IMPROVED AUTOMATIC CUFF BLOOD PRESSURE MEASUREMENT

By

Jiankun Liu

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

Electrical Engineering - Doctor of Philosophy

2016

ABSTRACT

IMPROVED AUTOMATIC CUFF BLOOD PRESSURE MEASUREMENT

By

Jiankun Liu

Hypertension affects approximately one-quarter of the world's adult population[1]. It is a major risk factor for stroke and heart disease, which are leading causes of death. Hypertension can be treated with lifestyle changes and medication. Medical therapy is associated with a 42% reduction in the risk of stroke and a 14% reduction in the risk of heart disease. However, the detection of high BP is often missed. An estimated 22% of people with hypertension do not know they have it[2]. Further, BP in known hypertensive patients is often uncontrolled. An estimated 32% of hypertensive patients receiving treatment do not have their BP under control. Hypertension management is especially difficult in low resource settings in which personnel trained in BP measurement are lacking. Hypertension management is even nontrivial in state-of-the-art clinics due to, for example, masked and white coat hypertension and large BP variability amongst few measurements. BP monitoring technology that is easy-to-use, low-cost and accurate could improve hypertension management.

Here in this thesis, our research in oscillometry began by using a physical model to elucidate the sources and mechanisms of the BP estimation error of the fixed-ratios method. We then conceived BP estimation methods based on the same model. The crux of the methods is to simultaneously estimate the arterial V-P relationship and BP of the patient

from a standard oscillometric waveform. We thereafter showed that these methods could largely reduce the oscillometric BP estimation error using a large patient data. We showed that the physical model-based methods will not only show lower BP errors than the conventional methods but also achieve acceptable accuracy (i.e., within AAMI bias and precision limits of 5 and 8 mmHg and a British Society of Hypertension grade of A or at least B). This is based on the fact that the new methods determine both the arterial stiffness and BP of the patient.

In conclusion, most automatic cuff blood pressure (BP) measurement devices estimate BP from the oscillometric cuff pressure waveform using population average methods. As a result, these devices may only work well over a limited BP range. We proposed a patient-specific method for BP estimation from the same waveform. The patient-specific method showed significantly improved precision accuracy, especially in the high pulse pressure range, and repeatability compared to available BP estimation methods. Future commercialization of this technique could ultimately help lead to reduced cardiovascular mortality and events as well as healthcare costs.

Dedicated to
my wonderful parents, Changping Liu and Zeping Zhang

ACKNOWLEDGEMENTS

I would like to thank my advisors Dr. Ramakrishna Mukkamala and Dr. Jin-oh Hahn for their continuous guidance and support since I joined Michigan State University at Jan 2011. I will be forever grateful for the opportunities they provided me in my career. I am also thankful for the trust they deposited in my work, for the motivation demonstrated along this arduous course, and for teaching the way of being an independent researcher.

I would also like to express appreciation to my dissertation committee members, Dr. Lalita Udpa, and Dr. Selin Aviyente who were more than generous with their expertise and precious time.

The realization of this work was only possible due to the several people's collaboration, to which I desire to express my gratefulness. I would like to thank Dr. Hao-Min Cheng, Dr. Chen-Huan Chen, and Dr. Shih-Hsien Sung for providing the data as well as their efforts and their help in discussion and interpreting the results presented in this thesis.

I would also like to thank all my colleagues and friends for the all the discussions and great times that I had during my PhD studies at Michigan State University, Dr. Mohsen Moselphour, Dr. Guanqun Zhang, Dr. Mingwu Gao, Anand Chandrasekhar, and Keerthana Natarajan.

Finally, I would like to express my special thanks to my lovely parents, Changping Liu and Zeping Zhang, for their everlasting supports. I would never have been able to accomplish what I have without them.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1. INTRODUCTION

Background

Hypertension affects approximately one-quarter of the world's adult population[3] and is the most prevalent chronic disease in the US and India[4], [5]. It is a major risk factor for stroke and heart disease, which are leading causes of death in these nations and worldwide[6]–[8]. Hypertension can be treated with lifestyle changes and medication. Medical therapy is associated with a 42% reduction in the risk of stroke and a 14% reduction in the risk of heart disease[9]. However, the detection of high BP and other major cardiovascular risk factors are often missed. An estimated one out of three people in India and one out of five adults in the US with hypertension do not know they have it[4], [10]. Further, BP in known hypertensive patients is often uncontrolled. An estimated 72% of hypertensive patients receiving treatment in India and 53% of such patients in the US do not have their BP under control[10], [11]. Hypertension detection and control are especially difficult in low resource settings in which personnel trained in BP measurement and the means for people to have their BP measured are lacking[12]. Hypertension detection and control are even nontrivial in state-of-the-art clinics due to, for example, masked and white coat hypertension and large BP variability amongst few measurements[13]. Regardless of the available resources, some people may not have the interest in taking time for BP measurements. Technology that would permit serial BP measurements in people during the normal course of their daily lives, with no or minimal added effort and cost, may improve hypertension detection and control in the US, India, and elsewhere[12], [14].

Existed BP measurement Techniques

A number of BP measurement methods are now available. However, these methods are invasive, operator-dependent, inaccurate, and/or expensive. None are close to unobtrusive.

Catheterization is the gold standard method. This method measures instantaneous BP (i.e., a BP waveform) by placing a strain gauge in fluid contact with blood. However, the method is invasive and restricted to critically ill patients with unstable BP.

Auscultation is the standard clinical method. This method measures systolic and diastolic BP by occluding an artery with an inflatable cuff and detecting the Korotkoff sounds using a stethoscope and manometer during cuff deflation. The first sound indicates the initiation of turbulent flow and thus systolic BP, while the fifth sound is silent and indicates the renewal of laminar flow and thus diastolic BP. The method is non-invasive but requires a skilled operator. Further, due to safety and ecological concerns, mercury manometers are being replaced with high maintenance aneroid manometers[13].

Oscillometry is the most popular non-invasive and automatic method. This method measures mean, diastolic, and systolic BP by likewise using an inflatable cuff but with a pressure sensor inside it. The measured cuff pressure not only rises and falls with cuff inflation and deflation but also shows tiny oscillations indicating the pulsatile blood volume (BV) in the artery. The amplitude of these oscillations varies with the applied cuff pressure, as the arterial BV to transmural pressure (V-P) relationship is nonlinear. The BP values are estimated from the varying oscillation amplitudes using population-based methods (e.g.,

fixed-ratios[15]). As a result, the method is notoriously inaccurate[12], especially as arterial compliance (AC = dV/dP) falls (i.e., the artery stiffens) as we and others showed[16]–[18]. Further, it is still cumbersome due to the need for cuff placement.

Finger-cuff photoplethysmography (PPG) is a non-invasive and automatic method used in research[19]. This method measures a BP waveform by using an inflatable cuff and a PPG sensor to directly obtain the BV. The BV at zero transmural pressure is estimated by inflating and deflating the cuff. The cuff pressure is then continually varied to maintain this BV throughout the cardiac cycle via a fast servo-control system. In this way, the applied cuff pressure equals BP. The method is more accurate than oscillometry but is prohibitively expensive and just as cumbersome.

Tonometry is another research method[20]. This method measures a BP waveform by pressing a manometer-tipped probe on an artery. The probe must flatten (i.e., applanate) the artery so that its transmural forces are perpendicular to the probe. Both manual and automatic applanation have proven difficult. As a result, while the method should not require any calibration, the measured waveform is routinely calibrated with cuff BP values in practice[21]. Further, an operator is needed even for automatic systems. Note that recently developed "e-skin" could function as a tonometer[22]. It may thus face similar challenges. Moreover, it is totally unproven in terms of tracking BP values.

Scope and Organization

In sum, hypertension is a major cardiovascular risk factor that is treatable, but undetected or uncontrolled, in many people in the US and India. Accurate and affordable BP

monitoring technology could improve hypertension detection and control, especially in low resource settings. However, the current conventional automatic blood pressure monitors use heuristic algorithm and thus prone to high error.

The main goal of this thesis is to searching for an improved automatic oscillometric BP monitoring technique. There are five chapters here. The current chapter (first chapter) gave an introduction and background for the blood pressure monitoring. In chapter two, we will systematically investigate the error mechanism of the conventional fixed-ratio blood pressure measurement method. The goal of chapter three is to develop a patient-specific blood pressure measurement method. In chapter four, we will show the superior performance of the patient-specific blood measurement on 145 human subjects. Finally, in chapter five perspective and significance of the work is explained.

CHAPTER 2. ERROR MECHANISM OF THE OSCILLOMETRIC FIXED-RATIO BLOOD PRESSURE MEASUREMENT METHOD

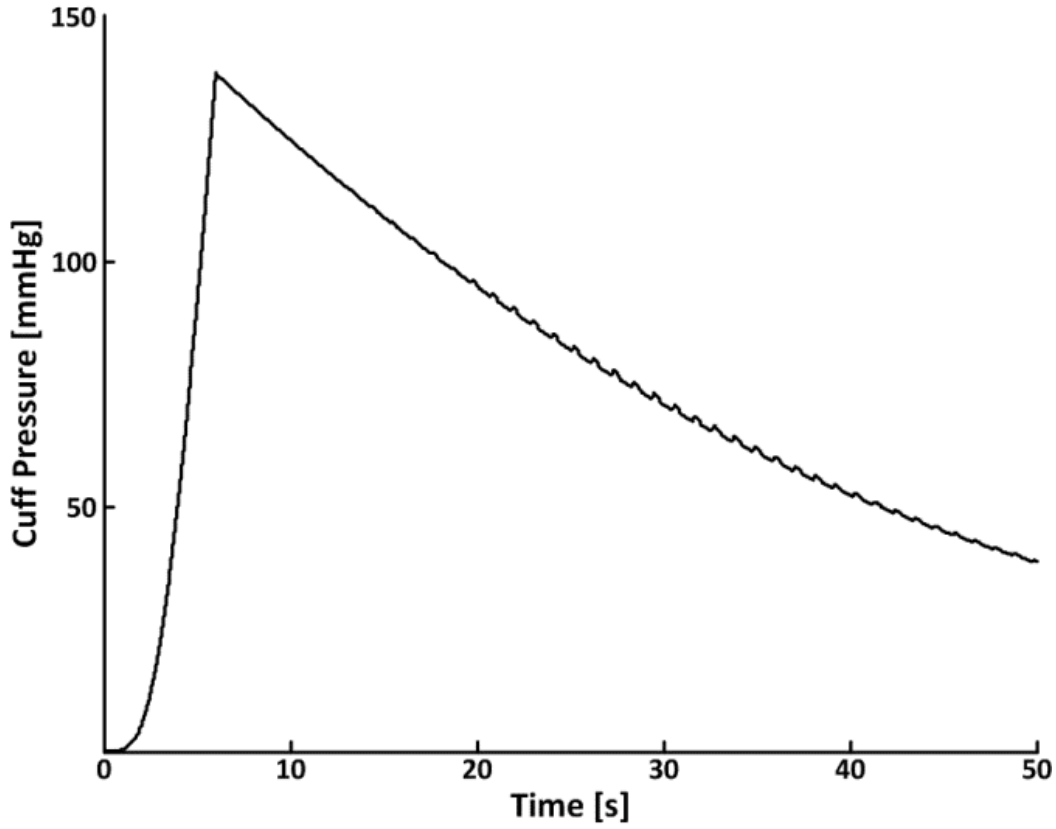
The oscillometric fixed-ratio method is widely employed for non-invasive measurement of systolic and diastolic pressures (SP and DP) but is heuristic and prone to error. We investigated the accuracy of this method using an established mathematical model of oscillometry. First, to determine which factors materially affect the errors of the method, we applied a thorough parametric sensitivity analysis to the model. Then, to assess the impact of the significant parameters, we examined the errors over a physiologically relevant range of those parameters. The main findings of this model-based error analysis of the fixed-ratio method are that: (1) SP and DP errors drastically increase as the brachial artery stiffens over the zero trans-mural pressure regime; (2) SP and DP become overestimated and underestimated, respectively, as pulse pressure (PP) declines; (3) the impact of PP on SP and DP errors is more obvious as the brachial artery stiffens over the zero trans-mural pressure regime; and (4) SP and DP errors can be as large as 50 mmHg. Our final and main contribution is a comprehensive explanation of the mechanisms for these errors. This study may have important implications when using the fixed-ratio method, particularly in subjects with arterial disease.

Introduction

Oscillometry is a popular method for non-invasive monitoring of blood pressure. This method determines systolic, diastolic, and mean arterial pressures using an occlusive brachial artery cuff, which acts as both an external pressure applicator and an arterial volume sensor.[23]–[27] More specifically, as shown in Fig. 1a, the cuff is inflated to a supra-systolic pressure level (e.g., 180 mmHg) and then slowly deflated to a sub-diastolic pressure level (e.g., 50 mmHg). So, during the deflation period, the brachial artery experiences trans-mural pressures ranging from negative to positive values. Since brachial artery compliance changes considerably around zero trans-mural pressure,[24] the amplitude of the brachial artery volume oscillation (due to the heart beat) varies greatly. This variation accordingly alters the amplitude of the resulting pressure oscillation that is sensed inside the cuff, as illustrated in Fig. 1b. Because the compliance of the arterial vessel becomes maximal when unloaded (i.e., at zero trans-mural pressure),[24] mean arterial pressure (MAP) is determined as the cuff pressure at which the maximum amplitude oscillation occurs. Systolic and diastolic pressures (SP and DP) are then determined as the cuff pressures at which the amplitude of cuff pressure oscillation is some ratio of its maximum value[25]. Due to the absence of a systematic method, the ratios are fixed to empirically selected values. As a result, the oscillometric fixed-ratio blood pressure measurement method is heuristic and susceptible to nontrivial errors arising from a number of factors.

A few investigators have used mathematical models of oscillometry to test factors that could affect the accuracy of the fixed-ratios method[24], [28], [29] . Drzewiecki et al. [24] varied SP and DP in their model over a wide range and showed that the fixed-ratio method

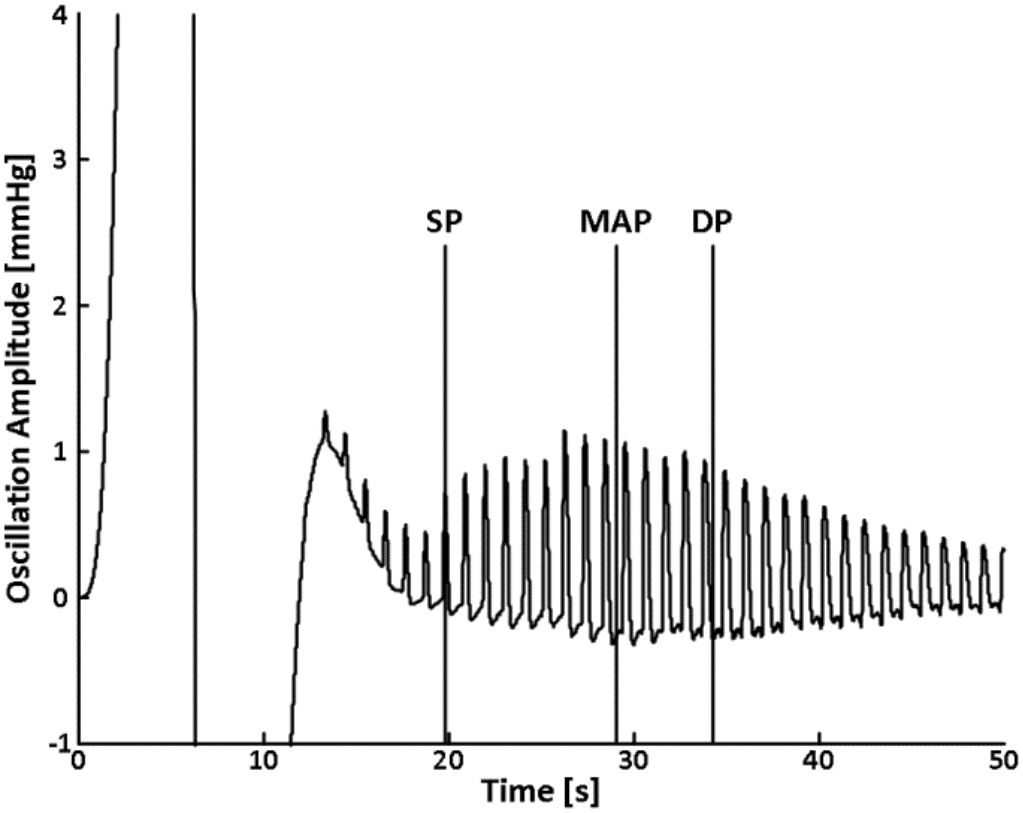
largely maintained its accuracy. In a more comprehensive study, Ursino and Cristalli[28] varied several model parameters and found that alterations in arterial properties and pulse pressure (PP) affected the



(a)

Figure 1: Oscillometric method for non-invasive blood pressure measurement. (a) Cuff pressure during cuff inflation and deflation. (b) Estimation of SP, DP, and MAP from cuff pressure oscillations via fixed-ratio method and maximum oscillation amplitude.

Figure 1 (Cont'd)



(b)

accuracy, leading to SP and DP errors as great as 15-20%. More recently, Raamat et al. [30] studied the effect of the arterial pressure waveform and the artery-cuff pressure-volume relationship in their model to conclude that alterations in these factors induced similar errors. These model-based studies have allowed the fixed-ratios method to be assessed in a manner that could not be achieved experimentally and have thus significantly contributed to the understanding of its potential pitfalls. However, the reported model-based errors appear smaller than those observed in practice (e.g., 40 mmHg for SP and 25 mmHg for DP) [31]–[35]perhaps due to the limited number of model parameters varied or the narrow parameter

range studied. Further, to the best of our knowledge, neither these studies nor others have revealed the mechanisms for the errors of the fixed-ratios method.

In this study, we investigated the errors of the oscillometric fixed-ratio blood pressure measurement method based on a mathematical model. First, we determined the factors that significantly affect its accuracy via a thorough parametric sensitivity analysis. Then, we showed that the errors could be much higher than those reported by previous model-based studies through a realistic range of parameter values. Lastly and most significantly, we unveiled the mechanisms for these errors.

Materials and Methods

Oscillometric Model

To reproduce the oscillometric measurement and study the root cause of its errors, we used the established mathematical model of Drzewiecki et al.[24] The model is illustrated in Fig. 2 and accounts for the pressure-dependent brachial artery compliance (Arterial P-A Relationship), the compressibility of air within the cuff as dictated by Boyle's law (Inflation/Deflation), and the deformation and stretch of the cuff bladder via a nonlinear pressure-volume relationship (Cuff Bladder). The inputs to the model are the brachial artery pressure waveform (P_a) and the volume of air pumped into and out of the cuff (V_p). The output is the cuff pressure (P_c), which also acts as feedback to both the blood vessel and the cuff. In this model, the cuff volume

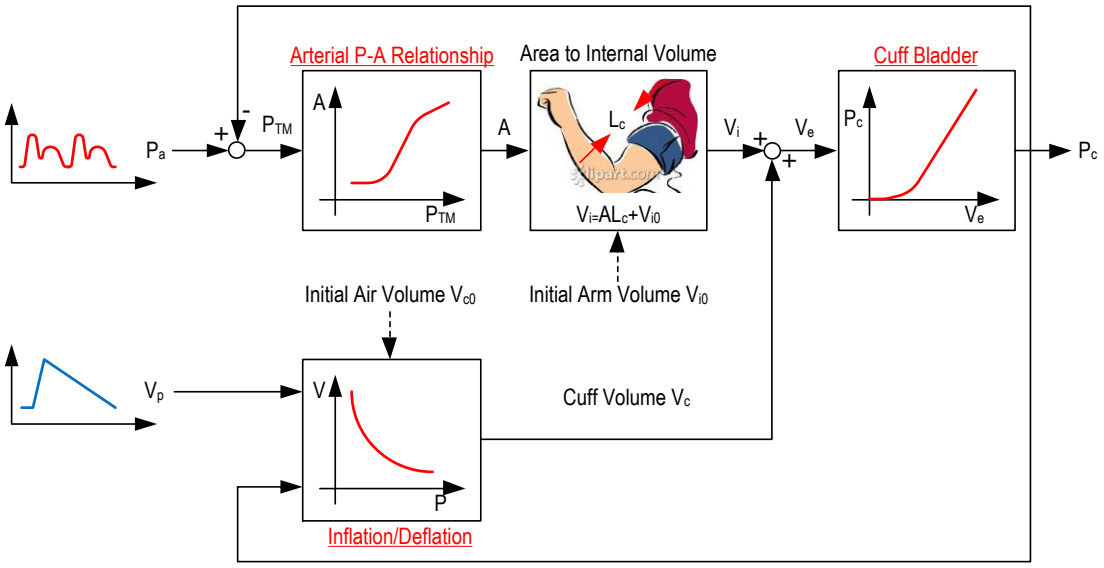


Figure 2: Functional block diagram of the mathematical model of oscillometry[4] used herein to investigate the accuracy of the non-invasive blood pressure measurement method. A: arterial lumen area; P_a: brachial arterial pressure; P_{TM}: arterial transmural pressure; L_c: length of cuff; P_c: cuff pressure; V_c: cuff volume; V_{c0}: initial cuff volume; V_e: cuff outer volume; V_i: cuff inner volume; V_{i0}: initial cuff inner volume; V_p: volume of air pumped into cuff.

