveform these timing references are located.

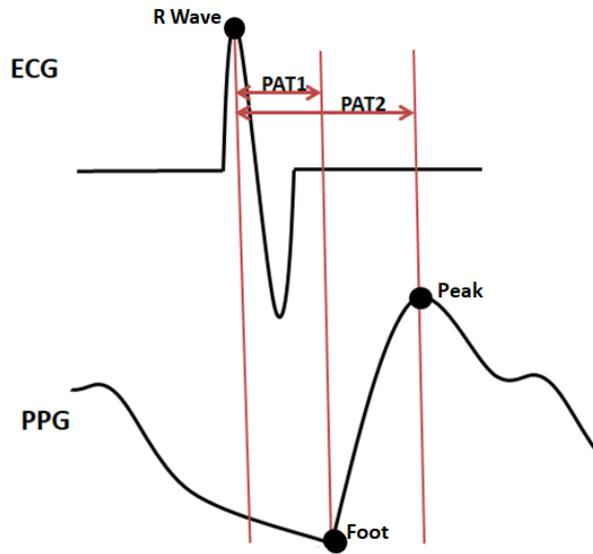


Figure 14. Shows where on the waveform PAT1 and PAT2 are located.

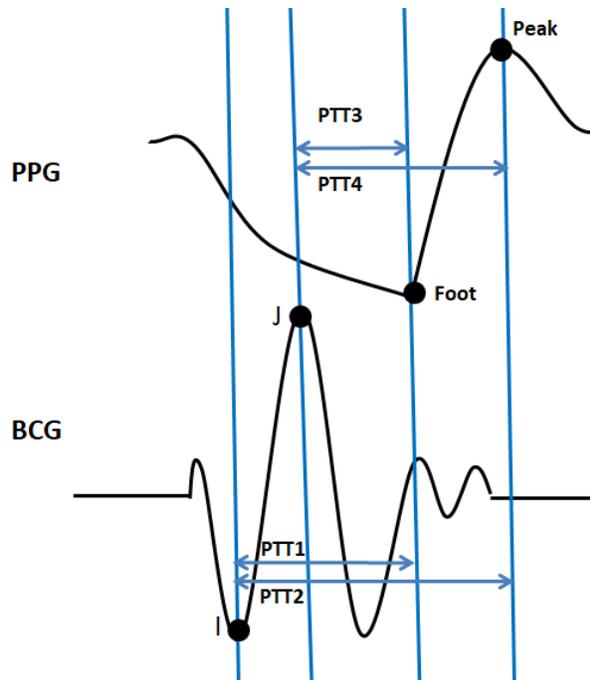


Figure 15. Shows where on the waveforms PTT1 - PTT4 are located.

Upon obtaining 7 values of PAT<sub>1/2</sub> and PTT<sub>1/2/3/4</sub> the median of these PAT/PTT is calculated. The median was chosen since often large outliers due to mismeasurement of characteristic points created large outliers within the 7 data points. Next a median value for SBP and DBP was obtained across each intervention. Finally, a plot was obtained of the PAT/PTT against SBP/DBP was obtained and a linear regression model was used to calculate a value of correlation coefficient. These correlations were then stored in an array with one coefficient for each metric (PAT<sub>1/2</sub> and PTT<sub>1/2/3/4</sub>) for each subject.

### 3.3: Evolution of Project

When the team was formed in 2016 the first goal was to make a stand-alone device that users could wear. This device was supposed to be able to measure an individual's blood pressure continuously without the need of a blood pressure cuff. Originally, the team wanted to incorporate what was coined "The Thermal Method", into the device in order to calculate blood pressure. The thermal method mechanism was to measure the movement of blood by tracking a previously heated segment of the blood through different parts of the body. This in turn would output values such as distance and time, which then would allow the device to calculate blood pressure. Unfortunately, this method of measuring blood pressure wasn't possible, but the team wanted to stick with the original goal of a stand alone device. This led the team to the second method attempted, "The Magnetic Method." The magnetic method was similar to the thermal method, in which the users blood velocity was measured using changes in magnetic fields of moving magnetized blood. Essentially, part of the user's blood would be magnetized, and the device would be able to track its velocity, which would

then output the proper variables needed to calculate blood pressure. This is using the theory known as the Hall Effect, where a potential difference is created across a magnetic field. This method also was scrapped as the feasibility of it was drawn into question.