(V_c) is defined as the difference between the external sheath volume (V_e) and the inside volume contacting the arm (V_i). Details follow.

Arterial P-A Relationship: The cross-sectional area of the brachial artery (A) is determined via its trans-mural pressure (i.e., the difference between arterial pressure and cuff pressure ($P_{TM} = P_a - P_c$)) according to the following nonlinear relationship:

$$A = d\frac{\ln(aP_{TM} + b)}{1 + \exp(-cP_{TM})} \qquad 1)$$

where a, b, c, and d are subject-dependent parameters (see the end of this section for a description of the effect of each of these parameters on the brachial artery compliance curve).

Area to Internal Volume: The brachial artery area A is linked to the cuff through the volume of the arm V_i as follows:

$$V_i = AL_c + V_{i0} \tag{2}$$

where L_c is the length of the arm cuff, and V_{i0} is the initial arm volume for a collapsed brachial artery.

Cuff Bladder: The cuff pressure P_c is determined by the external cuff volume, which is the sum of the cuff volume and arm volume (i.e., $V_e = V_c + V_i$), according to the following nonlinear relationship:

$$P_c = E_c \cdot \left[(V_e/V_{eo})^{1/n} - 1\right]^n, n = 4.0836 \tag{3}$$

Inflation/Deflation: The cuff volume V_c is determined by the cuff pressure P_c and the pumped volume into and out of the cuff V_p according to Boyle's law as follows:

$$P_A\left(V_p + V_{c0}\right) = (P_A + P_c)V_c \tag{4}$$

where P_A is atmospheric pressure, and V_{c0} is the initial air volume in the cuff.

V_p and P_a: The two model inputs are defined in terms of the following equations:

$$V_p(t) = \begin{cases} 81 \cdot t & 0 \le t \le 3 \\ 245 - 45 \cdot (t-3)/19 & t > 3 \end{cases} \tag{5}$$

and

$$P_a(t) = \overline{P_a} + A_0 \sin\left(\frac{2\pi f_{HR}}{60} t\right) + A_1 \sin\left(\frac{4\pi f_{HR}}{60} t + \phi_1\right) \tag{6}$$

where $\bar{P}_a$ is MAP, f_{HR} is heart rate (HR) in Hz, and A_0, A_1, and ϕ_1 are parameters defining PP. For a given V_p and P_a, the cuff pressure P_c is computed by simultaneously solving the above equations for each time instant using a root-finding algorithm (FZERO routine in MATLAB). See Drzewiecki et al.[4] for additional model details including all parameter values.

The effect of the parameters a, b, c, and d on the brachial artery compliance curve ($C_a(P_{TM}) = dA/dP_{TM}$) is graphically shown in Fig. 3. The parameter a slightly shifts the location of the peak of the compliance curve, but its effect is not significant. By contrast, the parameters b and c play a crucial role in contributing to the compliance curve. On one hand, decreasing b and c results in a decrease in the amplitude of the curve in the neighborhood of zero trans-mural pressure. On the other hand, their effects are distinct outside of this range. In particular, decreasing b has different impact on the compliance curve in the negative and positive trans-mural pressure regimes. In the negative trans-mural pressure regime, decreasing b mostly shifts the compliance curve to the right without changing the width of the curve itself. In the positive trans-mural pressure regime, decreasing b mostly yields an increase in the width of the compliance curve (see the 30 mmHg trans-mural pressure range in Fig. 3b, where the slopes of the curves become reversed), with a slight shift of the curve to the right. In contrast to b, decreasing c results in a widening of the compliance curve over the entire pressure range. Finally, the parameter d acts simply as a scale factor. By defining arterial stiffness as the change in pressure divided by the change in area in the neighborhood of zero trans-mural pressure, arterial stiffness increases as b, c and d decrease. It is important to emphasize that decreasing b and c increases arterial stiffness as defined here by

both reducing the amplitude of the curve and expanding its width, whereas decreasing d enhances the arterial stiffness only by reducing the amplitude of the curve.

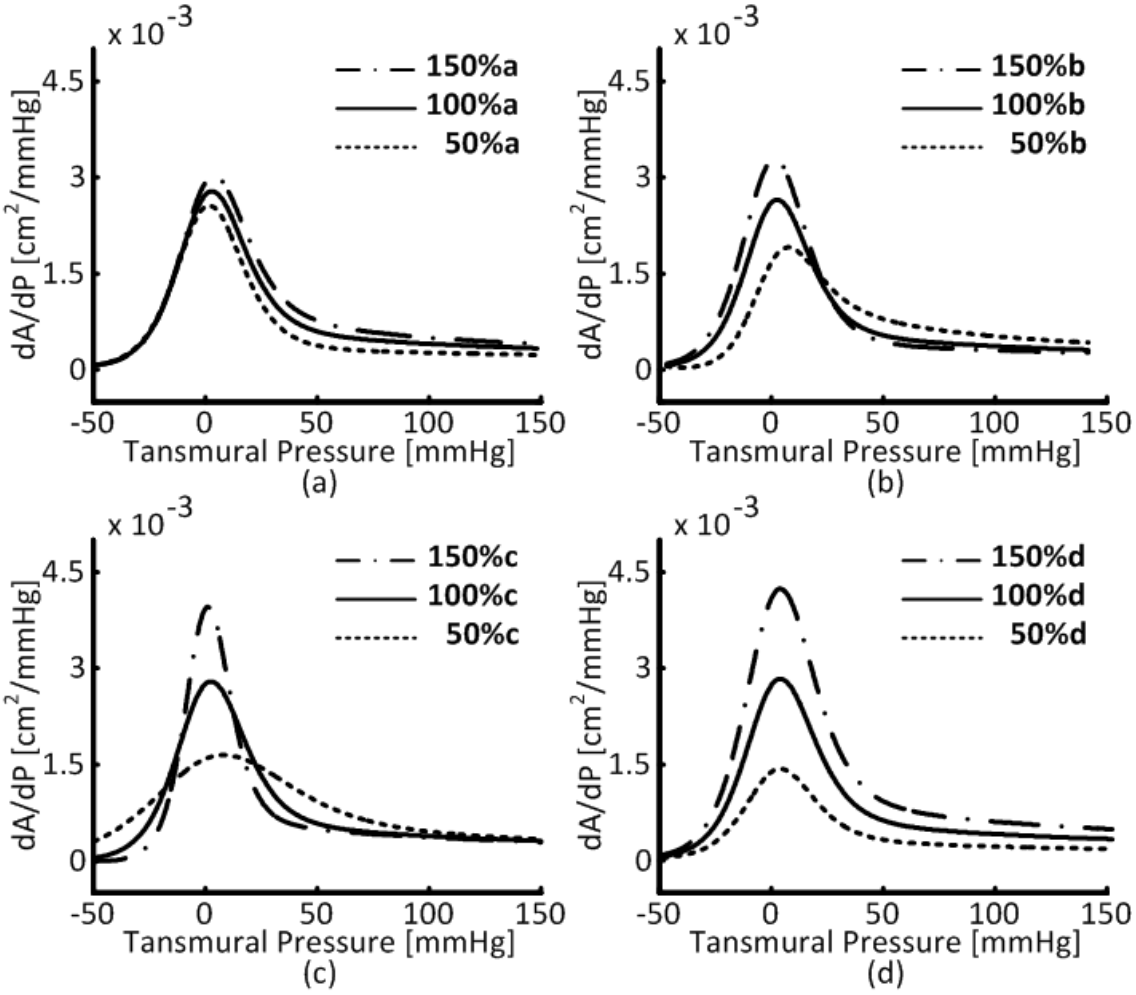


Figure 3: Model brachial artery compliance curve under different parameter values (see Equation (1)).

Error Analysis

To reveal the major factors affecting the accuracy of the oscillometric fixed-ratio method, we carried out a parametric sensitivity analysis. We specifically investigated the following seven parameters as candidate factors: PP, MAP, HR, and the brachial artery compliance parameters a, b, c, and d. We did not include the parameters defining the

occlusive cuff in the analysis, as they can be regarded as fixed once a particular cuff is chosen. (Note that while the results are presented here for only the bladder cuff in Drzewiecki et al.,[24] the results were highly comparable for both the bladder and the Critikon Duracuf cuffs in Drzewiecki et al.[24])

We studied the effects of the seven model parameters by quantifying the changes in the oscillometric blood pressure measurement errors caused by +/-50% variations in each parameter. In particular, we first generated the cuff pressure output using the nominal parameter values and then obtained the SP, DP, and MAP errors via the fixed ratio method and the maximum oscillation amplitude. We thereafter repeated this process with +50% and -50% variations to each of the parameters. We quantified the impact of each parameter on the blood pressure errors in terms of the percent change in error caused by the parametric variation.

In this analysis, we implemented changes in MAP and HR by directly altering $\bar{P}_a$ and f_{HR} and in PP by multiplying a factor of 1.5 (for 50% increase) and 0.5 (for 50% decrease) to A_0 and A_1. We used a systolic fixed ratio of 0.61 and a diastolic fixed ratio of 0.74, as these values resulted in small SP and DP errors for the nominal parameter values.

Finally, to scrutinize the impact of the significant parameters, we examined the blood pressure errors over physiologically relevant ranges of those parameters.

Results

Parametric Sensitivity Analysis

Table 1 summarizes the results of the parametric sensitivity analysis. There were appreciable changes in SP and DP errors but not MAP errors.

Table 1: Results of the parametric sensitivity analysis.

Oscillometric Error	PP +50%	PP -50%	MAP +50%	MAP -50%	HR +50%	HR -50%	a +50%	a -50%	b +50%	b -50%	c +50%	c -50%	d +50%	d -50%
SP	-9.37	+14.1	-3.02	+3.33	+0.33	-0.62	+3.60	+3.60	+3.93	-16.8	-4.72	+21.9	+0.40	-0.40
DP	+6.99	-9.93	-1.75	+5.73	-1.34	+3.90	+3.51	+3.51	+3.72	-14.1	+4.77	-19.5	-0.02	-0.10
MAP	+0.53	-0.92	-0.14	+0.44	-0.01	-0.13	+0.15	+0.38	+0.41	-1.59	+0.13	-0.55	+0.03	-0.00

Values represent the difference between the oscillometric error upon indicated parametric perturbation and the oscillometric error under the nominal parameters divided by the oscillometric error under the nominal parameters.

Recall that MAP is determined as the cuff pressure at which the maximum amplitude oscillation occurs on the basis that the compliance of the brachial artery is maximal at zero trans-mural pressure. Hence, since alterations in a, b, c, and d hardly changed the location of the peak of the arterial compliance curve (see above), MAP accuracy was maintained despite the major parametric variations.

The model parameters, PP, b, and c, had great impact on SP and DP errors. As PP decreased, the fixed-ratio method overestimated SP and underestimated DP. This finding is consistent with other studies.[9] As b and c declined, which increased the width and decreased the amplitude of the compliance curve, significant errors were incurred. In particular, both SP and DP were underestimated as b decreased, while SP was overestimated and DP was underestimated as c decreased. In contrast, the compliance parameter d (as well as the remaining model parameters) hardly impacted the errors. Hence, increasing arterial stiffness

(see definition above) specifically via an increase in the width of the compliance curve was a crucial factor.

Error Magnitudes

Fig. 5 illustrates the SP and DP errors over a physiologic range of PP and c. A physiologic range for the latter parameter was determined based on the human aorta data at autopsy shown in Fig. 4. The SP and DP errors gradually decreased as PP increased, whereas these errors dramatically increased as arterial stiffness increased (via a decrease in c). The errors were as high as 50 mmHg in the case of severe arterial stiffening. Such errors are consistent with the experimental investigations of Coleman et al.[32] who reported errors up to 35 mmHg for the OMRON MX3 Plus device and Greeff et al.[33] who reported errors up to 40-45 mmHg for the OMRON MIT and OMRON M7 devices.

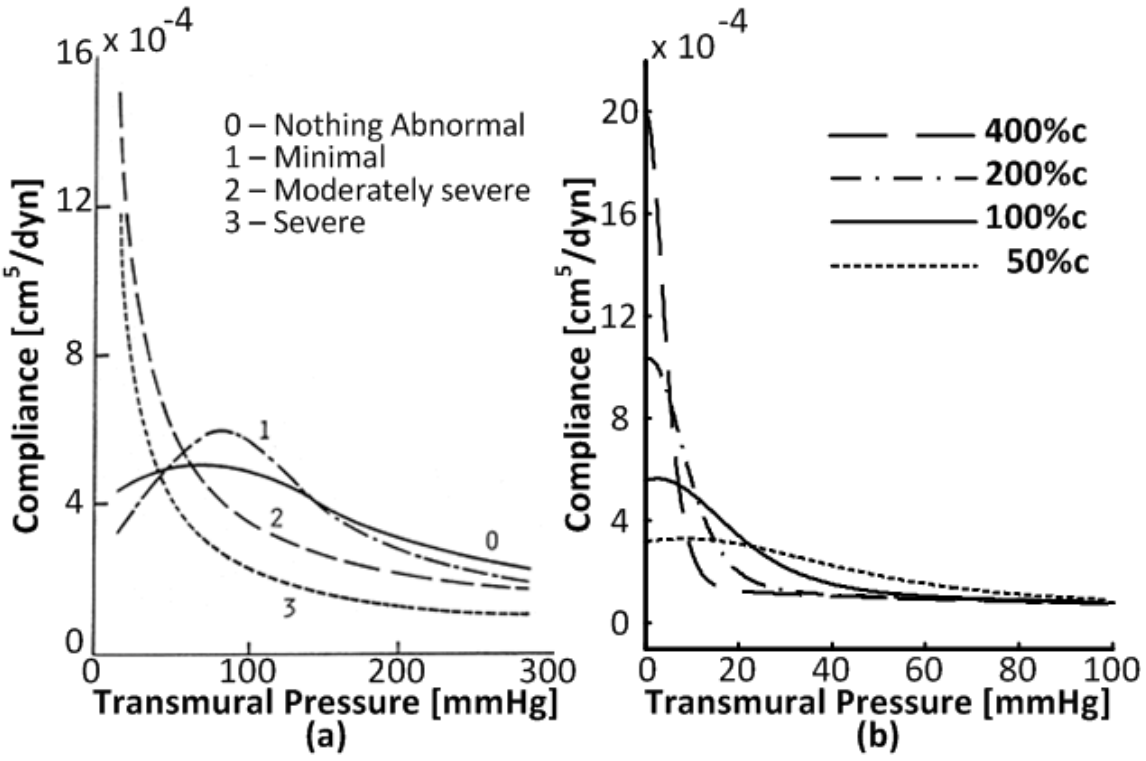
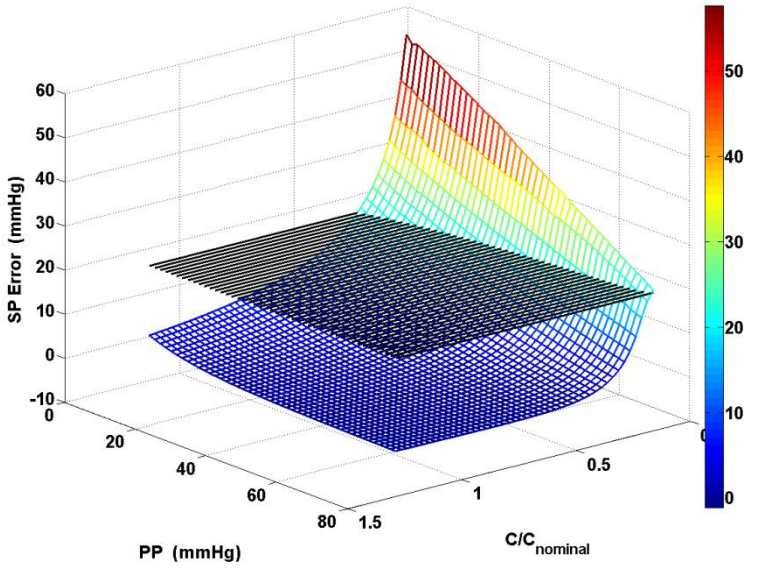
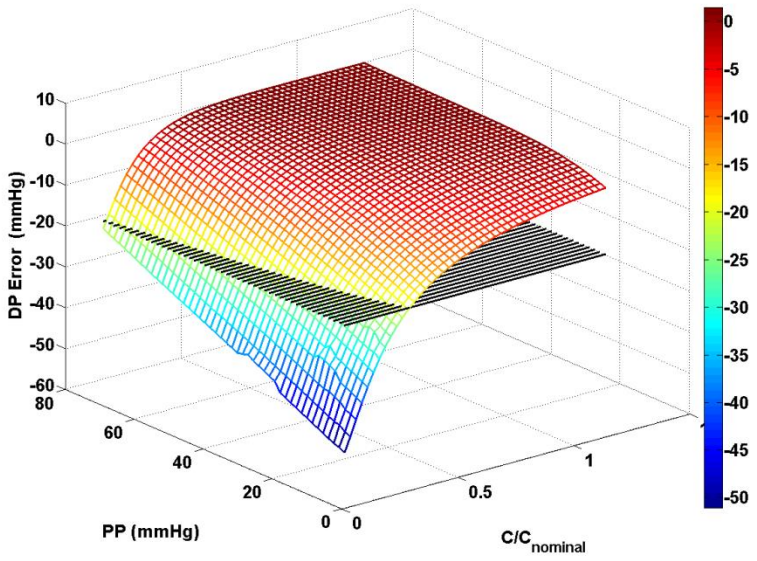


Figure 4: (a) Experimental brachial artery compliance curves determined from humans with varying degrees of atherosclerosis at autopsy[36] and (b) corresponding model brachial artery compliance curves determined by varying c.



(a)



(b)

Figure 5: (a) SP and (b) DP errors of the fixed-ratio method as a function of *c* and PP. Black plane indicates error of +/- 20 mmHg.

Discussion

The oscillometric fixed-ratio method is widely employed for non-invasive blood pressure measurement. Its accuracy under nominal physiologic conditions is supported by several studies.[37] However, our model-based analysis shows that the method becomes susceptible to major SP and DP errors when arterial stiffness (defined as the change in brachial artery pressure divided by the change in brachial artery area in the neighborhood of zero trans-mural pressure) and PP deviate significantly from nominal levels. While these findings are consistent with the previous model-based analysis of Ursino and Cristalli[28] (despite the use of different models), the error magnitudes shown here are markedly higher due to our exploration of a wider, realistic range of model parameter values. Further, we describe the mechanisms for these errors below.