After these minor setbacks, the team decided it was best if we didn't attempt to make and market a stand-alone device, which was proving to be difficult in such a short time frame. However, maybe it would be possible to create a phone application that could do just this. The application would use SCG signals from the chest and PPG signals from the finger using the phones accelerometer and phone camera respectively. These signals, the SCG and PPG, would allow the app to calculate the users PTT in real time. Then the PTT values with the PPG values would output blood pressure. Unfortunately, this phone application also had unforeseen obstacles such as a lack of expertise in programming and time constraints, so the team thought it would be best to take another route. This then led the team to their final goal which was, data processing using human subjects. In other words, the goal was to develop a mechanism for analyzing the signals obtained from a human subject study to draw meaningful conclusions from the data. The team was split up into two specialized groups. One group spent its time in the lab obtaining vitals from different participants while they partook in the intervention activities. These vitals were then saved and sent to our other team who developed an algorithm that could take these signals and turn them into a blood pressure reading. These signals included blood oxygen content, PTT, ECG waves, SCG, PPG and accelerometer readings. The goal was to maximize one's ability to track their blood pressure continuously and safely.

### 3.4: Budget

In order to execute this project, adequate funding and budgeting were required. Finances were handled through a financial liaison who was granted \$600 dollars per academic semester by the Gemstone office. These funds were guaranteed for about 4 months in the fall and spring. Unused funds from one semester were unable to be rolled over to the next semester. This was considered heavily in purchasing decisions in order to best utilize funds. In order to determine if additional funding would be necessary to execute different aspects of the project, the financial liaison mapped out a three year budget at the end of the first year to gauge whether or not the team would have to apply for external funds through grants. This budget plan would be adjusted as the project evolved. Ultimately, a decision was made in the spring of 2017 that external sources of funding would not be needed in order to meet our goals for our project.

Purchases corresponding with the team budget began in the fall of 2016. These purchases were approved by the financial liaison and by the Assistant Director of Operations. Once funds were granted to the team, the budget was allocated towards the procurement of bread boards, magnets, and hall sensors in 2016. At this stage, the team was intent on creating a non-invasive wearable device that continuously measured blood pressure. These tools were necessary to explore different methods to measure blood pressure. After the fall of 2016, the budget for the subsequent three semesters was allocated solely towards human subject testing. During this time \$750 dollars were used towards compensating subjects at a rate of 20 dollars per test. One hundred dollars from this allocation was used to buy coolers to preserve frozen ice for the cold pressor intervention of the IRB approved procedure. The budget was also utilized to buy

cleaning supplies and antibacterial wipes to create a sterile testing space and give subjects a safe and pleasant experience. In addition to the funds used through the Gemstone budget, the team’s mentor, Dr. Hahn, granted external funds in order to conduct additional subject testing and collect a more complete and diverse sample size.

## Chapter 4: Results

### 4.1: Human Subject Study Results

The obtained average value of the correlation coefficient across the 20 subjects that were analyzed was found to be very different between metrics. Table 3 below provides values of correlation coefficient -r for each metric against SBP as well as performance among quartiles of subjects. The value of -r is given to avoid placing minus signs in front of every cell. Q1 is the first quartile, Q2 is the median, Q3 is the third quartile, and the last row is the standard deviation of the Pearson correlation coefficient r. The Best category in Table 3 contains data that was gathered by selecting the highest r-value from the measurement methods (i.e. PAT1, PAT2, etc.) for each subject.