Error Mechanisms for Arterial Stiffness Variations

Variations in arterial stiffness via the model parameters b and c, which alter the shape of the brachial artery compliance curve (width in particular), significantly impact the accuracy of the fixed-ratio method. As exemplified for changes to c in Fig. 6, both parameters dictate the shape of the envelope of the cuff pressure oscillations (normalized to unity), which is the key factor in determining the accuracy of the method. So, even though the actual SP and DP are invariant in the figure, the fixed-ratio predictions (indicated with solid lines) deviate from these pressures with perturbations to c from its nominal value. By contrast, variations in arterial stiffness via the model parameter d, which alters the amplitude of the brachial artery compliance curve, have little impact on the accuracy, because the shape of the envelope of the cuff pressure oscillations hardly depends on the curve amplitude (not

shown). So, the width of the compliance curve normalized by its maximum amplitude in the neighborhood of zero trans-mural pressure specifically represents the important factor affecting the accuracy of the fixed-ratio method.

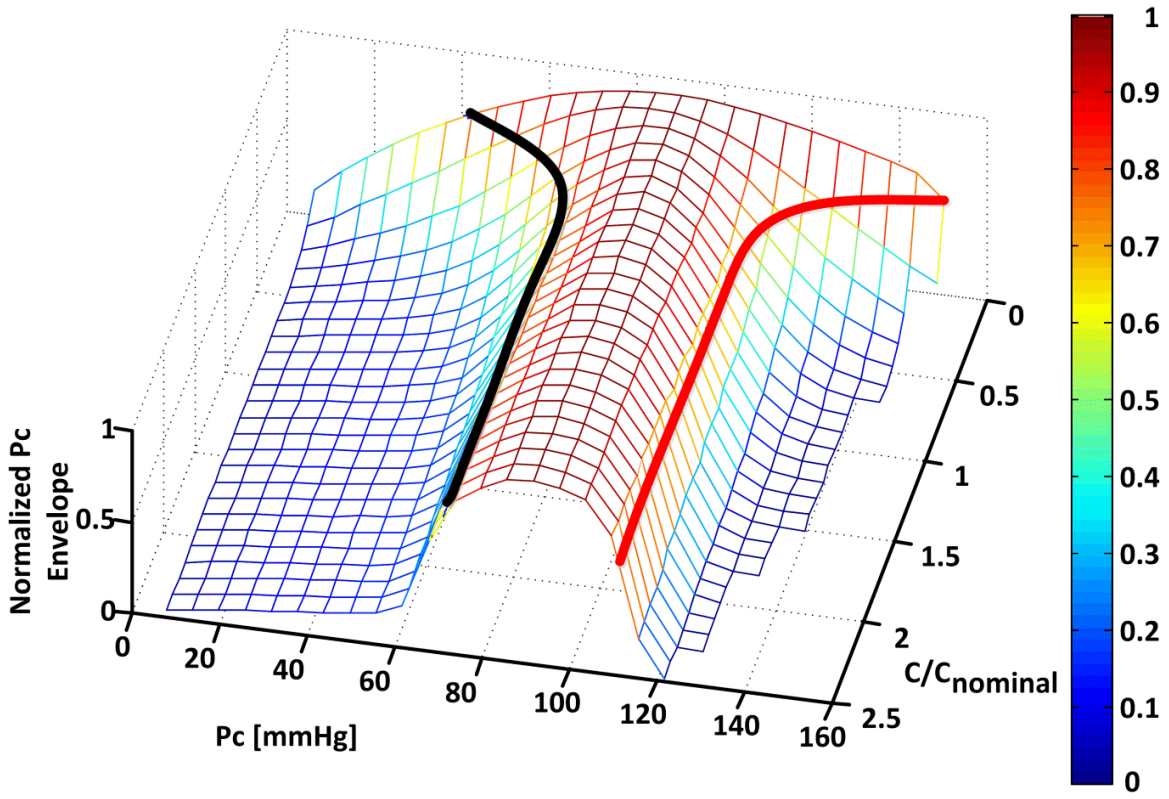


Figure 6: Envelope of the model cuff pressure (P_c) oscillations (normalized to unity) as a function of c. Solid lines indicate SP (red) and DP (black) estimated by the fixed-ratio method.

Fig. 7 illustrates the error mechanism when changes to c occur. From Fig. 6, the width of the cuff pressure oscillation envelope increases with decreasing c, which corresponds to arterial stiffening. For reduced c, the fixed-ratios predict higher SP and lower DP (see Fig. 7b), thereby overestimating SP and underestimating DP. On the other hand, for increased c, the fixed-ratios predict lower SP and higher DP (see Fig. 7c), resulting in underestimated SP and overestimated DP. Fig. 7 also indicates that the cuff pressure

oscillation envelope becomes flatter as c decreases. Hence, even small perturbations to the fixed-ratio values can yield large errors in SP and DP. In contrast, the envelope becomes steeper as c increases. So, the blood pressure errors are less sensitive to changes in the fixed-ratio values. In short, a reduction in c, which corresponds to arterial stiffening, is particularly problematic and results in overestimation of SP and underestimation of DP.

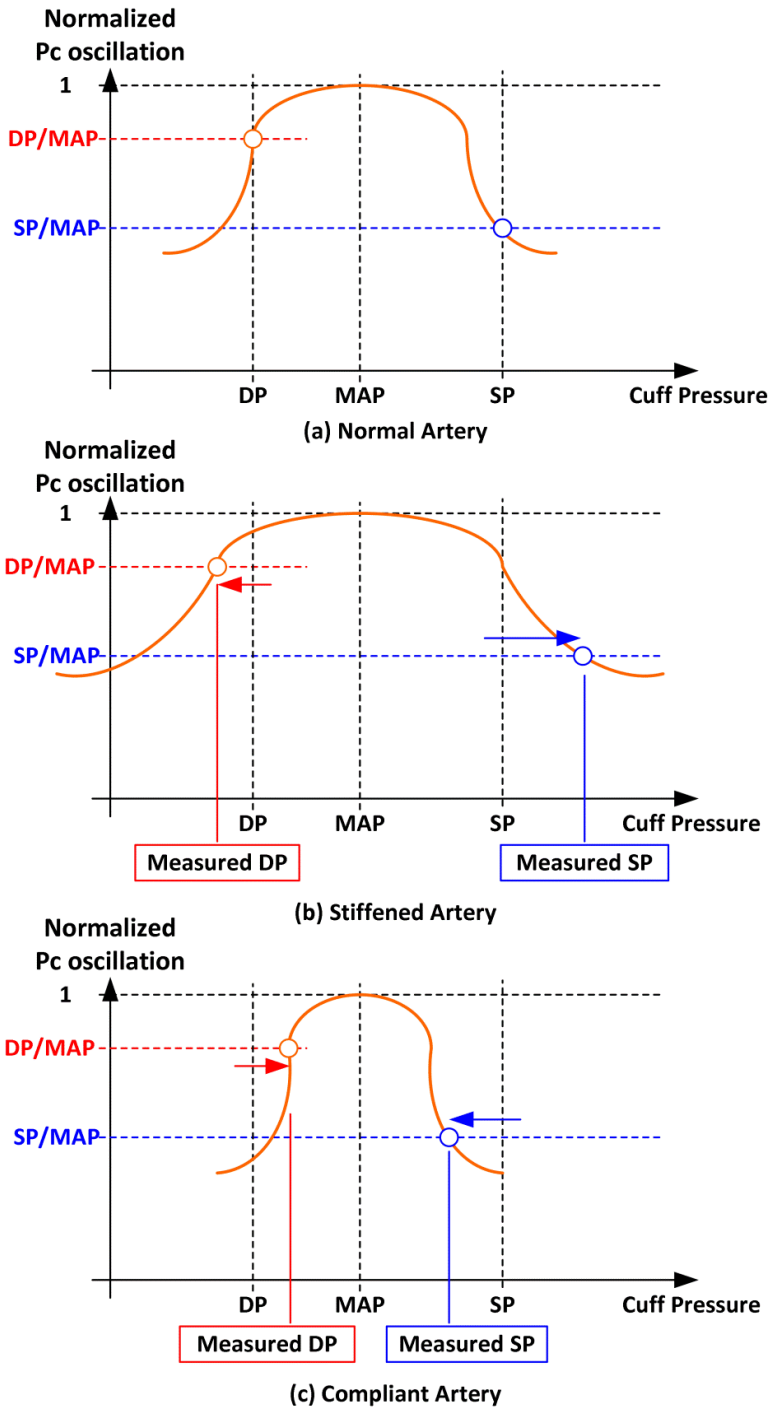


Figure 7: Error mechanism of the fixed-ratio method for changes in arterial stiffness at zero trans-mural pressure.

The error mechanism when changes to b occur is distinct due to the differing effect of b and c on the brachial artery compliance curve (see Fig. 3). First, recall that decreasing b in the negative trans-mural pressure regime, which corresponds to the region where SP is determined, shifts the compliance curve to the right without changing its width. Thus, the fixed-ratio predicts a lower SP, thereby underestimating this pressure. Second, recall that decreasing b in the positive trans-mural pressure regime, which corresponds to the region in which DP is determined, increases the width of the compliance curve while also slightly shifting the curve to the right. Hence, the fixed-ratio predicts a lower DP, resulting in underestimated DP. Further, for similar reasons as c, decreasing b, which corresponds to arterial stiffening, is far more problematic than increasing this parameter.

Error Mechanisms for PP Changes

In addition to arterial stiffening, changes to PP significantly impact the accuracy of the fixed-ratio method. Fig. 8 shows the envelope of the cuff pressure oscillations (again normalized to unity) for a range of PP values and three different values of c representing compliant (Fig. 8a), normal (Fig. 8b), and stiff (Fig. 8c) arteries. As PP increases, the actual SP and DP move away from MAP. The fixed-ratio predictions (indicated with solid lines) correctly show a tendency to likewise deviate from MAP. However, this tendency decreases markedly with increasing arterial stiffness (e.g., compare Fig. 8a to Fig. 8c). Further, the fixed-ratio predictions appear more erroneous over the low PP range than the high PP range (see Fig. 8 where the red and black solid lines appear closer than they should be for the lower range of PP). Hence, smaller PP, particularly in combination with stiffer arteries, compromises the accuracy of the fixed-ratio method. As a final point, Fig. 8 also indicates

that the value of PP in addition to the degree of arterial stiffening dictate the shape of the envelope of the cuff pressure oscillations.

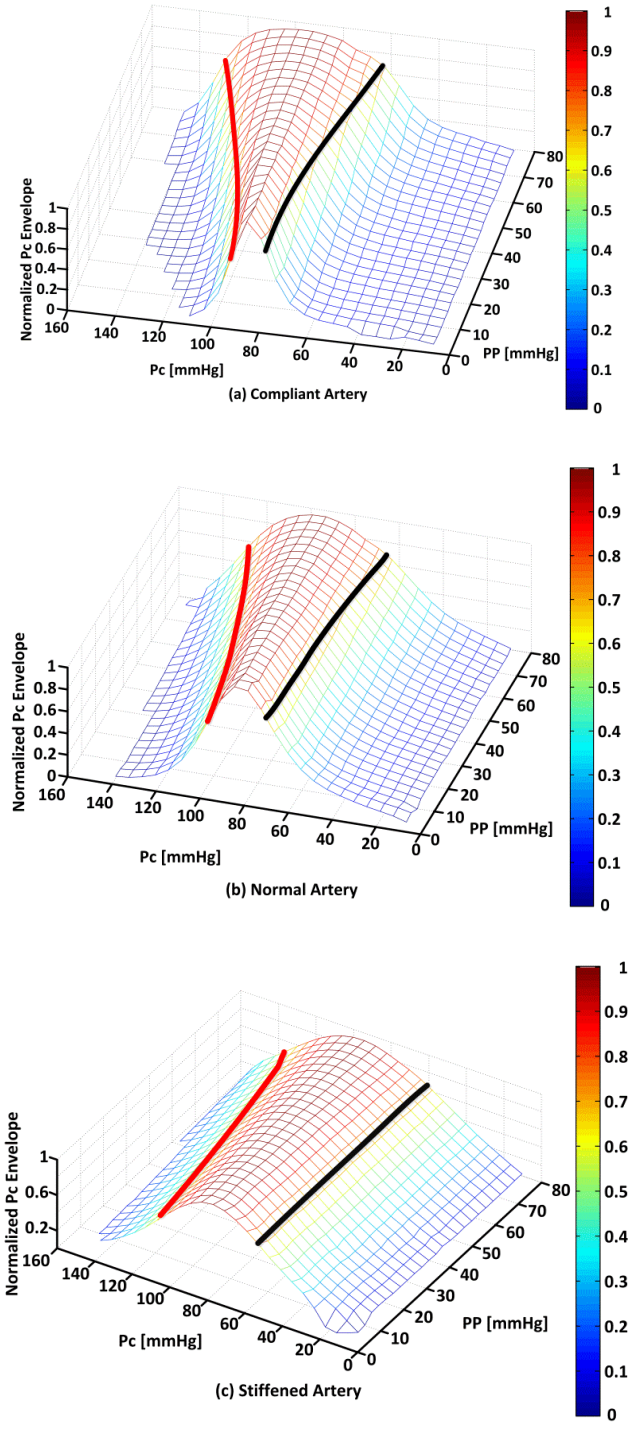


Figure 8: Envelope of the model P_c oscillations (normalized to unity) as a function of PP for three different values of c representing (a) compliant, (b) normal, and (c) stiff arteries. Solid lines indicate SP (red) and DP (black) estimated by the fixed-ratio method.

Fig. 9 illustrates the error mechanism when changes to PP occur. To describe this mechanism, it is important to first reiterate that the amplitude of the cuff pressure oscillations is determined by the amplitude of the brachial artery area oscillations. In fact, the two variables are proportional to each other in the mathematical model herein. The amplitude of the brachial artery area oscillations (δA) arises according to the following equation:

$$\delta A = \int_{DP-P_c}^{SP-P_c} dA = \int_{DP-P_c}^{SP-P_c} \frac{dA}{dP} dP = \int_{DP-P_c}^{SP-P_c} C_a(P_{TM}) dP \quad (7)$$

Hence, PP determines the width of the brachial artery compliance curve $C_a(P_{TM})$ that is integrated to establish the amplitude of the brachial artery area oscillations and thus the amplitude of the cuff pressure oscillations. Computing this area at each cuff pressure level (see green rectangles in left panels of Fig. 9) and plotting the resulting areas against the cuff pressures yield the cuff pressure envelope (see right panels of Fig. 9). In this way, PP impacts the shape of the cuff pressure envelope and thus the accuracy of the fixed-ratio method.

For normal or compliant brachial arteries (see Fig. 9a), the area difference across the cuff pressure levels is large for small PP (see upper, left panel) and small for large PP (see lower, left panel). The reason is that large PP will include area under the central part of the brachial artery compliance curve, which is responsible for the majority of its total area, for many cuff pressure levels, whereas small PP will not. Hence, as indicated in Fig. 9a as well as in Figs. 8a and 8b, the cuff pressure oscillation envelope becomes flatter as PP increases and steeper as PP decreases. On the other hand, for stiff brachial arteries (see Fig. 9b), the area difference across the cuff pressure levels is relatively small, because the brachial artery compliance curve is inherently flat (compare the left panels in Figs. 9a and 9b). As a result,

as indicated in Fig. 9b as well as in Fig. 8c, the impact of PP on the cuff pressure oscillation envelope is relatively small. For these reasons, as indicated in Fig. 5, the worst-case scenario for the fixed-ratio method is when PP is low and the brachial artery is stiff. In this scenario, SP will be markedly overestimated and DP will be significantly underestimated (see upper, right panel of Fig. 9b). However, when the brachial artery is normal or compliant, the fixed-ratio method may be more effective against PP changes, yet far from impervious, due to greater responsiveness of the cuff pressure oscillation envelope to PP (see right panels of Fig. 9a).

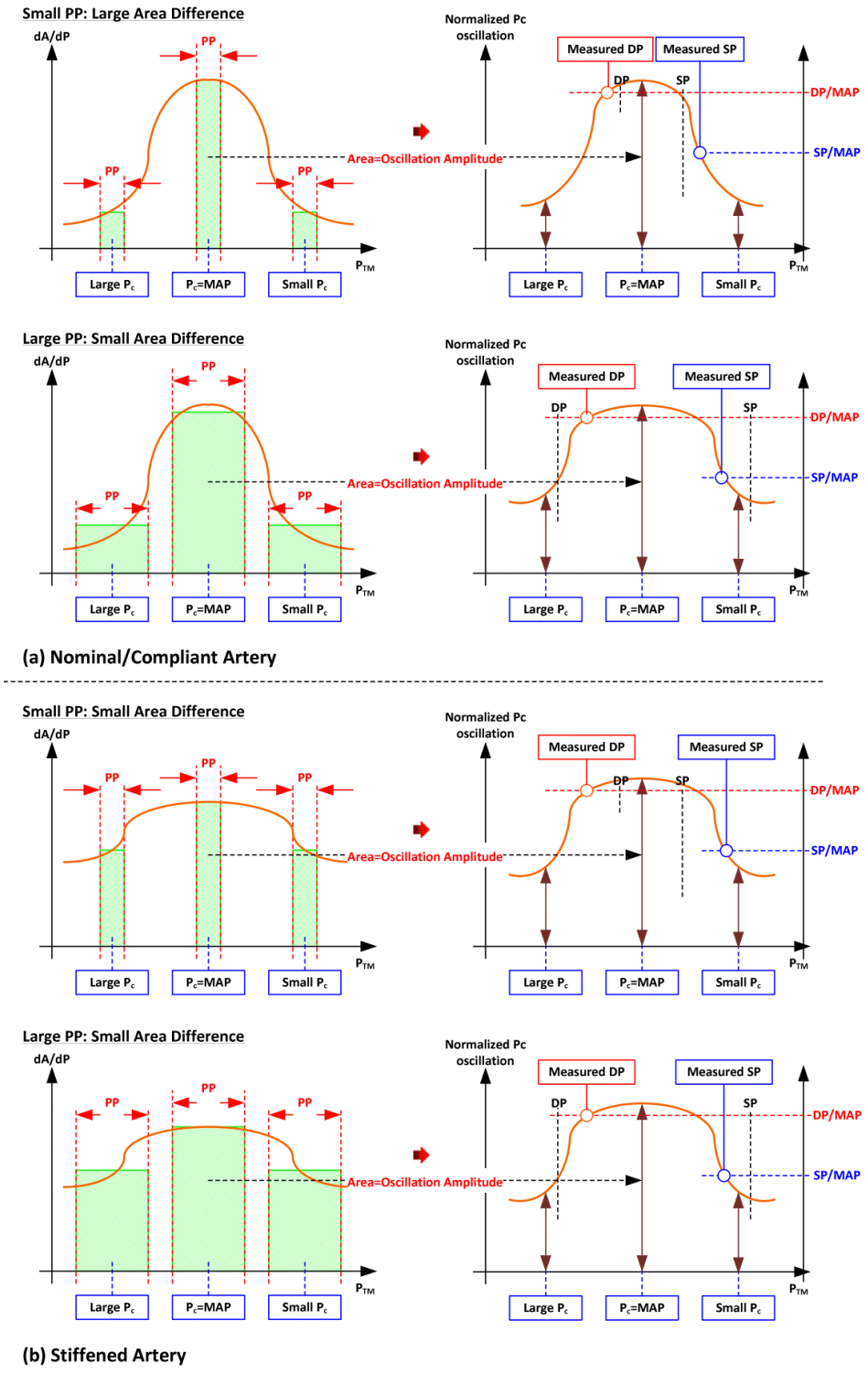


Figure 9: Error mechanism of the fixed-ratio method for changes in PP at different levels of arterial stiffness at zero trans-mural pressure.

Study Limitations

The main limitation of this study is that the mathematical model that we employed ignored the effect of arm tissue mechanics. More precisely, the model assumed incompressible arm tissue. We settled upon this model, despite this assumption, for three reasons. First, the model was shown to be able to generate realistic oscillometric cuff pressure waveforms.[24] Second, the model turned out to afford similar parametric sensitivity results as a model that accounted for arm tissue mechanics.[28] Finally, the model offered a simple foundation upon which error mechanisms could be elucidated. If arm tissue mechanics were taken into account, we surmise that the only difference in our results would have been greater fixed-ratio method error magnitudes.

Concluding Remarks

In summary, we employed a mathematical model to investigate the blood pressure measurement accuracy of the popular oscillometric fixed-ratio method. We found that its accuracy was highly sensitive to the levels of PP and brachial artery stiffness (at zero trans-mural pressure). In particular, over a physiologic range of these parameters, the SP and DP errors of the method increased as the brachial artery stiffened and reached 50 mmHg. We also explained, perhaps for the first time, the mechanisms for these errors. This study may have important implications when using the fixed-ratio method, particularly in subjects with arterial disease.

CHAPTER 3. PATIENT-SPECIFIC OSCILLOMETRIC BLOOD PRESSURE MEASUREMENT

Most automatic cuff blood pressure (BP) measurement devices are based on oscillometry. These devices estimate BP from the envelopes of the cuff pressure oscillations using fixed ratios. The values of the fixed ratios represent population averages, so the devices may only be accurate in subjects with normal BP levels. Methods: A patient-specific oscillometric BP measurement method was developed. The idea was to represent the cuff pressure oscillation envelopes with a physiologic model and then estimate the patient-specific parameters of the model, which includes BP levels, by optimally fitting it to the envelopes. The method was investigated against gold standard reference BP measurements from 57 patients with widely varying pulse pressures. A portion of the data was used to optimize the patient-specific method and a fixed-ratio method, while the remaining data were used to test these methods and a current office device. Results: The patient-specific method yielded BP root-mean-square-errors ranging from 6.0 to 9.3 mmHg. On average, these errors were nearly 40% lower than the errors of each existing method. Conclusion: The patient-specific method may improve automatic cuff BP measurement accuracy.

Introduction

Oscillometry is a widely used approach for automatic cuff blood pressure (BP) measurement [38]–[40]. In this approach, a cuff placed on the upper arm is inflated and then deflated while the pressure inside the cuff is measured. As shown in Figure 10, the resulting cuff pressure not only rises and falls but also shows small oscillations indicating the pulsatile blood volume within the brachial artery underneath the cuff. The amplitude of these oscillations changes with the applied cuff pressure, as the brachial artery compliance varies with transmural pressure (i.e., BP - cuff pressure). BP is then estimated from the oscillation amplitudes and cuff pressure.

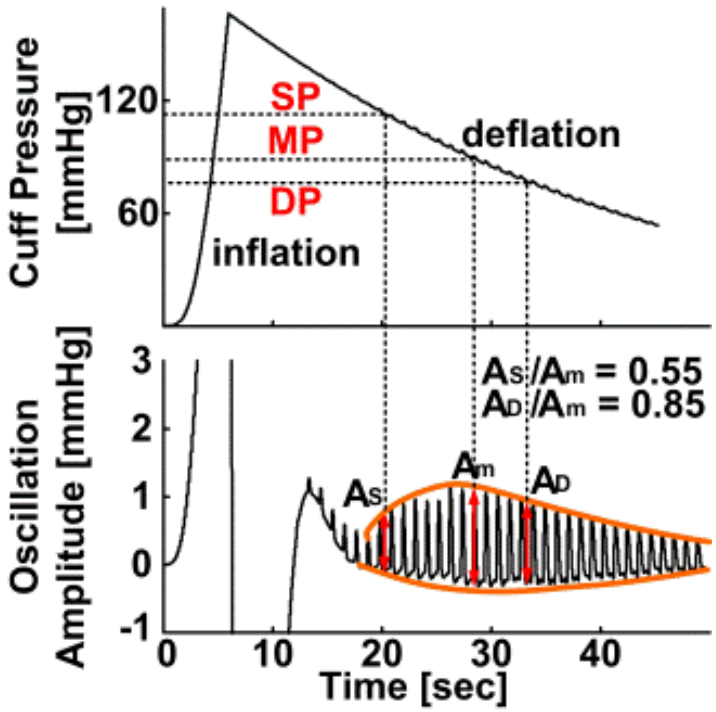


Figure 10: Conventional fixed-ratio method for estimating mean blood pressure (MP) and then systolic and diastolic blood pressure (SP and DP) from the oscillometric cuff pressure waveform. The fixed-ratio values (i.e., 0.55 and 0.85) represent population averages.

The BP estimation is conventionally performed via fixed ratios [25], [38], [39]. As shown in Figure 10, first, mean BP (MP) is estimated as the cuff pressure at which the oscillation amplitude is maximal, since the brachial artery compliance peaks near zero transmural pressure. Then, systolic and diastolic BP (SP and DP) are each estimated as the cuff pressure at which the oscillation amplitude is some fixed ratio of the maximal value. While current devices do not disclose their exact methods for estimating BP, they are believed to employ the fixed-ratio method or some variant thereof [38], [39], [41]. Since such methods are based on population averages, the devices may only work well in subjects with normal BP levels. Indeed, the accuracy of the devices is known to be compromised in subjects with large artery stiffening and thus high pulse pressure (PP = SP - DP) [39], [41] – a common condition that occurs with aging and disease.

In this study, we developed a patient-specific method to estimate BP from the oscillometric cuff pressure waveform. The basic idea is to represent the oscillation amplitudes and cuff pressure with a physiologic model and then estimate the patient-specific parameters of the model, which includes BP levels, by optimally fitting it to the measured data. We tested the method against gold standard reference BP measurements in patients referred for diagnostic cardiac catheterization – a population with widely varying PP. Our results indicate that the patient-specific method can afford greater BP estimation accuracy than the fixed-ratio method and a current device used for hypertension management in the office. A preliminary version of this study has been reported in abbreviated form [42].

Patient-specific Oscillometric Blood Pressure Measurement Method

The proposed method was inspired by Drzewiecki et al. who established a model to explain oscillometry [24]. Similar to available methods, a standard oscillometric cuff pressure waveform is obtained; the difference in the upper and lower envelopes of the oscillations (i.e., the high-pass filtered or AC waveform) as a function of the cuff pressure (i.e., the un-filtered waveform) is computed during the inflation or deflation period (whichever is longer); and BP is estimated from this oscillation amplitude versus cuff pressure function. However, in contrast to available methods, the BP estimation is based on a physiologic model and is thus patient-specific.

This novel BP estimation is implemented in four steps. First, the oscillation amplitude versus cuff pressure function is represented using a parametric model of the nonlinear brachial artery blood volume-transmural pressure relationship. Second, the model is optimally fitted to the measured function to estimate its unknown parameters including SP and DP. Third, the blood volume waveform is constructed using the parameter estimates and cuff pressure oscillations. Fourth, the BP waveform is derived by applying the blood volume and cuff pressure waveforms to the patient-specific brachial artery blood volume-transmural pressure relationship, and MP is computed from the derived waveform. These steps are fully summarized in Figures 11and 12 and further described below.

In the first step (see Figure 11), the oscillation amplitude versus cuff pressure function is represented using a parametric model of the nonlinear brachial artery blood volume-transmural pressure relationship. This model assumes a sigmoidal relationship as justified by

experimental data [24], [43] and is, in particular, based on a left-shifted, Fisk cumulative probability distribution function [44] as follows:

$$V_a(t) = d\left\{1 + \left[b^{-1}\left((P_a(t) - P_c(t) - a) + b\left(\frac{c-1}{c+1}\right)^{\frac{1}{c}}\right)\right]^{-c}\right\}^{-1} \quad (1)$$

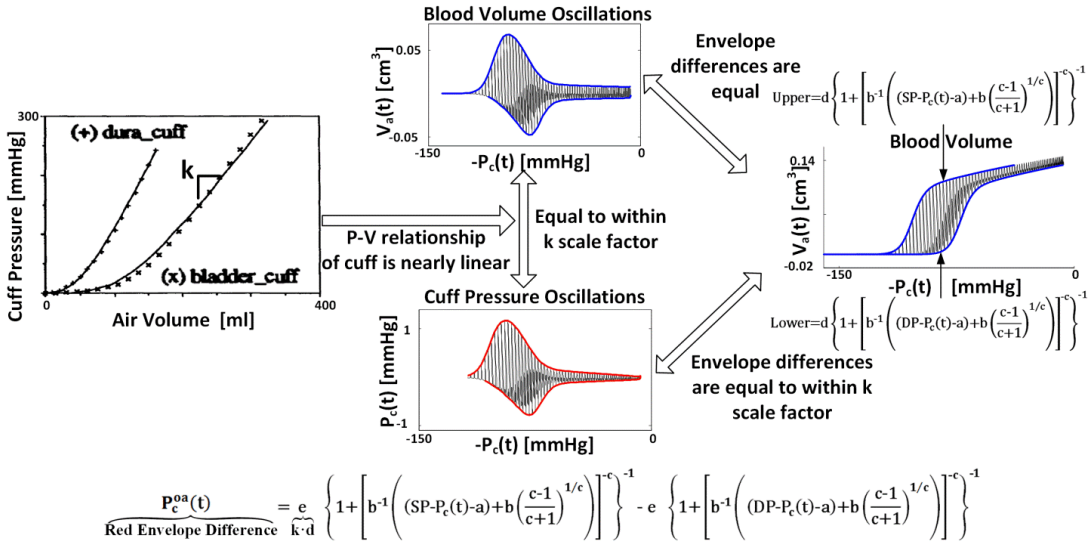
Here, t is time; $V_a(t)$ is the blood volume waveform; $P_a(t)$ is the BP waveform; $P_c(t)$ is the un-filtered cuff pressure waveform; and a, b, c, and d characterize brachial artery mechanics. In terms of the brachial artery compliance curve, which is simply the derivative of Eq. (1) with respect to transmural pressure [$P_a(t)$ - $P_c(t)$], a (units of mmHg) denotes the transmural pressure at which the curve is maximal; b (units of mmHg) and c (unitless) reflect the width of the curve and the degree of asymmetry about its maximum; and d (units of cm^3) determines the amplitude of the curve. Note that Eq. (1) is only valid over the range specified by $(P_a(t)-P_c(t)-a)+b((c-1)/(c+1))^{1/c} > 0$.

This model can directly represent a blood volume versus cuff pressure function. That is, the upper and lower envelopes of the blood volume waveform as a function of cuff pressure may be represented with the above model by setting $P_a(t)$ to SP and DP, respectively (see right plot in Figure 11 where the abscissae are specifically given by the negative of the un-filtered cuff pressure waveform). However, the blood volume waveform is not measured.

In order to apply the model to the measured cuff pressure waveform, two approximations are made. First, the difference in the upper and lower envelopes of the blood volume waveform as a function of negative cuff pressure is essentially equivalent to the difference in the upper and lower envelopes of the blood volume oscillations (i.e., the high-

pass filtered blood volume waveform) as a function of negative cuff pressure (compare right and upper plots in Figure 11). Second, the cuff pressure-air volume relationship of actual cuffs is nearly linear over a wide range (see left plot in Figure 11) [24]. So, the unmeasured blood volume oscillations may be proportional to the measured cuff pressure oscillations (see upper and lower plots in Figure 11) with a proportionality constant equal to k, which indicates the reciprocal of the compliance of the cuff. Note that these oscillations do not include the x-intercept of the cuff pressure-air volume relationship, as they are derived via high-pass filtering.

Step 1: Represent cuff pressure oscillation amplitude versus cuff pressure function with a parametric model of the brachial artery blood volume-transmural pressure relationship



$$\underbrace{P_c^{oa}(t)}_{\text{Red Envelope Difference}} = \underbrace{e}_{k\cdot d}\left\{1+\left[b^{-1}\left((SP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1} - e\left\{1+\left[b^{-1}\left((DP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1}$$

Step 2: Estimate the model parameters including SP and DP by fitting the model to the measured function

$$\min_{\{a,b,c,e,SP,DP\}} \sum_{t\in \text{Deflation Period}} \left[P_c^{oa}(t) - e\left\{1+\left[b^{-1}\left((SP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1} + e\left\{1+\left[b^{-1}\left((DP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1}\right]^2$$

Figure 11: Proposed patient-specific method for estimating blood pressure (BP) from the oscillometric cuff pressure waveform. The first two steps of the method yield estimates for SP and DP as well as the parameters, a, b, c, and e, which characterize the underlying model of the brachial artery blood volume-transmural pressure relationship.

Putting the above model and approximations together, the measured oscillation amplitude versus cuff pressure function is precisely represented with the model as follows:

$$P_c^{oa}(t) = e\left\{1+\left[b^{-1}\left((SP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{\frac{1}{c}}\right)\right]^{-c}\right\}^{-1} - e\left\{1+\left[b^{-1}\left((DP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{\frac{1}{c}}\right)\right]^{-c}\right\}^{-1} \quad (2)$$

where $P_c^{oa}(t)$ is the cuff pressure oscillation amplitude waveform and $e = k \cdot d$ (units of mmHg). $P_c^{oa}(t)$ and $P_c(t)$ are derived from the measured oscillometric cuff pressure waveform and thus known, whereas a, b, c, e, SP, and DP are patient-specific parameters and thus unknown.

In the second step (see Figure 11), the unknown parameters are estimated by optimally matching both sides of Eq. (2) to each other in the least squares sense. In particular, the following optimization problem is solved:

$$\min_{\{a,b,c,e,SP,DP\}} \sum_{t \in \substack{\text{Deflation} \\ \text{Period}}} \left[P_c^{oa}(t) - e\left\{ 1 + \left[b^{-1}\left((SP - P_c(t) - a) + b\left(\frac{c-1}{c+1}\right)^{\frac{1}{c}} \right) \right]^{-c} \right\}^{-1} + e\left\{ 1 + \left[b^{-1}\left((DP - P_c(t) - a) + b\left(\frac{c-1}{c+1}\right)^{\frac{1}{c}} \right) \right]^{-c} \right\}^{-1} \right]^2 \tag{3}$$

Hence, the first two steps produce estimates for SP and DP. The last two steps yield an estimate for MP as follows.

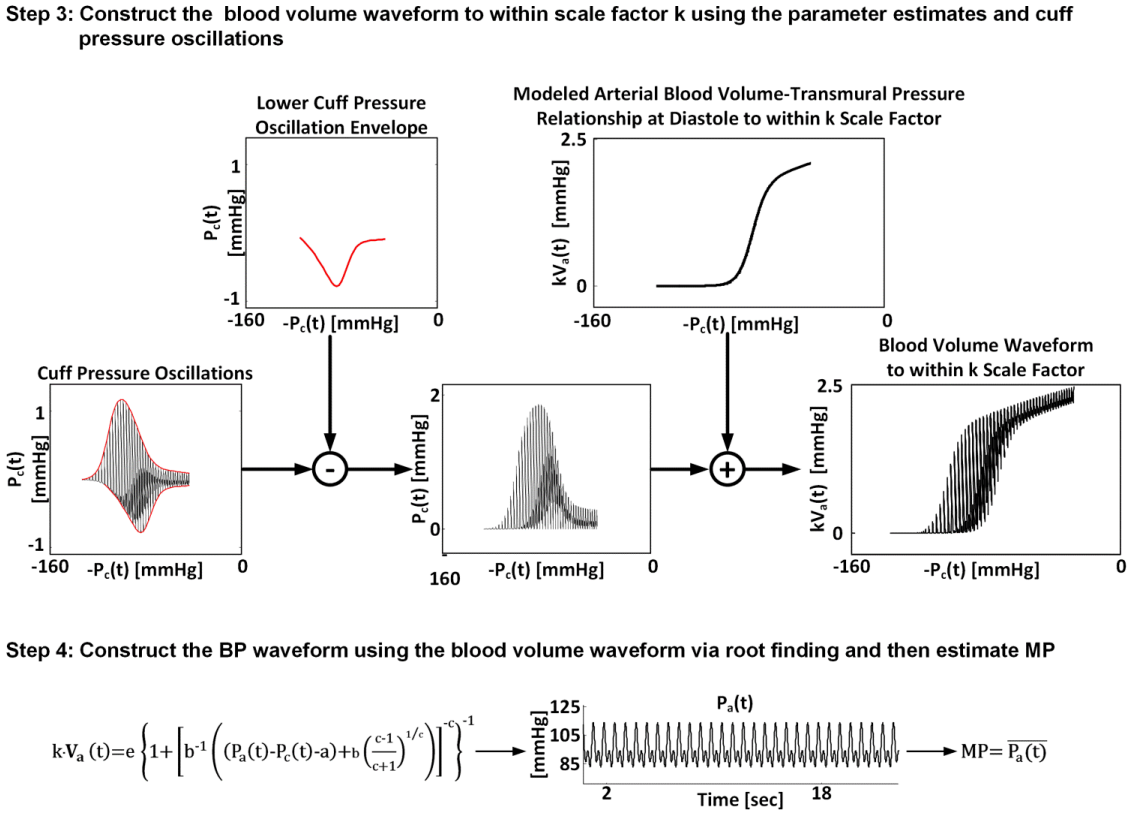


Figure 12: Proposed patient-specific method for estimating BP from the oscillometric cuff pressure waveform (cont.). The last two steps of the method use the parameter estimates from the first two steps to ultimately yield an estimate for MP. The left-most plot here and the three right-most plots in Figure 11 were simulated by a mathematical model of oscillometry [7] for illustrative purposes.

In the third step (see Figure 12), a scaled blood volume waveform [$k \cdot V_a(t)$] is constructed using the parameter estimates. The idea is to construct (to within a scale factor) the right-most plot in Figure 11, which indicates the blood volume waveform, by adding the cuff pressure oscillations to the lower envelope in this plot, which may be derived from the parameter estimates. More specifically and referring back to Figure 12, the lower envelope of the cuff pressure oscillations as a function of negative cuff pressure (second plot from left) is subtracted from the cuff pressure oscillations as a function of negative cuff pressure (left-most plot). The resulting positive amplitude oscillations as a function of negative cuff

pressure (middle plot) are then summed to a function defined by the model of Eq. (1) scaled by k with the parameter estimates for a, b, c, and e and $P_a(t)$ set to the DP estimate (second plot from right). The ordinates of the function resulting from these simple operations specify the scaled blood volume waveform (right-most plot; compare to right-most plot in Figure 11). Note that the scaled blood volume waveform may also be analogously obtained from the upper envelope.

In the fourth step (see Figure 12), the BP waveform is derived using the scaled blood volume waveform according to the model of Eq. (1) scaled by k. In particular, for each t, all quantities in this equation are known, except for $P_a(t)$. Hence, BP is derived at each time instance by finding the root of the equation. Finally, the time average of the constructed BP waveform is computed so as to yield an estimate for MP.

Material and Methods

The patient-specific oscillometric BP measurement method was investigated using data comprising the oscillometric cuff pressure waveforms for analysis and gold standard reference BP measurements from human subjects covering a wide PP range. These data were divided into distinct training and testing sets. While the proposed method is patient-specific, a training dataset was still needed to define its detailed aspects including the values of its user-selected variables. The training dataset was also utilized to establish a conventional fixed-ratio method. The testing dataset was utilized to assess the accuracy of the patient-specific method and to compare its performance to the fixed-ratio method as well as a current device. Details follow.

Patient Data

Patients admitted to the Taipei Veterans General Hospital (Taiwan) were studied under IRB approval and with adherence to the principles of the Declaration of Helsinki. The patient characteristics and study procedures are described in detail elsewhere [45], [46]. Information relevant to the present study is briefly described below.

Sixty patients referred for diagnostic cardiac catheterization were included. These patients (63 ± 14 years, 77% males) had clinical diagnoses of mainly hypertension (68% of the patients), coronary artery disease (65%), dyslipidemia (44%), and/or diabetes (33%) and were on various medications. All patients had normal sinus rhythm, and none of the patients showed an inter-arm BP difference of more than 3 mmHg.

A micromanometer-tipped catheter (SPC-320, Millar Instruments, USA) was placed in a brachial artery to measure the gold standard reference BP waveform. An oscillometric BP cuff (WatchBP Office, Microlife AG, Switzerland or VP-1000, Omron Colin, Japan) was placed over the opposite brachial artery to measure the oscillometric cuff pressure waveform for analysis as well as to document the SP, MP, and DP estimates of the Microlife or Omron device. The waveforms were simultaneously recorded at a sampling rate of 250 Hz. In many of the patients, the measurements were likewise recorded after administration of sublingual nitroglyercin to reduce BP.