Table 3: Performance of metric in predicting Systolic Blood Pressure

Systolic	PAT1	PAT2	PTT1	PTT2	PTT3	PTT4	Best
AVG	0.688081	0.729635	0.422985	0.430566	0.496144	0.524975	0.796804
Q1	0.479717	0.51814	0.168889	0.175854	0.207193	0.235765	0.752062
Q2 (MED)	0.716333	0.801752	0.350944	0.353652	0.338271	0.448593	0.841337
Q3	0.860213	0.878484	0.498768	0.541538	0.6078	0.669912	0.90036
Stand Dev	0.156873	0.154989	0.141219	0.153771	0.175878	0.181026	0.063347

Table 4 below shows the performance of each metric for DBP using -r once again. The r is negative since smaller PAT/PTT corresponds to higher blood velocity and therefore higher BP.

Table 4: Performance of metric in predicting Diastolic Blood Pressure

Diastolic	PAT1	PAT2	PTT1	PTT2	PTT3	PTT4	Best
AVG	0.658266	0.712125	0.448473	0.449139	0.494461	0.537834	0.781261
Q1	0.308558	0.466688	0.09023	0.087721	0.230233	0.321438	0.683589
Q2 (MED)	0.713728	0.807018	0.26726	0.281335	0.307302	0.490295	0.828498
Q3	0.85281	0.839798	0.643141	0.667316	0.66148	0.666719	0.885838
Stand Dev	0.291675	0.267534	0.255478	0.255261	0.267261	0.236763	0.20739

The root mean square error was calculated to determine how far off of the predicted line the measurements were found to be on average. The values of root mean square error (RMSE) are found in the table below for all of the interventions for systolic blood pressure.

Table 5: RMSE in systolic blood pressure in mmHg

Systolic	PAT1	PAT2	PTT1	PTT2	PTT3	PTT4
AVG	12.11249	11.40379	16.51401	16.44986	14.97978	14.77606
Q1	9.15388	7.988515	11.95547	11.88434	10.41303	10.40102
Q2	11.72283	10.20322	15.18092	14.36025	14.47762	14.11507
Q3	13.55096	13.76893	20.62977	20.66333	18.24279	18.07131
Std Dev	4.874713	4.873283	5.917459	5.915116	5.266967	5.065745

The RMSE for the diastolic blood pressure is provided in the table below.

Table 6: RMSE in diastolic blood pressure in mmHg

Diastolic	PAT1	PAT2	PTT1	PTT2	PTT3	PTT4
Avg	7.70574	7.060575	10.05336	10.05351	9.431654	9.09604
Q1	6.01231	5.578805	6.731597	6.536714	6.645191	5.926041
Q2	7.361244	6.268726	9.077824	8.998052	9.354402	9.564114
Q3	8.059138	7.309004	12.61686	12.65087	11.75841	11.54723
Std Dev	2.858637	2.957188	4.325729	4.308349	3.812078	3.627143

#### 4.2: Survey Results

Based on the survey given at the conclusion of the human subjects testing that can be found in the appendix, Figures 15 through 20 below show the answers recorded.

The two most comfortable locations were found to be the upper arm and the chest.