Data Analysis

The data for study were divided into a training set comprising 40 of the patient records and a testing set consisting of the remaining 20 patient records. The patient records

in each dataset were randomly selected. All oscillometric cuff pressure waveforms in the two datasets were essentially artifact-free based on visual inspection. However, the fidelity of the reference BP waveforms in three of the patient records in the training dataset was questionable. These patient records were excluded from further analysis yielding a total of 57 patient records for analysis.

The training dataset was first analyzed. More specifically, the patient-specific method was fully defined by minimization of the average of the root-mean-square-error (RMSE) between the SP estimate and reference SP and the RMSE between the DP estimate and reference DP in this dataset. The method that resulted was actually slightly sub-optimal but potentially more robust. This method was implemented as follows. First, the upper and lower envelopes of the oscillations as a function of cuff pressure were identified by detecting the maximum and minimum of each beat, applying a median filter to the maxima and minima to remove respiratory contamination, and linearly interpolating between the filtered maxima and minima. Then, the difference between these envelopes, which is the oscillation amplitude versus cuff pressure function, was represented with the physiologic model of Eq. (2). Next, the unknown model parameters were estimated by solving the optimization problem of Eq. (3) but with constraints on the parameters. The parameter constraints included imposing the valid range of Eq. (1) and setting a, which denotes the peak position of the brachial artery compliance curve, to near 0 mmHg and fixing the value of b for each value of c such that the curve is right-skewed by 35% about its peak. Note that the peak position of the compliance curve is not an identifiable parameter but may be near zero transmural pressure anyhow and that the compliance curve may indeed be typically right-

skewed due to differences in collapsed and distended artery mechanics [24]. Also note that fixing the c and d parameters in addition to the a and b parameters degraded the BP estimation accuracy, thereby suggesting that a patient-specific brachial artery blood volume-transmural pressure relationship was necessary. The four-parameter constrained optimization problem was specifically solved using sequential quadratic programming [47] to yield estimates for SP, DP, and the other parameters. The parameter estimates were generally unique as ascertained via multiple initial seeds. Finally, MP was estimated as outlined in detail in Section 2.

A fixed-ratio method was also established using the training dataset. That is, after estimating MP via the cuff pressure at which the oscillation amplitude is maximal, values of fixed ratios for SP and DP were defined by minimizing the RMSE between the SP and DP estimates and their reference values. The optimal values that resulted were 0.55 for SP and 0.78 for DP, which are consistent with previous reports [24], [25], [39].

The testing dataset was then analyzed. First, the patient-specific and fixed-ratio methods were applied to the oscillometric cuff pressure waveforms. Then, the SP, MP, DP, and PP estimates of these methods as well as the Microlife or Omron device were assessed against their reference values via the standard bias error (i.e., mean of the errors) [μ] and precision error (i.e., standard deviation of the errors) [σ] as well as the RMSE (i.e., total magnitude of the errors) [$= \sqrt{(\mu^2+\sigma^2)}$]. Finally, the bias and precision errors of the patient-specific method were compared to those of the existing methods using the paired t-test and Pitman-Morgan test [48], respectively. Similar results from the training dataset were also

obtained excluding the statistical comparisons with the current device, which, unlike the other two methods, was not optimized with respect to this dataset.

In both datasets, reference SP and DP were specifically computed by detecting the maximum and minimum of each beat of the simultaneously recorded invasive BP waveform during the cuff deflation period (typically about 20 s) and then averaging the respective values over the beats. Reference MP was computed as the time average of the invasive BP waveform during the same period.

Results

Table 2 shows the average, standard deviation, and range of reference SP, MP, DP, and PP before and after nitroglycerin administration in the combined training and testing datasets. These BP statistics were similar between the two datasets. The average of baseline SP was close to hypertensive levels, whereas the average of baseline DP was at normotensive levels. Hence, the average of baseline PP was high. Nitroglycerin reduced the average of SP, which impacted the averages of MP and PP. The standard deviations of PP and SP were highest and near 20 mmHg. PP and SP ranged from normal to high levels, so a number of the patients may not have had large artery stiffening.

Table 2: Reference Blood Pressure (BP) Levels in the Combined Training and Testing Datasets

Condition	SP [mmHg]	MP [mmHg]	DP [mmHg]	PP [mmHg]
Baseline	137±19 (96-182)	95±11 (68-126)	68±10 (44-88)	68±19 (36-110)
Nitroglycerin	126±19 (95-164)	88±11 (68-118)	67±9 (44-90)	59±17 (30-95)

Values are average±standard deviation (range). SP, MP, and DP are systolic, mean, and diastolic BP, respectively, and PP is pulse pressure.

Table 3: BP Error Metrics for the Patient-Specific Method and Existing Methods in the Training Dataset

Method	SP Error [mmHg]		MP Error [mmHg]		DP Error [mmHg]		PP Error [mmHg]	
	Bias	Precision	Bias	Precision	Bias	Precision	Bias	Precision
Patient-Specific	-0.6	5.0	2.0	5.7	-0.5	5.2	-0.1	8.1
Fixed-Ratios	-0.7	8.4*	3.5	10.0*	0.5*	7.5*	-1.2*	13.2*
Microlife	-5.8	7.4	-4.8	8.4	6.9	7.1	-12.7	9.8

* denotes p<0.05 compared with patient-specific method. The Microlife device was not statistically compared to the patient-specific method.

Table 3 shows the SP, MP, DP, and PP bias and precision errors for the patient-specific and fixed-ratio methods as well as the Microlife device in the training dataset. The patient-specific method produced small bias errors and precision errors of 5.0 to 8.1 mmHg. The fixed-ratio method yielded similar bias errors but higher precision errors of 7.5 to 13.2 mmHg ($p < 0.05$). Although it may not be fair to compare the Microlife device to these two methods in the training dataset, it is noted that the device did show higher bias and precision errors than the patient-specific method. If the opposite were true, then the current device would be clearly superior.

Table 4: BP Error Metrics for the Patient-Specific Method and Existing Methods in the Testing Dataset

Method	SP Error [mmHg]		MP Error [mmHg]		DP Error [mmHg]		PP Error [mmHg]	
	Bias	Precision	Bias	Precision	Bias	Precision	Bias	Precision
Patient-Specific	-2.6	6.7	3.5	5.0	2.7	6.0	-5.3	7.7
Fixed-Ratios	3.8*	9.4*	-4.0*	14.0*	-4.8*	8.4*	8.6*	11.2*
Omron	-2.9	8.9#	-6.0*	11.5*	8.1*	5.9	-11.0*	8.9

* and # denote p<0.05 and p<0.10 compared with patient-specific method, respectively.

Table 4 shows the same quantitative BP error metrics for the two methods and the Omron device in the testing dataset, while Figure 13 shows the Bland-Altman plots of these three methods in this dataset so that their accuracy can be visually assessed and compared.

The patient-specific method achieved bias errors of 2.6 to 5.3 mmHg in magnitude and precision errors of 5.0 to 7.7 mmHg. The fixed-ratio method showed significantly different bias errors ($p < 0.05$) with higher magnitudes of 3.8 to 8.6 mmHg and larger precision errors of 8.4 to14.0 mmHg ($p < 0.05$). The Omron device yielded larger bias error magnitudes of 6.0 to 11.0 for MP, DP, and PP than the patient-specific method ($p < 0.05$) and larger precision errors of 8.9 and 11.5 mmHg for SP and MP than this method ($p < 0.10$ or $p < 0.05$). These two methods showed precision errors for PP that did not statistically differ. However, the patient-specific method produced two large absolute errors for PP (see Figure 13), which substantially compromised its precision error. Indeed, after removing the bias component, the percent of PP errors >5 and >10 mmHg were 40% and 11% for the patient-specific method but 75% and 25% for the Omron device. In this quantitative sense, the PP precision accuracy of the patient-specific method was superior to the current device. Overall, the average RMSE of the patient-specific method was 7.3 mmHg, which was about 40% smaller than the corresponding RMSE of each existing method. The improved accuracy afforded by the patient-specific method was significant for all four BP estimates. In addition, the patient-specific method showed BP errors that were least correlated with the reference BP values.

Over the combined training and testing datasets, the patient-specific method yielded model parameter estimates that were distributed (mean±SD) as follows: $a = 2.5$ mmHg, $b = 73.3 \pm 30.0$ mmHg, $c = 5.5 \pm 0.9$ unitless, and $e = 8.2 \pm 1.5$ mmHg. The c and e parameters were 5.2 ± 0.6 unitless and 8.3 ± 1.4 mmHg before nitroglycerin administration and 5.9 ± 1.0 unitless and 8.9 ± 1.5 mmHg after nitroglycerin administration, respectively ($p < 0.05$ via paired t-

tests). These significant c and e increases following nitroglycerin administration correspond to enhanced brachial artery compliance. So, the patient-specific method predicted vascular changes consistent with the known effect of the drug.

The BP estimation accuracy of the method was therefore not impacted by nitroglycerin administration but neither was the accuracy of the existing methods (results not shown).

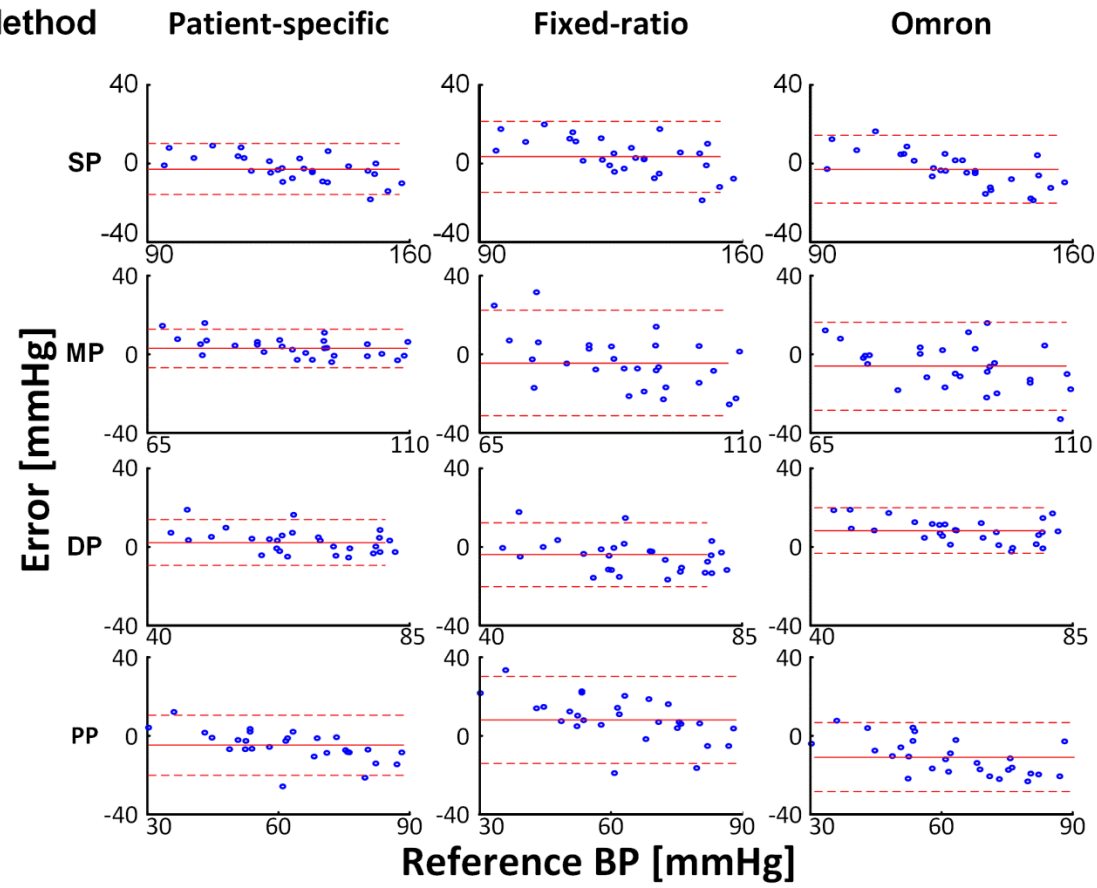


Figure 13: Bland-Altman plots (mean±1.96·SD) for the patient-specific method and existing methods in the testing dataset.

Discussion

In summary, we conceived a method to estimate BP from the oscillometric cuff pressure waveform. While current methods may perform the BP estimation based on population averages (see Figure 10), the proposed method leverages a physiologic model in combination with optimization to achieve patient-specific BP estimation (see Figures 11 and 12). In this way, automatic cuff BP measurement accuracy may potentially be maintained over a wide range of BP levels.

We investigated the patient-specific method against gold standard reference BP measurements via a high-fidelity brachial artery catheter from 57 patients whose PP and SP ranged from normal to very high levels (see Table 2). We used 65% of the data to develop or train the method and the remaining 35% of the data to test it.

The patient-specific method yielded SP, MP, DP, and PP estimates with bias error magnitudes between 2.6 and 5.3 mmHg and precision errors between 5.0 and 7.7 mmHg for an overall average RMSE of 7.3 mmHg in the testing dataset (see Table 4 and Figure 13). The corresponding RMSE of the method in the training dataset was 1.2 mmHg lower (see Table 3). The accuracy of the method in the testing dataset was well within the AAMI limits of 5 and 8 mmHg bias and precision errors for SP, MP, and DP and close to these limits for PP; however, these results were not obtained with an AAMI data collection protocol [49].

There are several potential sources of the BP estimation error of the method. Firstly, the underlying physiologic model ignores arm tissue compressibility and brachial artery wall viscoelasticity. However, compressibility of tissue around zero transmural pressure, which is

most crucial in oscillometry and typically amounts to an applied cuff pressure of about 100 mmHg, may not be that significant, as it is largely compressed already. Furthermore, the wall viscosity of the muscular, but medium-sized, brachial artery may not be that significant compared to its elasticity as argued elsewhere [50]. Secondly, the oscillometric cuff pressure waveforms that were available for analysis were either converted from volts to mmHg with inexact calibration information in the case of the training dataset (Microlife device) or did not include a high resolution (low quantization error) AC component in the case of the testing dataset (Omron device). Hence, if the waveforms were of higher quality, the method could possibly have yielded lower errors. Finally, the method assumes that cuff pressure oscillations are proportional to blood volume oscillations and thus neglects nonlinearity of the arm cuff pressure-volume relationship. However, cuff nonlinearity is greatest at low cuff pressures (see left plot of Figure 11), and the patients for study were not hypotensive (see Table 2). So, unlike the other potential error sources, we do not believe that cuff nonlinearity was a major contributor to the error.

For comparison, we also investigated the conventional fixed-ratio method (see Figure 10) by establishing the fixed ratio values using the training dataset and assessing the method in the testing dataset. The overall average RMSE of the method was 9.9 mmHg in the training dataset and 12.1 mmHg in testing dataset (see Tables 3 and 4 and Figure 13). Hence, the patient-specific method reduced the BP estimation error of the conventional method by about 40% in each dataset. The error reduction was achieved mainly via lower precision errors for all four BP estimates. This comparison was apples-to-apples. That is, not only were the analyzed oscillometric cuff pressure waveforms and training and testing datasets the

same but also the oscillation amplitude versus cuff pressure functions from which BP was estimated.

In addition, we included the BP estimates of a device designed for hypertension management in the office rather than for home monitoring of normal subjects (Microlife or Omron). The overall average RMSE of the device was 11.3 mmHg in the training dataset (see Microlife in Table 3) and 11.6 mmHg in the testing dataset (see Omron in Table 4 and Figure 13). Hence, the patient-specific method reduced the BP estimation error of a current device by 37% in the more meaningful testing dataset. The error reduction was achieved via lower bias errors for MP, DP, and PP and lower precision errors for SP and MP. Also, though not reflected in these error metrics, the patient-specific method achieved substantially better precision accuracy for PP, which is a more powerful predictor of cardiovascular outcomes in the elderly than SP [51]. However, this comparison was not exactly apples-to-apples. In particular, the oscillometric cuff pressure waveforms analyzed by the Microlife and Omron devices were surely well calibrated and of high resolution. So, the device benefitted from higher quality waveforms for analysis than the other two methods. The device also must have derived different oscillation amplitude versus cuff pressure functions to estimate BP. We suspect that the device performs this initial step, which can also impact the accuracy, quite well.

We utilized the most accurate reference BP measurement method available, namely micromanometer-tipped brachial artery catheterization. For practical reasons, invasive BP has not been assessed as a predictor of risk for stroke and heart disease. Rather, non-invasive BP via auscultation (i.e., manual cuff BP measurement using a stethoscope and mercury

manometer) is the proven cardiovascular risk factor [52]. However, auscultation is not as accurate as invasive BP due to various factors including operator error and the well-known auscultatory gap [53]. It may thus be reasonable to assume that invasive BP would constitute a superior predictor of stroke and heart disease. In this sense, the improved accuracy of the patient-specific method shown here may be particularly significant.

Nevertheless, because non-invasive BP via auscultation is the proven cardiovascular risk factor and for practical reasons, most, if not all, BP estimation methods of current office and home devices are built from data using auscultation as the reference [40], [54]. The Microlife and Omron devices studied herein were likely built to predict auscultation BP. There are systematic differences between invasive SP and auscultation SP as well as invasive DP and auscultation DP [49]. These differences could at least partly explain the higher bias error magnitudes of the current device (see Tables 3 and 4). However, even if the bias errors were ignored altogether, the patient-specific method still attained precision errors that were 25% lower for SP and 57% lower for MP than the current device while reducing PP errors >5 and 10 mmHg by 52% compared to this device.

We believe that inclusion of 57 patients for study is not insignificant. Furthermore, even after dividing the patient records into training and testing sets, the improved accuracy of the patient-specific method over the competing methods was statistically significant. Still, the main limitation of this study is the 20 patient sample size of the testing dataset. Future studies are needed in a larger cohort of subjects to fully assess the accuracy of the proposed method relative to existing methods.

In conclusion, we have developed a patient-specific method for automatic cuff BP measurement via oscillometry and have shown that it can be appreciably more accurate than the current state-of-the-art. With further successful testing, the method could possibly facilitate hypertension management in low and high resource settings.

CHAPTER 4. PATIENT-SPECIFIC OSCILLOMETRIC BLOOD PRESSURE MEASUREMENT: VALIDATION FOR ACCURACY AND REPEATABILITY

Oscillometric devices are widely used for automatic cuff blood pressure measurement. These devices estimate blood pressure from the oscillometric cuff pressure waveform using population average methods. As a result, the devices may only be accurate over a limited blood pressure range. The objective of this study was to evaluate a recently proposed patient-specific method, which estimates blood pressure by fitting a physiologic model to the same waveform. A total of 145 cardiac catheterization patients and normal adults were included for study. The oscillometric cuff pressure waveform was obtained with a current office device, while reference blood pressure was simultaneously measured via brachial artery catheterization or auscultation, during baseline and/or nitroglycerin administration. Fifty-seven of the subject records were utilized to refine the patient-specific method, while the remaining 88 subject records were employed to evaluate the method. The patient-specific method yielded significantly lower precision errors for systolic, mean, diastolic, and pulse pressures than the office device (by 29 to 79% on average) in subjects with high pulse pressure (> 50 mmHg) while showing similar precision errors to the device in subjects with normal pulse pressure (< 50 mmHg). The patient-specific method also resulted in significantly lower standard deviations of the differences in repeated systolic, mean, and pulse pressure estimates than the office device (by 64% on average) in subjects with consecutive measurements. The patient-specific method may afford more accurate automatic

cuff blood pressure measurement in patients with large artery stiffening while limiting the number of required cuff inflations/deflations per measurement.

Introduction

Automatic cuff blood pressure (BP) measurement devices are routinely employed for hypertension detection and control. Most of these devices are based on oscillometry.[38]–[40] Oscillometric devices act as both an actuator to alter the transmural pressure of the brachial artery via cuff inflation/deflation and a sensor to measure the small oscillations in the pressure inside the cuff, which reflect the pulsatile blood volume in the artery. Since the volume-pressure relationship of the brachial artery is nonlinear, the amplitude of the cuff pressure oscillations varies with the applied cuff pressure. BP is estimated from the oscillation amplitude versus cuff pressure function (henceforth referred to as the "oscillogram").