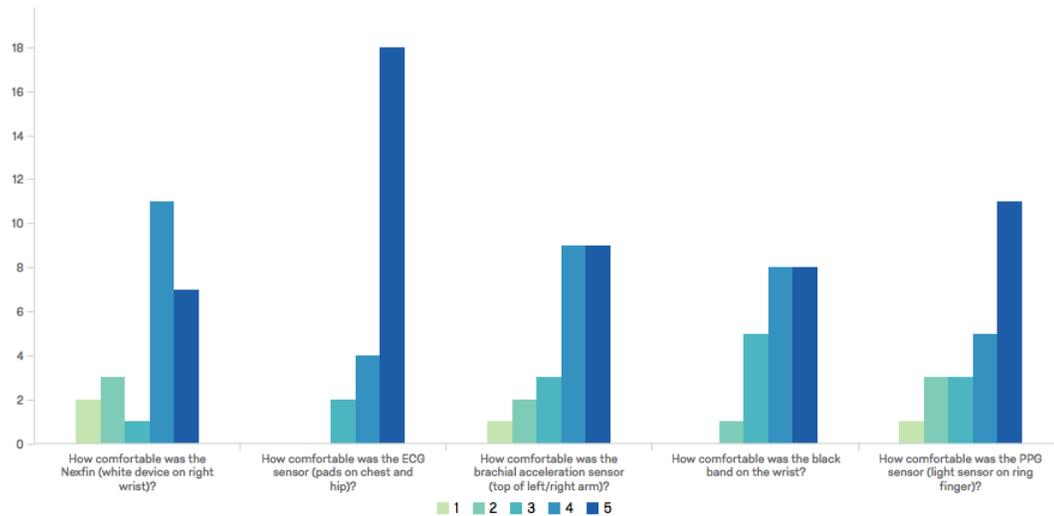


Figure 16. Answers to Question 1: *How comfortable was the Nexfin, ECG sensor, Brachial acceleration sensor, wrist band, PPG sensor?* Participants could answer with an integer 1 (least comfortable) – 5 (most comfortable).

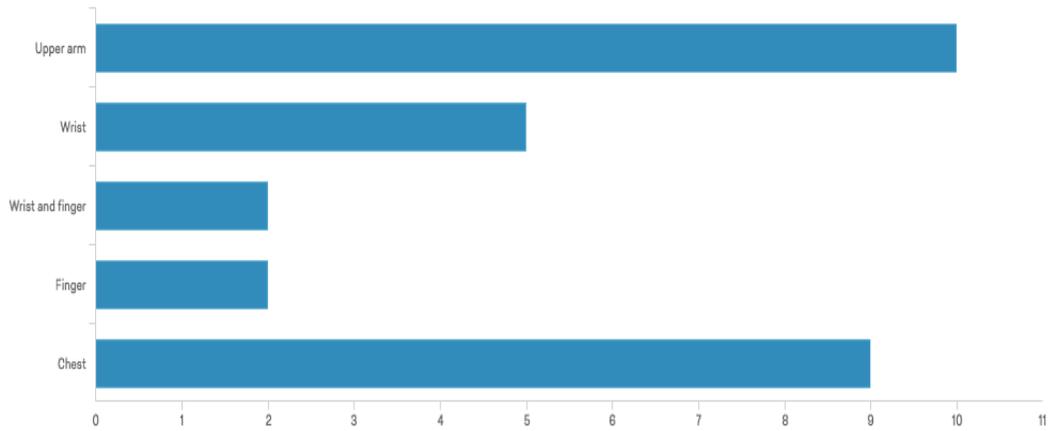


Figure 17. Answers to survey question 2: What location was it most comfortable to wear a sensor for long periods of time? Participants could answer with an integer 1 - 10 with 1 being the least comfortable and 10 being the most comfortable. Axis shows number of participants endorsing each statement.

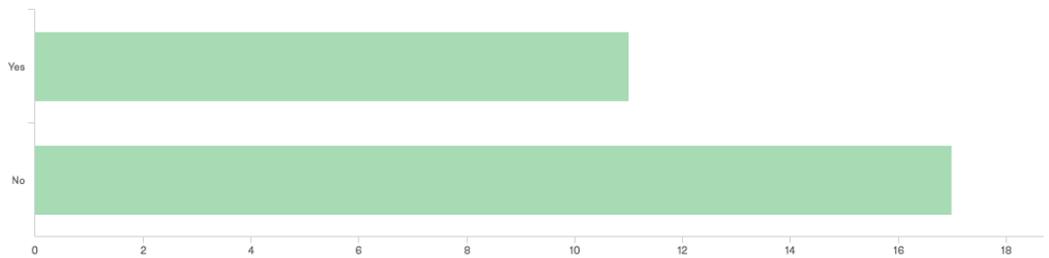


Figure 18. Answers to survey question 3: Have you owned a fitness tracker (such as a FitBit) before? The x-axis shows the amount of participants that selected either yes or no.

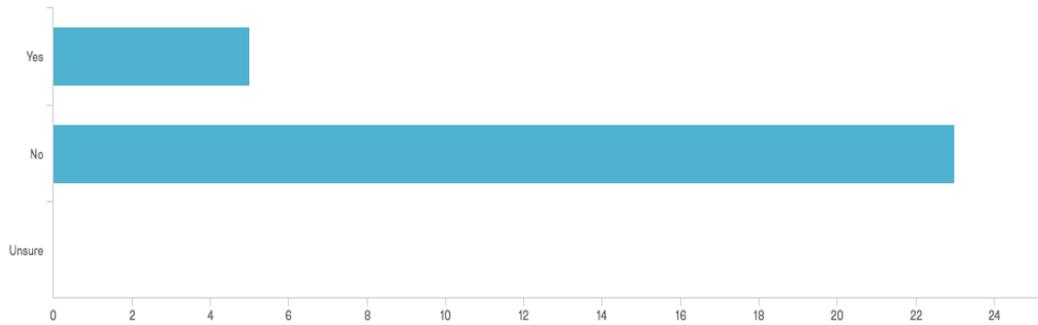


Figure 19. Answers to survey question 4: Do you own an ambulatory blood pressure monitor at home? The x-axis shows the amount of participants endorsing statements

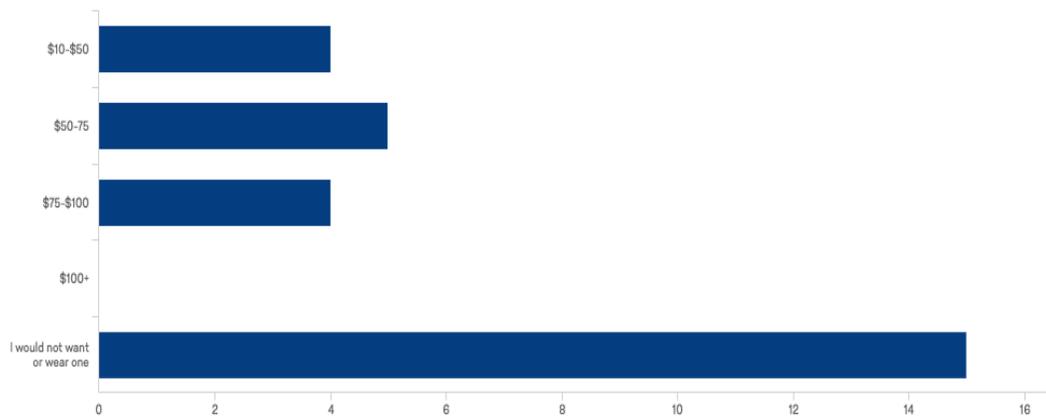


Figure 20. Answers to survey question 5 (bar graph): How much would you pay for a device that could continuously measure blood pressure? The x-axis shows the amount of participants that selected each option.

## Chapter 5: Discussion

### 5.1 Correlation between BP and PTT

The results of human subject study generally show that the waveforms that were most prominent performed better in predicting both SBP and DBP. Our study found the metric PAT2 to be most highly correlated and best fit for predicting both SBP and DBP over all other metrics tested. The correlation we obtained of approximately 0.73 is comparable to similar studies measuring PAT2 (Kim et al., 2015). The RMSE for PAT2 was also found to be the best at 11.4 mmHg. Correlations for DBP in this study were higher than those obtained in this previous study. The correlation found for PTT was lower than what was obtained in this previous study, with our study obtaining  $r = 0.52$  for PTT4 and less for the remainder of the PTT metrics. Our PTT were obtained using the BCG waveform collected from the subject's arm. This arm BCG waveform was chosen based on the level of comfort given by the subjects for the arm band. Measuring BCG waveforms from the arm introduces additional noise due to small movements made by the subject.

These small movements introduce noise into the BCG signal at a power that is much greater than the signal power of the BCG. This very low level of SNR leads to shifts in key features in the BCG waveform, such as the I and J waves. This can account for some of the reduction in performance we observe in the PTT measurement as compared to the previous studies which obtained higher values of the correlation using a scale, which is mounted on the floor and is less influenced by shifting of the subject during testing.