The BP estimation method is proprietary but believed to be achieved based on population averages.[38], [39], [41] For example, the standard method is to first estimate mean BP (MP) as the cuff pressure at which the oscillogram is maximal and then estimate each of systolic and diastolic BP (SP and DP) as the cuff pressure at which the oscillogram is some fixed ratio of its maximal value.[25], [38], [39] The fixed ratio values are determined by obtaining the oscillogram and reference BP from a group of subjects and then finding the values that maximize the agreement between the estimated and reference BP in the group. As a result, the devices may only be accurate in new subjects with typical BP levels. Indeed, it is well known that oscillometric device accuracy degrades in patients with high pulse pressure (PP) due to large artery stiffening.[39], [41]

In a recent study, we proposed and demonstrated proof-of-concept of a patient-specific method for oscillometric BP measurement.[55] The method represents the oscillogram with a physiologic model and then estimates the patient-specific model

parameters, which includes BP levels, by optimally fitting the model to the oscillogram. In this way, the accuracy could be maintained over a wider BP range. Furthermore, by employing a physiologic model, the method could be more robust to deviations in the oscillogram caused by respiration and heart rate variability and thus more repeatable.

In this study, our aim was to more thoroughly assess the patient-specific method. We analyzed data from 145 human subjects whose PP varied from normal levels to high levels induced by large artery stiffening. Our results showed that the method was able to significantly improve upon current methods in terms of both precision accuracy, especially in subjects with high PP levels, and repeatability.

Methods

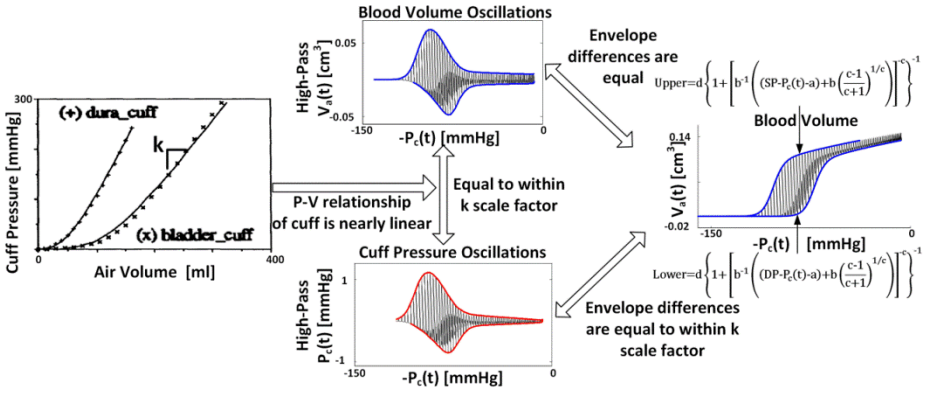
Patient-Specific Oscillometric Blood Pressure Measurement Method

The method is illustrated in Fig. 14 and described in detail elsewhere.[55] Briefly, BP is estimated from a standard oscillogram in four steps. The first two steps produce estimates of SP and DP (see Fig. 14a), while the last two steps yield an estimate of MP (see Fig. 14b). In the first step, the oscillogram (difference between the upper and lower envelopes in red) is represented with a parametric model accounting for the nonlinear brachial artery blood volume-transmural pressure relationship (Eq. (1)). The unknown parameters represent SP, DP, and brachial artery mechanics [a, b, c, e]. In terms of the brachial artery compliance curve (i.e., the derivative of the nonlinear relationship with respect to transmural pressure), a reflects the transmural pressure at which the curve is maximum; b and c denote the width of the curve and extent of asymmetry about its maximum; and e indicates the amplitude of the curve. The parameter e is actually

determined by the reciprocal of the cuff compliance [k], which is assumed to be constant as justified by experimental data (see approximately linear cuff pressure-air volume relationships), in addition to brachial artery mechanics. In the second step, the patient-specific parameters are estimated by optimally fitting the model to the oscillogram in the least squares sense (Eq. (2)). In the third step, the blood volume waveform is constructed to within a k scale factor using the parameter estimates and cuff pressure oscillations through a sequence of simple operations. Finally, in the fourth step, the entire BP waveform is derived from the scaled blood volume waveform and the estimated and likewise scaled brachial artery blood volume-transmural pressure relationship (Eq. (3)) via root finding, and MP is computed as the time average of the derived waveform.

(a)

Step 1: Represent cuff pressure oscillation amplitude versus cuff pressure function ("oscillogram") with a parametric model of the brachial artery blood volume-transmural pressure relationship



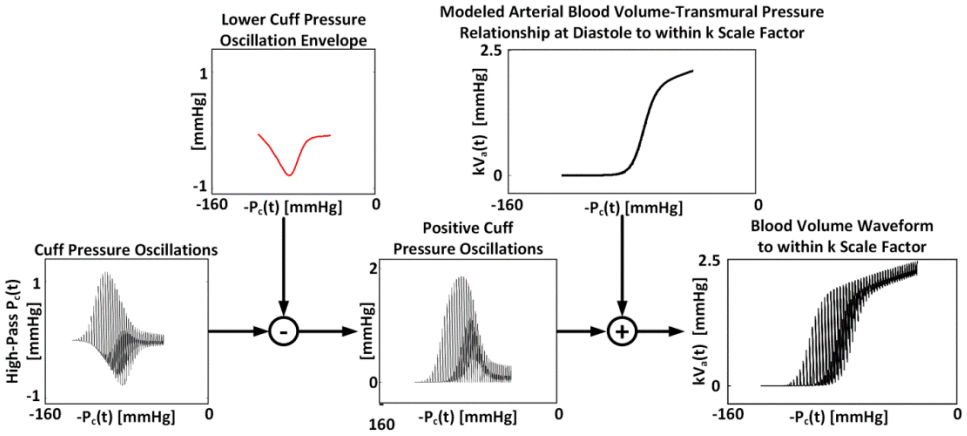
$$\underbrace{P_c^{oa}(t)}_{\text{Red Envelope Difference}} = \underbrace{e}_{k\cdot d}\left\{1+\left[b^{-1}\left((SP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1} - e\left\{1+\left[b^{-1}\left((DP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1} \quad (1)$$

Step 2: Estimate the model parameters including SP and DP by fitting the model to the oscillogram

$$\min_{\{a,b,c,e,SP,DP\}} \sum_{t\in \underset{\text{Period}}{\text{Deflation}}} \left[P_c^{oa}(t) - e\left\{1+\left[b^{-1}\left((SP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1} + e\left\{1+\left[b^{-1}\left((DP-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1}\right]^2 \quad (2)$$

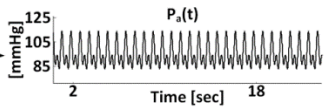
(b)

Step 3: Construct the blood volume waveform to within scale factor k using the parameter estimates and cuff pressure oscillations



Step 4: Construct the BP waveform using the blood volume waveform via root finding and then estimate MP

$$kV_a(t) = e\left\{1+\left[b^{-1}\left((P_a(t)-P_c(t)-a)+b\left(\frac{c-1}{c+1}\right)^{1/c}\right)\right]^{-c}\right\}^{-1} \quad (3) \longrightarrow$$



$$\longrightarrow MP = \overline{P_a(t)}$$

Figure 14**:** The patient-specific method for estimating blood pressure (BP) from the oscillogram.[55]. (a) The first two steps produce estimates for systolic and diastolic pressure (SP and DP) and the parameters, a, b, c, and e, which characterize the underlying model of the brachial artery blood volume-transmural pressure relationship. (b) The last two steps use the resulting parameter estimates and measured cuff pressure oscillations to produce an estimate for mean pressure (MP).

Human Data

To assess the patient-specific method, a total of 158 human subjects were studied at Taipei Veterans General Hospital (Taiwan). All procedures were approved by the Institutional Review Board of the hospital and adhered to the principles of the Declaration of Helsinki. Written, informed consent was obtained from all subjects prior to study.

Amongst the subjects, 138 were adult patients admitted for diagnostic cardiac catheterization. The study procedures for these subjects are described in detail elsewhere.[45], [46] Briefly, all patients had normal sinus rhythm and inter-arm BP differences of no more than 3 mmHg. A micromanometer-tipped catheter (SPC-320, Millar Instruments, Houston) was inserted into a brachial artery to measure the gold standard reference BP waveform. An inflatable cuff of an office oscillometric device (WatchBP Office, Microlife AG, Switzerland or VP-1000, Omron Colin, Japan) was placed over the other brachial artery to measure the raw cuff pressure waveform for analysis and obtain the BP estimates of the device. The waveforms were simultaneously recorded during baseline and/or sublingual nitroglycerin administration. When the Microlife device was used, two cuff pressure waveforms were recorded per condition via repeated cuff inflation/deflation cycles.

The remaining 20 subjects were normal adults. The inflatable cuff of the Microlife device was placed over a brachial artery to again measure the cuff pressure waveform for analysis and obtain the BP estimates of the device. Using a three-way stopcock, the same cuff was interfaced to a mercury sphygmomanometer to simultaneously obtain reference SP and DP from the same arm via auscultation. The auscultation measurements were performed

strictly according to AHA guidelines. Two pairs of cuff pressure waveforms and auscultation measurements were recorded via repeated cuff inflation/deflation cycles.

The cuff pressure waveforms for analysis and invasive reference BP waveforms were visually screened for substantial artifact due to motion or otherwise. All waveforms with such artifact were excluded from subsequent analysis. A total of 315 pairs of cuff pressure waveforms and reference BP measurements from 145 patients and normal subjects remained for analysis. The measurement pairs from 57 of the patients were identical to those previously analyzed to demonstrate proof-of-concept of the patient-specific method.[55] Hence, these data were utilized as training data to refine the method, while the remaining new data from 88 patients and normal subjects were utilized as testing data to more thoroughly evaluate the method. Note that while patient-specific methods do not require training data in theory, all methods need such data in practice to define their user-selected variables. Table 5 summarizes the measurement and subject characteristics of the training and testing datasets for analysis. Table 6 shows the average, standard deviation, and range of reference SP, MP, DP, and PP during baseline and nitroglycerin administration for the patients and normal subjects in the testing dataset. Hence, the BP levels varied widely, with PP and SP ranging from normal levels to high levels due to large artery stiffening. The corresponding statistics for the training dataset, which are reported elsewhere[55], indicated a fairly similar BP range.

Data Analysis

First, the training dataset was analyzed. The requisite oscillogram for BP estimation was constructed from each cuff pressure waveform as described previously.[55]

The user-selected variables of the patient-specific method were determined by maximizing the agreement between its BP estimates and the reference BP values while minimizing the number of parameters for estimation to enhance robustness. The resulting user-selected variables were similar to those established previously.[55] The only differences were fixing the a parameter, which indicates the peak position of the brachial artery compliance curve, to 1.5 instead of 2.5 mmHg and the b parameter for each value of the c parameter such that the compliance curve was right-skewed by 40 rather than 35% about its maximum. Note that these parameter settings are buttressed by directly measured compliance curves.[24] Hence, the optimized patient-specific method estimated four parameters [SP, DP, c, e] from the oscillogram and yielded BP estimates with similar accuracy to the originally established method on the training dataset (see results in reference[55]).

Table 5: Measurement and subject characteristics

	Training Data		Testing Data		
	Cohort 1	Cohort 2	Cohort 1	Cohort 2	Cohort 3
Measurement Characteristics					
Device	Omron	Microlife	Omron	Microlife	Microlife
Reference	Invasive	Invasive	Invasive	Invasive	Auscultation
# of Subjects	20	37	58	11	19
# of Baseline Measurements	20	37	36	11	19
# of Nitroglycerin Measurements	8	36	32	11	0
# of Repeated Measurements	0	73	0	16	16
Total # of Measurements	28	146	68	38	35
Subject Characteristics					
Age [years]	65.1±15.4	65.2±12.3	59.8±15.0	69.0±12.4	34.0±9.4
Weight [kg]	64.5±12.4	74.6±13.4	70.12±11.5	68.9±14.2	60.4±15.8
Height [cm]	164.0±6.4	163.6±8.0	161.6±7.8	162.2±10.4	164.2±9.3
Waist circumference [cm]	84.6±11.4	90.0±12.3	91.8±9.5	97.2±11.9	75.8±11.2
Men [%]	85	75.7	74.1	72.7	36.8
Smoking [%]	35	18.9	20.7	27.3	N/A
Clinical diagnosis [%]					
Hypertension	65	59.5	56.9	90.9	N/A
Type 2 Diabetes Mellitus	20	29.7	31	54.5	N/A
Dyslipidemia	45	37.8	41.4	36.4	N/A
Coronary Artery Disease	40	59.5	56.9	63.6	N/A
Chronic Renal Failure	5	2.7	3.4	18.2	N/A
Medications [%]					
α-Blockers	20	13.5	12.1	27.3	N/A
β-Blockers	30	43.2	37.9	63.6	N/A
Calcium Channel Blockers	25	48.6	41.4	27.3	N/A
Diuretics	20	18.9	20.7	36.4	N/A
Antiplatelet Agents	65	86.5	70.7	81.8	N/A

Table 6: Reference blood pressure (BP) levels in the testing data

Reference BP	Condition	SP [mmHg]	MP [mmHg]	DP [mmHg]	PP [mmHg]
Invasive	Baseline	136±20 (109-192)	97±13 (76-127)	72±11 (46-95)	64±16 (45-107)
	Nitroglycerin	130±18 (99-169)	92±12 (72-115)	70±11 (46-70)	60±18 (31-102)
Auscultation	Baseline	105±11 (88-130)	N/A	71±10 (54-88)	34±9 (21-54)

Values are mean±SD (minimum-maximum). SP, MP, and DP are systolic, mean, and diastolic BP, respectively, and PP is pulse pressure.

A fixed-ratio method was likewise developed using the training dataset by maximizing the agreement between its BP estimates from the same oscillograms and the reference BP values. The resulting fixed ratio values were 0.57 for SP and 0.75 for DP. This method also performed similarly to a previous fixed-ratio method on the training dataset (see results in reference[55]).

Then, the testing dataset was analyzed. The patient-specific and fixed-ratio methods were applied to oscillograms likewise constructed from the cuff pressure waveforms. The BP estimates of these methods and the office device were compared for accuracy and repeatability.

For accuracy, note that the testing dataset included reference BP via brachial artery catheterization or auscultation (see Table 5). Further note that the patient-specific and fixed-ratio methods were trained based on the former reference method (see Table 5), whereas the office device was surely developed based on the latter reference method. Since there are systematic differences between the two reference methods (i.e., invasive SP and DP are a few mmHg higher and lower than auscultation SP and DP, respectively),[49] bias accuracy could not be fairly quantified and compared. To quantify precision accuracy, the errors between the SP, MP, DP, and PP estimates and the reference BP values were computed. The bias component of each of these errors for each method in each of the three cohorts in the testing dataset (see Table 5) was then removed. The resulting precision errors were divided

into two groups: normal PP (reference PP < 50 mmHg) and high PP (reference PP > 50 mmHg). Note that a 50 mmHg threshold was chosen so as to arrive at groups of approximately equal size. In the case of repeated measurement pairs, only the first measurement pair was included in the groups. The root-mean-square (RMS) of the errors and distribution of errors (i.e., percent of absolute errors < 5, < 10, and < 15 mmHg) in each PP group were then computed. Finally, to compare precision accuracy, the Pittman-Morgan test was applied to the RMS of the errors (which were nearly void of a bias component) of pairs of methods in each PP group.[48] A $p < 0.0167$ (= 0.05/3) was considered significant based on Bonferroni correction for pairwise comparison of three methods.

For repeatability, the mean and standard deviation of the differences between each of the repeated estimates of SP, MP, DP, and PP of each method were computed. The paired t-test and Pittman-Morgan test were then applied to compare the resulting bias and precision of pairs of methods, respectively. A $p < 0.0167$ was likewise considered significant.

Results

Table 7 summarizes the SP, MP, DP, and PP precision accuracy results for the patient-specific method, fixed-ratio method, and Omron/Microlife device in the normal PP and high PP groups of the testing dataset. These results were obtained from 88 subjects wherein the normal PP and high PP groups constituted 42 and 58% of the data, respectively. The mean±SD of PP was 39.9±8.0 mmHg in the normal PP group and 69.4±15.0 mmHg in the high PP group. The RMS errors of the patient-specific method ranged from 6.3 to 7.6 mmHg over both PP groups, and its error distributions were fairly similar between the groups. Hence, the patient-specific method was able to maintain the precision accuracy over a wide

PP range. Furthermore, the precision errors of this method were significantly lower (or not different) relative to the fixed-ratio method in both PP groups. In particular, the RMS errors for SP, DP, and PP of the patient-specific method were, on average, 36% smaller than those of the fixed-ratio method, while the absolute precision errors exceeding 10/15 mmHg of the new method were, on average, 50/75% less than the standard method. More notably, the precision errors of the patient-specific method were significantly lower relative to the currently employed Omron/Microlife device in the high PP group while being similar in the normal PP group. Specifically, in the high PP group, the RMS errors for all BP levels of the patient-specific method were, on average, 29% smaller than those of the Omron/Microlife device, while the absolute precision errors exceeding 10/15 mmHg of the new method were, on average, 51/79% less than the office device. Hence, the patient-specific method was able to reduce the number of large precision errors and improve the precision accuracy, especially over the high PP range. Fig. 15a shows Bland-Altman plots for visual assessment of the high PP group results.

Table 7: BP precision error metrics for the patient-specific method and two available methods in the testing data

Normal PP Group (Reference PP < 50mmHg with Mean±SD = 39.9±8.0 mmHg)																
	SP Precision Error				MP Precision Error				DP Precision Error				PP Precision Error			
Method	RMS [mmHg]	<5 [%]	<10 [%]	<15 [%]	RMS [mmHg]	<5 [%]	<10 [%]	<15 [%]	RMS [mmHg]	<5 [%]	<10 [%]	<15 [%]	RMS [mmHg]	<5 [%]	<10 [%]	<15 [%]
Patient-specific	7.4	56	73	91	6.5	59	85	100	6.3	63	84	93	6.4	58	86	97
Fixed-ratio	10.1*	30	60	84	8.9	40	77	88	9.5*	30	65	86	10.5*	39	69	89
Omron/Microlife	7.8	41	63	95	7.1	48	77	92	6.4	69	86	93	5.5	67	95	100

High PP Group (Reference PP > 50mmHg with Mean±SD = 69.4±15.0 mmHg)																
	SP Precision Error				MP Precision Error				DP Precision Error				PP Precision Error			
Method	RMS [mmHg]	<5 [%]	<10 [%]	<15 [%]	RMS [mmHg]	<5 [%]	<10 [%]	<15 [%]	RMS [mmHg]	<5 [%]	<10 [%]	<15 [%]	RMS [mmHg]	<5 [%]	<10 [%]	<15 [%]
Patient-specific	7.6	42	85	96	6.4	55	87	96	6.5	52	92	98	6.7	49	87	100
Fixed-ratio	13.0*	34	52	71	7.8	52	84	90	9.1*	50	80	88	12.8*	30	50	74
Omron/Microlife	10.6*	38	76	84	9.7*	50	73	88	8.5*	39	80	92	9.8*	38	71	90

*$p < 0.0167$ compared to patient-specific method. Only root-mean-square (RMS) of precision errors were statistically compared; bias errors could not be fairly quantified and compared as described in the text.

Table 8 summarizes the SP, MP, DP, and PP repeatability results for the three methods in the testing dataset. These results were obtained from 32 subjects for SP, DP, and PP and 16 subjects for MP. The bias and precision of the differences in repeated estimates for all BP levels of the patient-specific method ranged from 0.1 to 1.1 mmHg and 2.1 to 5.9 mmHg, respectively. These values were significantly lower (or not different) relative to the other methods. In particular, the bias of the differences in repeated estimates for SP and PP of the patient-specific method were, on average, 79% smaller than those of the fixed-ratio method, while the precision of the differences in repeated estimates for SP, MP, and PP of the new method were, on average, 53% smaller than those of the standard method and 64% smaller than those of the Microlife device. Hence, the patient-specific method was able to improve the BP measurement repeatability. Fig. 15b shows Bland-Altman plots for visual assessment of these results.