Overall, we found that the PAT1/2 performed better than any of the PTT metrics. This contradicts the previous study which found PTT to be more highly correlated with SBP. However this previous study did not use an arm accelerometer to obtain BCG and were therefore able to obtain a higher signal to noise ratio (SNR) in their BCG measurement with reduction in noise due to erratic movements of the subject during testing. Since a BCG scale is not something that can be stood on at all times, we conclude that moving towards a continuous mobile measurement of BP, it would be better suited using PAT2 since it uses PPG and ECG sensors which have less noise associated with motion and could be worn comfortably while the subject is active throughout the day. Thus, in the case of mobile application it is better to opt for signals which are less noisy and whose timing references are less likely to shift due to noise generated by motion.

PTT 3 and 4 are found to outperform the PTT 1 and 2 which again contradicts previous studies. (Kim et al., 2015) The PTT 1 and 2 correspond to measurements using the I-wave as the proximal timing reference. The I-wave is considered a better metric since it corresponds to the actual ejection of blood from the heart and therefore directly measures the PTT. The J-wave is reverberation caused by this ejection and can vary slightly over different beats. Since it does not directly correspond to the actual PTT, it is considered a weaker measure of PTT and the I-wave is generally used. However, this study has found that the J-wave outperforms the I-wave in this case. This is due to limitations in signal processing which prevent the I-wave from always being measured accurately. Since the J-wave is larger peak and therefore a higher energy signal, it is less easily shifted by noise. Therefore, it performed better in this high noise case since

it provides a higher SNR and more prominent peak. Thus the J-wave is found to be better suited for a mobile application which involves high noise since it is more robust to additional noise.

Generally, the metrics involving the foot of the PPG waveform (PAT1, PTT1 and PTT3) performed worse than their counterparts using the maximum of the PPG as the distal timing reference. While the difference is often small, it is found across every pair of signals measured in both the SBP and DBP cases. This may be due to similar issues with additional noise causing larger shifts in the measurement of the foot features. So with the maximum easier to obtain and more robust to noise, it may also provide the best distal timing reference for measurement of both PAT and PTT in the case of mobile measurement where the PPG sensor might be slightly slipping over the subject introducing noise into the measurement.

Several subjects were found to have higher correlations in both SBP and DBP using PTT over the PAT case. This could be due to several extrinsic factors, such as how much the subject moved during testing or the signal power of each signal dependent on the measurement in each subject. If the best metric is used for each subject, it is found that these PAT/PTT methods are able to provide a correlation of approximately  $-r = 0.80$  which is comparable to previous studies. (Kim et al., 2015).

### 5.2 Insights on Potential Implementation

One of the results from the human subjects testing survey tells us what part of the body participants found most comfortable to continuously wear a BP measuring device. The most comfortable location was found to be the upper arm (the

accelerometer), with 35.7% of the people preferring this location. The second most comfortable position was on the chest (the ECG electrodes), with 32.1%. The last three locations were the wrist, the finger, and the wrist and finger, with 17.8%, 7%, and 7% respectively.

Interestingly, the data highlights the placement of the ECG electrodes as the second most comfortable location. Although this location may sound unusual, many participants commented that the sensors were practically unnoticeable on the upper chest. Past research of a continuous BP measurement device generally focuses on the wrist or fingers but findings such as these could lead to further research into a blood pressure device for the chest instead.

In order to get a blood pressure measurement, we need to get a combination of PPG, BCG, and ECG readings. Most smartphones today come with built in accelerometers that can measure BCG data as well as have the ability to record PPG measurements as well. Being able to measure the ECG would allow blood pressure to be able to be calculated by the use of the smartphone and an auxiliary device, using the same means we calculated it as described above. This device could be the ECG chest sensors. Additionally, from our data analysis, we found ECG was easiest to process and was rated one of the most preferred sensor locations by participants, which shows that this would be a feasible placement for sensors.

### 5.3 Market Analysis

Among our subjects, all of whom were college students, 50% of surveyed subjects said they would not spend any money or would expend minimal finances on one of these devices. Our team believes there is a strong market in the world for a

device of this nature. According to the 2016 Centers for Disease Control, it is estimated that 67 million American adults suffer from high blood pressure, yet only half of them have their blood pressure under control (O'Brien, 2018). Additionally, hypertension is the cause of approximately 1000 deaths per day in America, costing the U.S. healthcare system \$47.5 billion yearly medical expenses (O'Brien, 2018). The Global Blood Pressure Cuffs Market is project to have a compounded annual growth rate of 7.1% from 2015 to 2020 (O'Brien, 2018). In a market that already yields 47.5 billion dollars this annual growth rate is significant. The rising growth rate that we have experienced during the lifespan of this project paired with the money that has already been spent managing hypertension, which shows that there is value in research that could make continuous blood pressure measurement more accessible. While college students did not seem interested in spending any of their limited income on one of these devices, their opinions can change easily in the upcoming years. Furthermore, we believe our survey was skewed by the age range of our participants, and would expect different results if older people were utilized as subjects throughout our research.

Additionally, the market is not just shaped by those who have hypertension and need to monitor their blood pressure at all times. In fact, around 80% of American adults and adolescents are insufficiently active on a daily basis (Piercy, 2018). Our research that aims to create efficient methods for continuous blood pressure measurement could be best marketed as a feature for an exercise and wellness app that helps people achieve wellness at all levels. For example, this device could let anyone from a child ages 6-17 know that they should do 60 minutes or more a day of moderate to vigorous physical activity to a pregnant woman needing to do 150 minutes of aerobic

activity a week (Piercy, 2018). A device that could include so many unique aspects of health while also continuously observing blood pressure would be extremely enticing to the increasingly healthy lifestyle the new generations are enamored with. Along with this, people can see if there is a problem with their blood pressure through these devices. Instead of not being able to realize there could be a problem until a annual checkup with a doctor, someone could notice issues with their blood pressure at any time of the year and get it examined before further problems occur.

## Chapter 6: Conclusion

Overall, this study was successful in collecting and analyzing data on 20 human subjects. Findings from the human subjects survey informed the further analysis of sensor data to focus only on sensors which subjects found more comfortable. Using sensors to collect ECG, PPG, and BCG waveforms, several measurements of PAT and PTT were obtained. Correlating these measured PAT/PTT values to SBP and DBP resulted in comparable results to previous studies. From results, it was concluded that most robust measurements were best suited for a mobile measurement system since increased noise due to mobile sensors requires an increased SNR for detecting signal characteristics for timing references. Thus, it was found that R-wave of ECG and maximum of the PPG wave provided the highest correlation due to their ease of detection and robustness against signal noise.

Future areas of research could be conducted in developing a neural net for determining which beats are worth processing. Looking at Figure 20 below, it depicts the nature of all individual points without use of averaging or finding median.