Table 8: BP repeatability metrics for the patient-specific method and two available methods in the testing data

Method	SP Difference b/w Repeated Estimates [mmHg]		MP Difference b/w Repeated Estimates [mmHg]		DP Difference b/w Repeated Estimates [mmHg]		PP Difference b/w Repeated Estimates [mmHg]	
	Bias	Precision	Bias	Precision	Bias	Precision	Bias	Precision
Patient-specific	1.1	3.3	0.2	2.1	0.1	4.3	1.0	5.9
Fixed-ratio	4.3*	7.3*	0.1	5.4*	-1.6	4.8	5.9*	10.0*
Microlife	1.6	8.1*	0.8	10.9*	0.9	6.4	0.7	12.5*

*$p < 0.0167$ compared to patient-specific method.

Secondary results (which are not shown) were as follows. Firstly and as alluded to earlier, the bias accuracy for the SP and DP estimates of the patient-specific method tended to be superior relative to the Omron/Microlife device when invasive BP was the reference (bias error of -2.4 vs. -5.4 mmHg for SP and -0.1 vs. 1.5 mmHg for DP) but tended to be worse compared to the office device when auscultation BP was the reference (4.0 vs. 2.4 mmHg for SP and -6.6 vs. -3.9 mmHg for DP). However, the precision accuracy of the patient-specific method was similar relative to the office device when auscultation BP was the reference (precision error of 5.3 vs. 6.4 mmHg for SP and 5.2 vs. 5.1 mmHg for DP). Further, the c and e parameter estimates of the patient-specific method were 5.2±0.7 (mean±SD) unitless and 8.2±1.4 mmHg during baseline and 5.9±1.0 unitless and 8.9±1.4 mmHg during nitroglycerin administration, respectively ($p \leq 0.013$ via t-tests). Increases in the c and e parameters both correspond to enhanced brachial artery compliance, so the patient-specific method was able to correctly track the drug-induced compliance changes. Finally, and perhaps as a result, the precision accuracy of the patient-specific method tended to be less impacted by nitroglycerin administration than the Omron/Microlife device (average difference in RMS error from baseline to nitroglycerin administration of -0.98 mmHg vs. -1.95 mmHg).

Discussion

Most automatic cuff BP measurement devices employ population average methods to estimate BP from an oscillogram and may thus be accurate only over a limited BP range. We recently proposed a patient-specific method to estimate BP from the oscillogram by leveraging a physiologic model in conjunction with model fitting (see Fig. 14).[55] In this way, the routinely used devices may not only maintain accuracy over a wider BP range but also be less sensitive to common physiologic deviations in the oscillogram and thus more repeatable. Here, we refined the method and compared it to existing methods for accuracy and repeatability in human subjects with normal PP levels and high PP levels induced by large artery stiffening (see Tables 5 and 6).

The patient-specific method achieved BP errors reflecting precision accuracy that ranged from 6.3 to 7.6 mmHg (see Table 7). Hence, the method maintained the precision accuracy over both the normal and high PP ranges. Further, this level of precision accuracy was within the AAMI precision limits of 8 mmHg. However, the method did not meet the AAMI standard, because an AAMI data collection protocol was not employed.

The patient-specific method was compared to both the standard fixed-ratio method, which was developed using the same training dataset as the new method, and a currently used office device (Omron or Microlife). Overall, the office device attained greater precision accuracy than the fixed-ratio method (see Table 7), thereby suggesting that the device estimates BP based on other useful features in the oscillogram in addition to, or instead of, amplitude ratios. However, the level of precision accuracy of the office device was not within 8 mmHg for the high PP range. Compared to this device, the patient-specific method revealed significantly lower precision errors for all BP levels in the high PP range (by 29 to

79% on average) while showing similar precision errors in the normal PP range (see Table 7 and Fig. 15a).

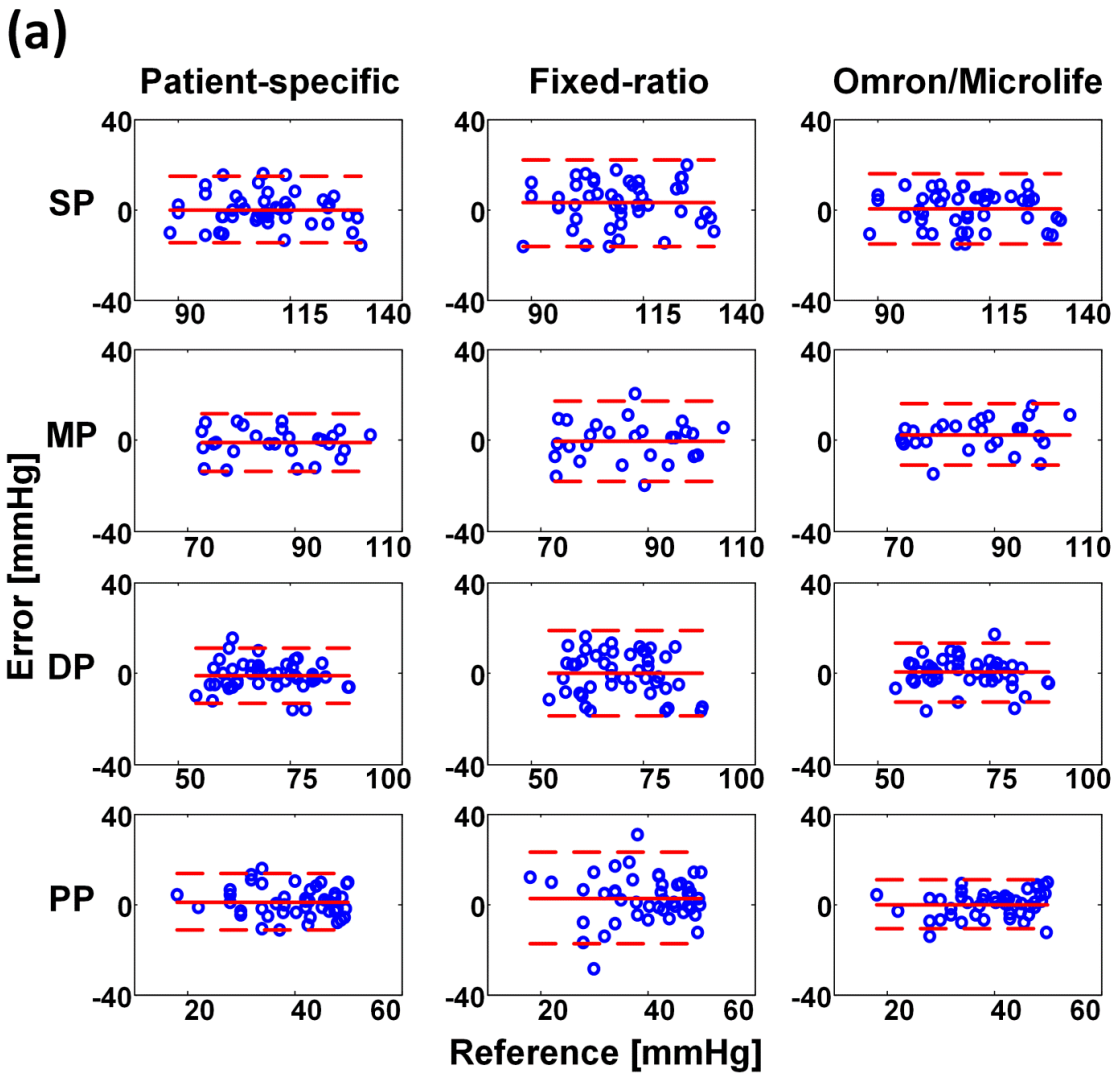


Figure 15**:** Bland-Altman plots (mean±1.96·SD) of the (a) precision errors in the normal pulse pressure (PP) group (reference PP < 50 mmHg); (b) precision errors in the high PP group (reference PP > 50 mmHg); and (c) differences in repeated estimates for the patient-specific method and two available methods in the testing data.

Figure 15 (Cont'd)

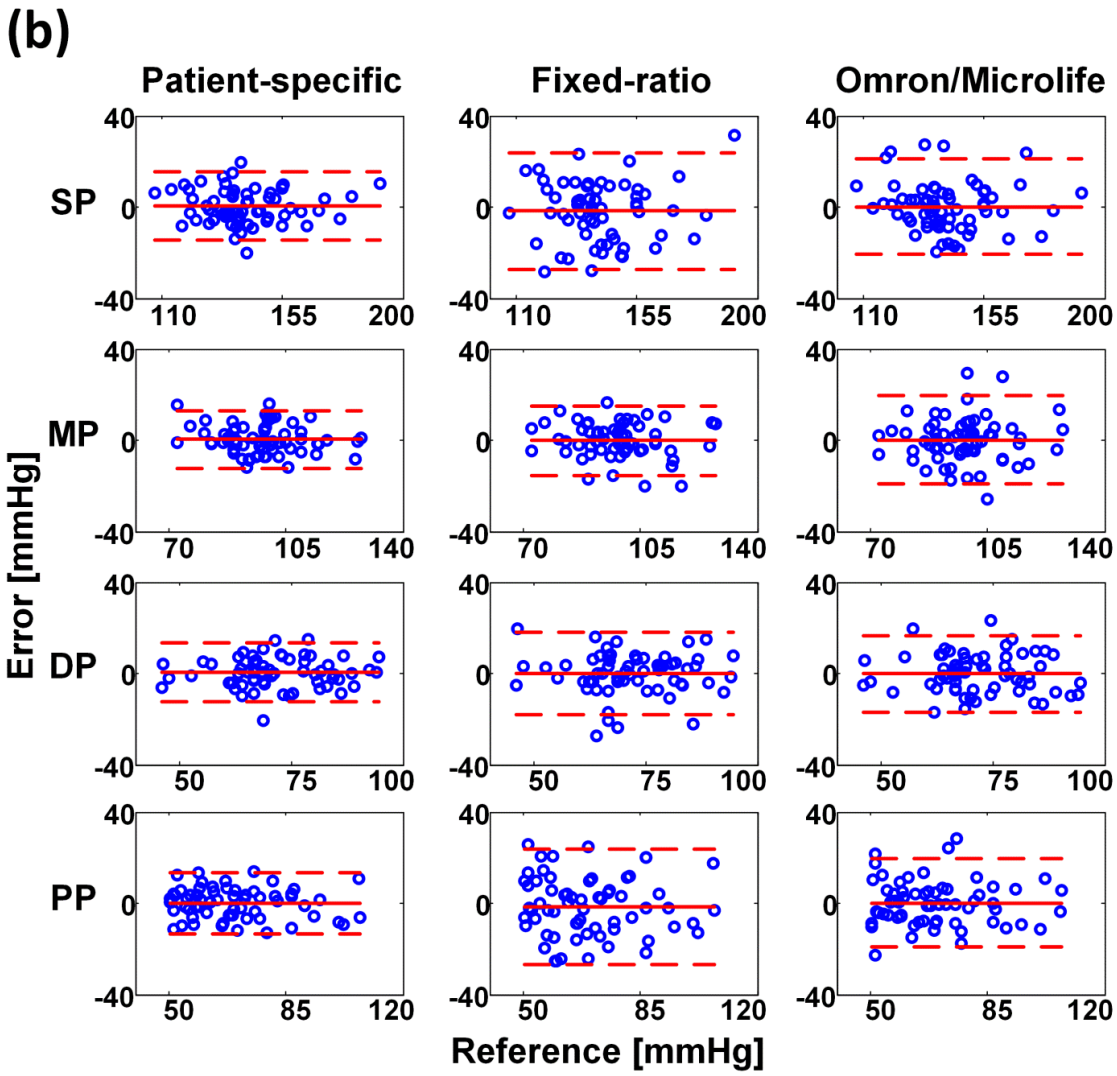
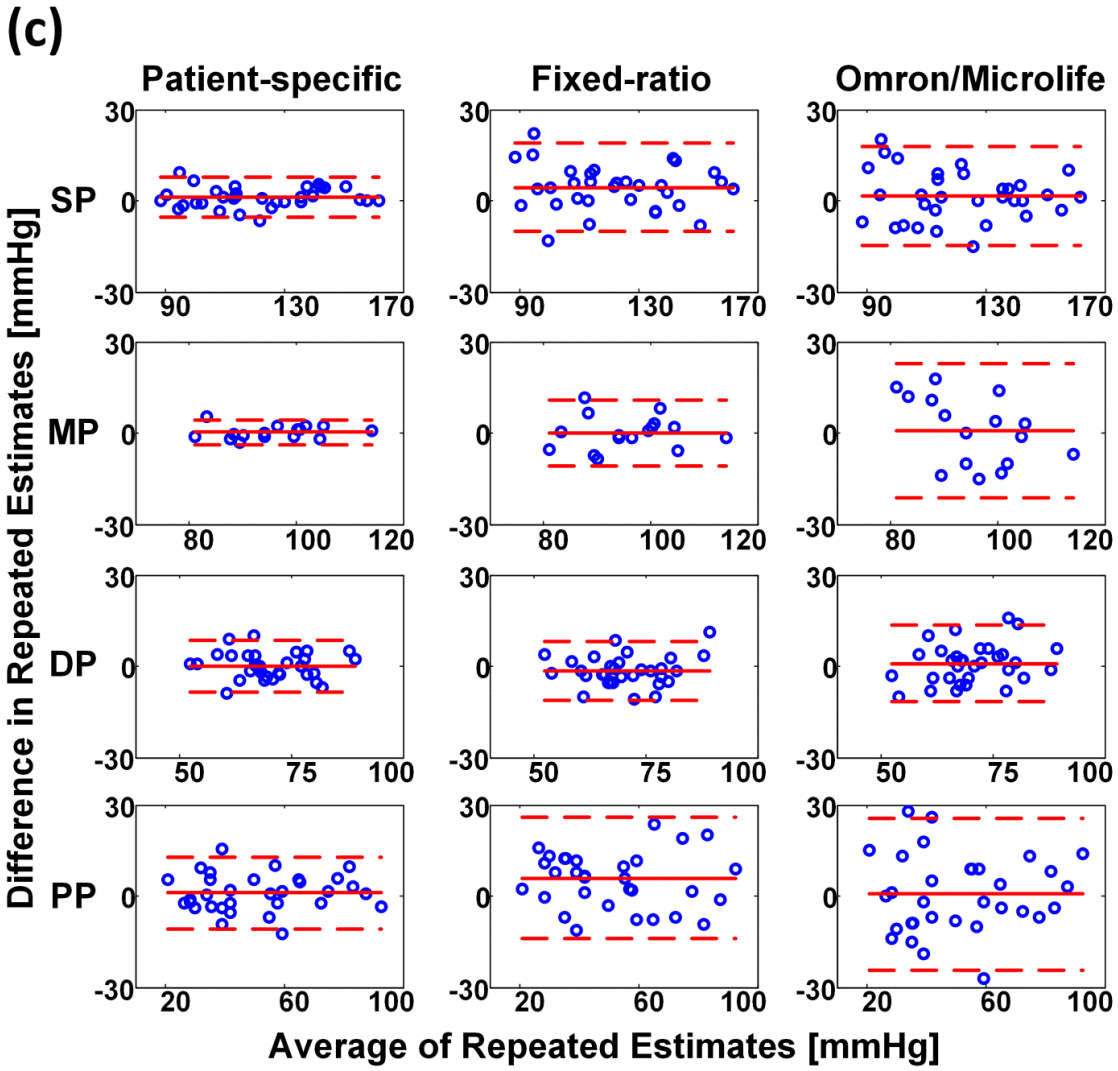


Figure 15 (Cont'd)



The reference method was either auscultation BP or invasive BP in the normal PP range but almost exclusively invasive BP in the high PP range. The well-known auscultatory gap is strongly related to carotid artery stiffening and aging[56] and thus high PP. Perhaps as a result, the ability of auscultation to stratify risk for stroke and heart disease diminishes with aging.[52] Since auscultation BP was not utilized as the reference in the high PP range, the improvement in precision accuracy attained by the patient-specific method here may be particularly significant. The improved precision accuracy with respect to invasive BP could also be significant in terms of monitoring central BP, which may offer superior cardiovascular risk stratification to brachial BP.[57] That is, a major source of error of non-invasive measurements of central BP is the discrepancy between the BP estimates of current oscillometric devices, which are used to calibrate the arterial tonometry waveforms, and invasive brachial BP.[58], [59] Hence, the patient-specific method may be able to enhance the accuracy of non-invasive central BP monitoring.

The bias accuracy of the methods could not be fairly assessed and compared due to the systematic differences in the two reference methods[49] employed for testing as well as testing them. While the inability to address bias accuracy represents the main study limitation, precision accuracy may be much more important anyhow. For example, the bias accuracy of the patient-specific method, which was developed using the invasive BP reference, could be easily be corrected for an auscultation BP reference by subtracting and adding a constant (e.g., 3-4 mmHg[56]) to its SP and DP estimates, respectively.

The patient-specific method also achieved a bias and precision of the differences in repeated BP estimates that ranged from 0.1 to 1.1 mmHg and 2.1 to 5.9 mmHg, respectively

(see Table 8). This level of repeatability was within the AHA recommended limits of 5 mmHg for SP, MP, and DP and near these limits for PP.[60]

While the office device was more accurate than the fixed-ratio method, the standard method appeared more repeatable (see Fig. 15b). However, the level of repeatability of the fixed-ratio method was not close to the AHA limits for SP and PP (see Table 8). Compared to this method, the patient-specific method revealed significantly lower bias of the differences in repeated SP and DP estimates (by 79% on average) and precision of the differences in repeated SP, MP, and PP estimates (by 53% on average) (see Table 8 and Fig. 15b).

In sum, the patient-specific method afforded superior precision accuracy, especially in the high PP range wherein gold standard invasive BP served as the reference, and repeatability compared to population-based methods. Hence, the new method could possibly improve cardiovascular risk stratification in the elderly and other patients with large artery stiffening while limiting the number of required cuff inflations/deflations per BP measurement.[60]

The accuracy of current oscillometric BP measurement devices is also known to degrade in other conditions including arrhythmias, especially atrial fibrillation, and pre-eclampsia.[60], [61] Future studies would have to be conducted to determine if the patient-specific method can offer improvements in such conditions. Subsequent studies to confirm the results of this study and assess the cardiovascular risk stratification ability of the method may also be worthwhile.

Conclusion

Hypertension detection and control currently represent a major healthcare problem

around the world, especially in low resource settings. Effective BP measurement technology is essential to alleviate this problem. Amongst the available technologies, oscillometry offers a number of advantages. In particular, it is non-invasive (unlike catheterization), easy-to-use (unlike manual auscultation or tonometry), inexpensive (unlike volume clamping), unaffected by the auscultatory gap and terminal digit bias (unlike manual auscultation), less sensitive to cuff position and ambient sound (compared to automatic auscultation), environmentally safe (unlike mercury manometers), and more convenient in terms of maintenance (compared to aneroid manometers). However, the disadvantage of oscillometry is that it is not as accurate as other technologies (catheterization and manual auscultation). The reason is that BP is estimated from the oscillogram using population average methods. We evaluated a recently proposed patient-specific method for estimating BP from a standard oscillogram. The new method showed significantly improved accuracy over a wide PP range as well as repeatability compared to the standard BP estimation method and a current office device. With further successful testing, the patient-specific method could possibly facilitate the management of hypertension by affording more accurate automatic cuff blood pressure measurement in patients with large artery stiffening while limiting the number of required cuff inflations/deflations per measurement.

CHAPTER 5. CONCLUSION AND FUTURE WORKS

Hypertension is a major cardiovascular risk factor that is treatable, yet undetected or uncontrolled in many people, especially in low resource settings. Ubiquitous blood pressure (BP) monitoring technology could improve hypertension detection and control, but such technology has been elusive.

We commenced our research on oscillometry five years ago. First, we studied the standard oscillometric BP estimation algorithm using a mathematical model [62]. Then, with the aid of a SCH EXP grant, we built upon this and other such population-based algorithms by developing a patient-specific algorithm [63] and showing that it could yield more accurate and repeatable BP estimates than current devices offered by leading manufacturers [64]. Finally, we conceived, and demonstrated the feasibility of, an idea to extend the oscillometric principle for cuff-less monitoring of finger BP. We elaborate upon these efforts below.