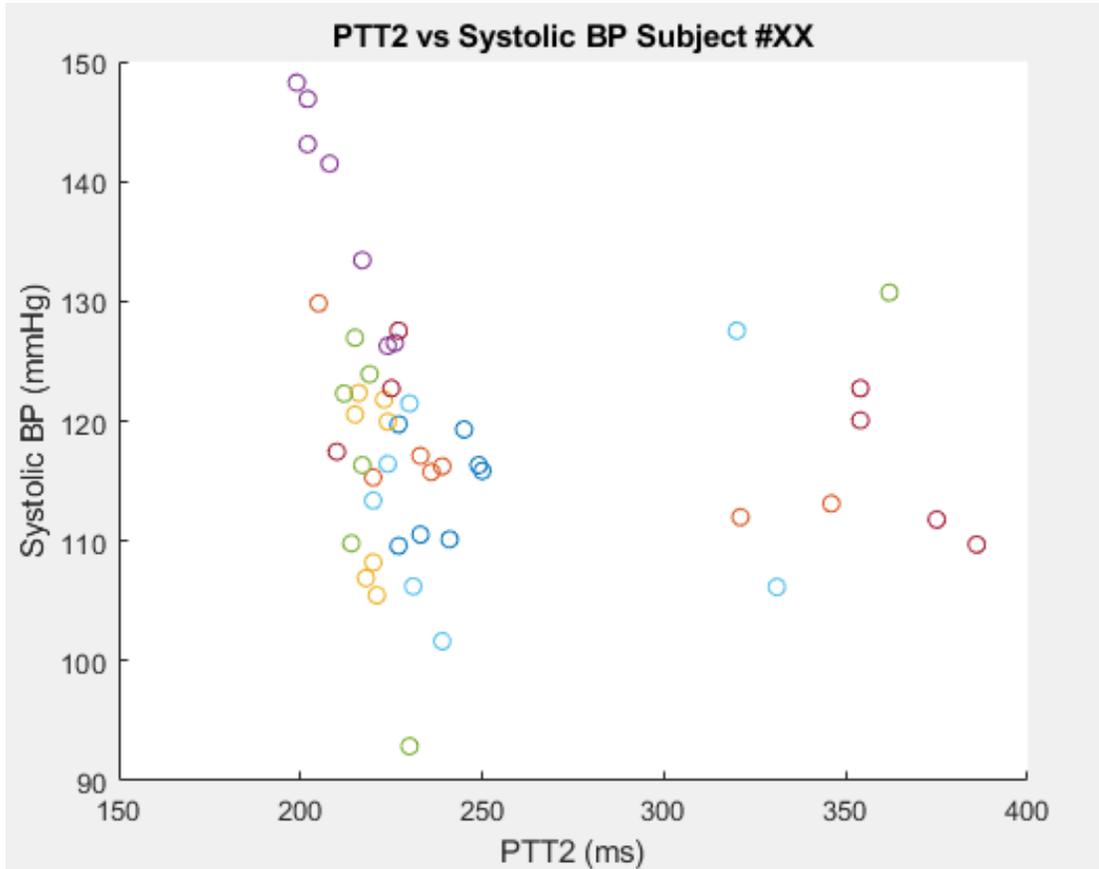


Figure 21. Example of raw data for a subject with low correlation

In this case, it may be useful to employ a neural network to perform clustering for separation of the group of points on the right which exist outside of the general trend. This would be useful for many subjects whose data sets had high correlation for large group of points. In this case, a group of points whose PTT is outside of reasonable range is measured. A neural network could classify points as appearing in one region or another which would allow for points occurring in the unreasonable region for a particular subject to be disregarded.

Other limitations of this study include the use of a laboratory setting and instrumentation for the collection of our data. The processing and accuracy might be

lower when implemented in a noisy environment likely to be encountered by an actual mobile application. Other limitations may include limited memory and computing power. While we believe that these obstacles could be overcome, further research needs to be done to demonstrate that a mobile application is feasible in a real-time environment.

In conclusion, we successfully were able to demonstrate prediction of blood pressure using pulse transit time metrics. Our obtained correlations were similar to those found in previous studies. These results can be used to inform the design and implementation of a future mobile application.

## Appendix

Thank you for participating in our research study! We really appreciated your cooperation throughout the process. If you could please take this quick (under 5 minute) survey we would be grateful. Thank you, and we hope you enjoyed your time.

---

Please indicate the level of comfort for each device or sensor. A value of 1 corresponds with the least comfortable and a value of 5 corresponds with most comfortable.

---

	Uncomfortable	Slightly uncomfortable	Neutral	Slightly comfortable	Comfortable
0	1	2	3	4	5

How comfortable was the Nexfin (white device on right wrist)?

( \_\_\_\_\_ )

How comfortable was the ECG sensor (pads on chest and hip)?

( \_\_\_\_\_ )

How comfortable was the brachial acceleration sensor (top of left/right arm)?

( \_\_\_\_\_ )

How comfortable was the black band on the wrist?

( \_\_\_\_\_ )

How comfortable was the PPG sensor (light sensor on ring finger)?

( \_\_\_\_\_ )

What location was it most comfortable to wear a sensor for long periods of time?

Choose which locations you would actually use:

---

- Upper arm
- Wrist
- Wrist and finger

- Finger
- Chest

Have you owned a fitness tracker (such as a FitBit) before?

---

- Yes
- No

Do you own an ambulatory blood pressure monitor at home?

---

- Yes
- No
- Unsure

How much would you pay for a device that could continuously measure Blood Pressure.  
What is the highest you would consider?

---

- \$10-\$50
- \$50-75
- \$75-\$100
- \$100+
- I would not want or wear one



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