Our future works is to create cuff-less BP monitoring technology that can be readily used by the masses. In conventional oscillometry, an inflatable cuff is employed as both an actuator to vary the external pressure of an artery and a sensor to measure this pressure and the resulting variable-amplitude blood volume oscillations in the artery. BP is then estimated from the oscillation amplitudes as a function of the applied pressure (i.e., the "oscillogram"). Our idea is to extend oscillometry for cuff-less monitoring of finger BP using only a smartphone. In this case, the subject serves as the actuator by pressing her finger against a smartphone to steadily increase the external pressure of the underlying artery, while the smartphone, embedded with a basic photoplethysmograph (PPG) and pressure transducer, acts as the sensor to measure the blood volume oscillations and applied pressure. The phone

also provides visual feedback to guide proper finger pressing. BP is then likewise estimated from the oscillogram. We developed a crude prototype to initially test this idea, and the error in mean BP was typically less than 10 mmHg.

We propose to establish hardware and software technology to effectively implement the oscillometric finger pressing paradigm for cuff-less BP monitoring. The future work includes:

(1) To develop a PPG-pressure sensor unit to simultaneously measure the finger blood volume and applied finger pressure. We will explore various force and pressure sensors, infrared, reflectance-mode PPG configurations, and additional structures to optimize the fidelity of the raw measurements. We will also determine the physical dimensions of the sensor unit and the position of this unit within its encasing that facilitate finger pressing.

(2) To develop visualization tools to guide finger pressing. We will study various finger pressing protocols to balance the ease of implementation, as ascertained via user surveys, with the success of implementation, as determined via the level of agreement between the actual and target pressures. We will then develop an instructional video and display for real-time, visual feedback on the actuation to facilitate user conformance to the protocol.

(3) To develop algorithms to construct the oscillogram and assess the actuation. We will develop an algorithm to construct the oscillogram from the raw measurements that is robust against artifact due to both motion and imprecise application of external pressure. We will also develop an algorithm to identify successful actuation in terms of the extent to which the oscillogram shows the anticipated physiologic morphology. If the actuation is deemed unsuccessful, the system will ask the user to repeat the finger pressing protocol.

(4) To develop algorithms to estimate BP from a finger pressing oscillogram. We will extend our model-based BP estimation method developed for arm cuff oscillograms via SCH EXP-funded research to successful finger pressing oscillograms. Since the finger oscillograms will contain further artifact due to imprecise application of external pressure, we will also explore simpler, yet potentially more robust, data-driven BP estimation methods.

(5) To evaluate the integrated hardware and software prototypes. We will assess prototype systems in normotensive and hypertensive subjects. We will evaluate its BP estimation accuracy using reference cuff BP values, the repeatability of its BP estimates, and the frequency of unsuccessful measurements. We will also conduct surveys to assess adoptability.

Successful completion of this project will be followed by efforts towards incorporating the hardware and software technology into smartphones. These phones may also include software to, for example, warn users of high BP, securely transmit the measured BP to caregivers, and send text reminders to patients with uncontrolled BP to take their medications. In this way, a complete hypertension management system will be available in the pockets of many.

BIBLIOGRAPHY

BIBLIOGRAPHY

[1] A. Chockalingam, "Impact of World Hypertension Day.," *Can. J. Cardiol.*, vol. 23, no. 7, pp. 517–9, May 2007.

[2] A. S. Go, D. Mozaffarian, V. L. Roger, E. J. Benjamin, J. D. Berry, W. B. Borden, D. M. Bravata, S. Dai, E. S. Ford, C. S. Fox, S. Franco, H. J. Fullerton, C. Gillespie, S. M. Hailpern, J. A. Heit, V. J. Howard, M. D. Huffman, B. M. Kissela, S. J. Kittner, D. T. Lackland, J. H. Lichtman, L. D. Lisabeth, D. Magid, G. M. Marcus, A. Marelli, D. B. Matchar, D. K. McGuire, E. R. Mohler, C. S. Moy, M. E. Mussolino, G. Nichol, N. P. Paynter, P. J. Schreiner, P. D. Sorlie, J. Stein, T. N. Turan, S. S. Virani, N. D. Wong, D. Woo, and M. B. Turner, "Heart disease and stroke statistics--2013 update: a report from the American Heart Association.," *Circulation*, vol. 127, no. 1, pp. e6–e245, Jan. 2013.

[3] A. Chockalingam, "Impact of World Hypertension Day," *Can J Cardiol*, vol. 23, no. 7, pp. 517–9, May 2007.

[4] "http://www.cadiresearch.org/topic/hypertension/hypertension-india." .

[5] "http://www.gallup.com/poll/145868/chronic-health-conditions-prevalent-2010-2009.aspx." .

[6] "http://www.worldlifeexpectancy.com/news/india-vs-china-top-10-causes-of-death." .

[7] "http://www.cdc.gov/nchs/fastats/lcod.htm." .

[8] "The world health report 2002 - Reducing Risks, Promoting Healthy Life," World Health Organization, Geneva, 2002.

[9] R. Collins, R. Peto, S. MacMahon, P. Hebert, N. Fiebach, K. Eberlein, J. Godwin, N. Qizilbash, J. Taylor, and C. Hennekens, "Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context," *Lancet*, vol. 335, no. 8693, pp. 827–38, Apr. 1990.

[10] "http://www.cdc.gov/bloodpressure/facts.htm." .

[11] R. Gupta, P. Deedwania, V. Achari, A. Bhansali, B. Gupta, A. Gupta, T. Mahanta, A. Asirvatham, S. Gupta, A. Maheshwari, B. Saboo, M. Jali, J. Singh, S. Guptha, and K. Sharma, "Normotension, prehypertension, and hypertension in urban middle-class subjects in India: prevalence, awareness, treatment, and control," *Am J Hypertens*, vol. 26, no. 1, pp. 83–94, Jan. 2013.

[12] "Affordable technology : blood pressure measuring devices for low resource settings," *Geneva World Heal. Organ.*, 2005.

[13] N. Ghuman, P. Campbell, and W. White, "Role of ambulatory and home blood pressure

recording in clinical practice," *Curr Cardiol Rep*, vol. 11, no. 6, pp. 414–21, Nov. 2009.

[14] R. Agarwal, J. Bills, T. Hecht, and R. Light, "Role of home blood pressure monitoring in overcoming therapeutic inertia and improving hypertension control: a systematic review and meta-analysis," *Hypertension*, vol. 57, no. 1, pp. 29–38, Jan. 2011.

[15] L. Geddes, M. Voelz, C. Combs, D. Reiner, and C. Babbs, "Characterization of the oscillometric method for measuring indirect blood pressure," *Ann Biomed Eng*, vol. 10, no. 6, pp. 271–80, Jan. 1982.

[16] J. Liu, J. Hahn, and R. Mukkamala, "Error mechanisms of the oscillometric fixed-ratio blood pressure measurement method," *Ann Biomed Eng*, vol. 41, no. 3, pp. 587–97, Mar. 2013.

[17] A. Thompson, K. Eguchi, M. Reznik, S. Shah, and T. Pickering, "Validation of an oscillometric home blood pressure monitor in an end-stage renal disease population and the effect of arterial stiffness on its accuracy," *Blood Press Monit*, vol. 12, no. 4, pp. 227–32, Aug. 2007.

[18] N. van Popele, W. Bos, N. de Beer, D. van Der Kuip, A. Hofman, D. Grobbee, and J. Witteman, "Arterial stiffness as underlying mechanism of disagreement between an oscillometric blood pressure monitor and a sphygmomanometer," *Hypertension*, vol. 36, no. 4, pp. 484–8, Oct. 2000.

[19] B. Imholz, W. Wieling, G. van Montfrans, and K. Wesseling, "Fifteen years experience with finger arterial pressure monitoring: assessment of the technology," *Cardiovasc Res*, vol. 38, no. 3, pp. 605–16, Jun. 1998.

[20] T. Kenner, "Arterial blood pressure and its measurement," *Basic Res Cardiol*, vol. 83, no. 2, pp. 107–21.

[21] H. Cheng, D. Lang, C. Tufanaru, and A. Pearson, "Measurement accuracy of non-invasively obtained central blood pressure by applanation tonometry: A systematic review and meta-analysis," *Int J Cardiol*, vol. 167, no. 5, pp. 1867–76, Sep. 2013.

[22] G. Schwartz, B. Tee, J. Mei, A. Appleton, D. Kim, H. Wang, and Z. Bao, "Flexible polymer transistors with high pressure sensitivity for application in electronic skin and health monitoring," *Nat Commun*, vol. 4, p. 1859, Jan. 2013.

[23] J. É. Marey, "Pression et vitesse du sang (Suite (1))'.," *Physiol. Expérimentale*, no. 2, 1876.

[24] G. Drzewiecki, R. Hood, and H. Apple, "Theory of the oscillometric maximum and the systolic and diastolic detection ratios.," *Ann. Biomed. Eng.*, vol. 22, no. 1, pp. 88–96, 1994.

[25] L. A. Geddes, M. Voelz, C. Combs, D. Reiner, and C. F. Babbs, "Characterization of the oscillometric method for measuring indirect blood pressure.," *Ann. Biomed. Eng.*, vol. 10, no. 6, pp. 271–80, Jan. 1982.

[26] M. Yelderman and A. K. Ream, “Indirect measurement of mean blood pressure in the anesthetized patient.,” *Anesthesiology*, vol. 50, no. 3, pp. 253–6, Mar. 1979.

[27] G. W. Mauck, C. R. Smith, L. A. Geddes, and J. D. Bourland, “The meaning of the point of maximum oscillations in cuff pressure in the indirect measurement of blood pressure--part ii.,” *J. Biomech. Eng.*, vol. 102, no. 1, pp. 28–33, Feb. 1980.

[28] M. Ursino and C. Cristalli, “A mathematical study of some biomechanical factors affecting the oscillometric blood pressure measurement.,” *IEEE Trans. Biomed. Eng.*, vol. 43, no. 8, pp. 761–78, Aug. 1996.

[29] R. Raamat, J. Talts, K. Jagomägi, and J. Kivastik, “Errors of oscillometric blood pressure measurement as predicted by simulation.,” *Blood Press. Monit.*, vol. 16, no. 5, pp. 238–45, Oct. 2011.

[30] R. Raamat, J. Talts, K. Jagomägi, and J. Kivastik, “Errors of oscillometric blood pressure measurement as predicted by simulation.,” *Blood Press. Monit.*, vol. 16, no. 5, pp. 238–45, Oct. 2011.

[31] A. Stang, S. Moebus, S. Möhlenkamp, N. Dragano, A. Schmermund, E.-M. Beck, J. Siegrist, R. Erbel, K.-H. Jöckel, and Heinz Nixdorf Recall Study Investigative Group, “Algorithms for converting random-zero to automated oscillometric blood pressure values, and vice versa.,” *Am. J. Epidemiol.*, vol. 164, no. 1, pp. 85–94, Jul. 2006.

[32] A. Coleman, P. Freeman, S. Steel, and A. Shennan, “Validation of the Omron MX3 Plus oscillometric blood pressure monitoring device according to the European Society of Hypertension international protocol.,” *Blood Press. Monit.*, vol. 10, no. 3, pp. 165–8, Jun. 2005.

[33] A. de Greeff, Z. Beg, Z. Gangji, E. Dorney, and A. H. Shennan, “Accuracy of inflationary versus deflationary oscillometry in pregnancy and preeclampsia: OMRON-MIT versus OMRON-M7.,” *Blood Press. Monit.*, vol. 14, no. 1, pp. 37–40, Feb. 2009.

[34] D. Longo, G. Toffanin, R. Garbelotto, V. Zaetta, L. Businaro, and P. Palatini, “Performance of the UA-787 oscillometric blood pressure monitor according to the European Society of Hypertension protocol.,” *Blood Press. Monit.*, vol. 8, no. 2, pp. 91–5, Apr. 2003.

[35] L. M. Vera-Cala, M. Orostegui, L. I. Valencia-Angel, N. López, and L. E. Bautista, “Accuracy of the Omron HEM-705 CP for blood pressure measurement in large epidemiologic studies.,” *Arq. Bras. Cardiol.*, vol. 96, no. 5, pp. 393–8, May 2011.

[36] H. A. Richter and C. Mittermayer, “Volume elasticity, modulus of elasticity and compliance of normal and arteriosclerotic human aorta.,” *Biorheology*, vol. 21, no. 5, pp. 723–34, 1984.

[37] H. A. Richter and C. Mittermayer, “Volume elasticity, modulus of elasticity and compliance of normal and arteriosclerotic human aorta.,” *Biorheology*, vol. 21, no. 5, pp.

723–34, 1984.

[38] B. S. Alpert, D. Quinn, and D. Gallick, “Oscillometric blood pressure: a review for clinicians.,” *J. Am. Soc. Hypertens.*, vol. 8, no. 12, pp. 930–8, Dec. 2014.

[39] G. A. van Montfrans, “Oscillometric blood pressure measurement: progress and problems.,” *Blood Press. Monit.*, vol. 6, no. 6, pp. 287–90, Dec. 2001.

[40] H. Smulyan and M. E. Safar, “Blood pressure measurement: retrospective and prospective views.,” *Am. J. Hypertens.*, vol. 24, no. 6, pp. 628–34, Jun. 2011.

[41] “National High Blood Pressure Education Program (NHBPEP)/National Heart, Lung, And Blood Institute (NHLBI) AND American Heart Association (AHA) Working Meeting on Blood Pressure Measurement.” [Online]. Available: https://www.nhlbi.nih.gov/files/docs/resources/heart/bpmeasu.pdf. [Accessed: 18-Jul-2015].

[42] J. Liu, H.-M. Cheng, C.-H. Chen, S.-H. Sung, J.-O. Hahn, and R. M., “Model-based oscillometric blood pressure measurement: Preliminary validation in humans.,” *Conf. Proc. IEEE Eng. Med. Biol. Soc.*, vol. 2014, pp. 1961–4, Aug. 2014.

[43] G. Drzewiecki and J. J. Pilla, “Noninvasive measurement of the human brachial artery pressure-area relation in collapse and hypertension.,” *Ann. Biomed. Eng.*, vol. 26, no. 6, pp. 965–74, Jan. 1998.

[44] M. P. McLaughlin, “Compendium of Common Probability Distributions.” [Online]. Available: http://www.causascientia.org/math_stat/Dists/Compendium.pdf. [Accessed: 23-Aug-2015].

[45] H.-M. Cheng, S.-H. Sung, Y.-T. Shih, S.-Y. Chuang, W.-C. Yu, and C.-H. Chen, “Measurement of central aortic pulse pressure: noninvasive brachial cuff-based estimation by a transfer function vs. a novel pulse wave analysis method.,” *Am. J. Hypertens.*, vol. 25, no. 11, pp. 1162–9, Nov. 2012.

[46] H.-M. Cheng, S.-H. Sung, Y.-T. Shih, S.-Y. Chuang, W.-C. Yu, and C.-H. Chen, “Measurement accuracy of a stand-alone oscillometric central blood pressure monitor: a validation report for Microlife WatchBP Office Central.,” *Am. J. Hypertens.*, vol. 26, no. 1, pp. 42–50, Jan. 2013.

[47] “Optimization Toolbox™ User’s Guide.” [Online]. Available: http://uk.mathworks.com/help/pdf_doc/optim/optim_tb.pdf. [Accessed: 19-Jul-2015].

[48] W. G. Snedecor, G. W., Cochran, “Statistical methods.” [Online]. Available: http://catalog.lib.msu.edu/record=b2300696~S39a. [Accessed: 19-Jul-2015].

[49] “American National Standard for Manual, electronic or Automated Sphygmomanometers,” *Association for the Advancement of Medical Instrumentation.*, 2003. [Online]. Available: https://fmc4me.qa-

intranet.fmcna.com/idc/idcplg?IdcService=GET_FILE&Rendition=Primary&RevisionSelectionMethod=Latest&dDocName=PDF_100032384. [Accessed: 19-Jul-2015].

[50] A. J. Bank, D. R. Kaiser, S. Rajala, and A. Cheng, "In vivo human brachial artery elastic mechanics: effects of smooth muscle relaxation.," *Circulation*, vol. 100, no. 1, pp. 41–7, Jul. 1999.

[51] A. M. Dart and B. A. Kingwell, "Pulse pressure--a review of mechanisms and clinical relevance.," *J. Am. Coll. Cardiol.*, vol. 37, no. 4, pp. 975–84, Mar. 2001.

[52] S. Lewington, R. Clarke, N. Qizilbash, R. Peto, and R. Collins, "Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies.," *Lancet*, vol. 360, no. 9349, pp. 1903–13, Dec. 2002.

[53] J. M. Askey, "The auscultatory gap in sphygmomanometry.," *Ann. Intern. Med.*, vol. 80, no. 1, pp. 94–7, Jan. 1974.

[54] "Differences in Common Clinical Blood Pressure Measurement Technologies," *Welch Allyn*. [Online]. Available: https://www.welchallyn.com/content/dam/welchallyn/documents/upload-docs/Research/Case-Study/Blood Pressure Technology White Paper.pdf. [Accessed: 19-Jul-2015].

[55] J. Liu, H.-M. Cheng, C.-H. Chen, S.-H. Sung, M. Moslehpour, J.-O. Hahn, and R. Mukkamala, "Patient-Specific Oscillometric Blood Pressure Measurement," *Press*.

[56] J. M. Askey, "The Auscultatory Gap in Sphygmomanometry," *Ann. Intern. Med.*, vol. 80, no. 1, p. 94, Jan. 1974.

[57] C. Vlachopoulos, K. Aznaouridis, M. F. O'Rourke, M. E. Safar, K. Baou, and C. Stefanadis, "Prediction of cardiovascular events and all-cause mortality with central haemodynamics: a systematic review and meta-analysis.," *Eur. Heart J.*, vol. 31, no. 15, pp. 1865–71, Aug. 2010.

[58] Y.-T. Shih, H.-M. Cheng, S.-H. Sung, W.-C. Hu, and C.-H. Chen, "Quantification of the calibration error in the transfer function-derived central aortic blood pressures.," *Am. J. Hypertens.*, vol. 24, no. 12, pp. 1312–7, Dec. 2011.

[59] H.-M. Cheng, D. Lang, C. Tufanaru, and A. Pearson, "Measurement accuracy of non-invasively obtained central blood pressure by applanation tonometry: a systematic review and meta-analysis.," *Int. J. Cardiol.*, vol. 167, no. 5, pp. 1867–76, Sep. 2013.

[60] T. G. Pickering, J. E. Hall, L. J. Appel, B. E. Falkner, J. Graves, M. N. Hill, D. W. Jones, T. Kurtz, S. G. Sheps, and E. J. Roccella, "Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Cou," *Hypertension*, vol. 45, no. 1, pp. 142–

61, Jan. 2005.

[61] E. O'Brien, R. Asmar, L. Beilin, Y. Imai, J.-M. Mallion, G. Mancia, T. Mengden, M. Myers, P. Padfield, P. Palatini, G. Parati, T. Pickering, J. Redon, J. Staessen, G. Stergiou, and P. Verdecchia, "European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement.," *J. Hypertens.*, vol. 21, no. 5, pp. 821–48, May 2003.

[62] J. Liu, J.-O. Hahn, and R. Mukkamala, "Error mechanisms of the oscillometric fixed-ratio blood pressure measurement method.," *Ann. Biomed. Eng.*, vol. 41, no. 3, pp. 587–97, Mar. 2013.

[63] J. Liu, H.-M. Cheng, C.-H. Chen, S.-H. Sung, M. Moslehpour, J.-O. Hahn, and R. Mukkamala, "Patient-Specific Oscillometric Blood Pressure Measurement.," *IEEE Trans. Biomed. Eng.*, vol. PP, no. 99, p. 1, Oct. 2015.

[64] J. Liu, H.-M. Cheng, C.-H. Chen, S.-H. Sung, J.-O. Hahn, and R. Mukkamala, "Patient-Specific Oscillometric Blood Pressure Measurement: Validation For Accuracy And Repeatability." .