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Topical Review

A survey on signals and systems in ambulatory blood pressure monitoring using pulse transit time

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Abstract
Blood pressure monitoring based on pulse transit or arrival time has been the focus of much research in order to design ambulatory blood pressure monitors. The accuracy of these monitors is limited by several challenges, such as acquisition and processing of physiological signals as well as changes in vascular tone and the pre-ejection period. In this work, a literature survey covering recent developments is presented in order to identify gaps in the literature. The findings of the literature are classified according to three aspects. These are the calibration of pulse transit/arrival times to blood pressure, acquisition and processing of physiological signals and finally, the design of fully integrated blood pressure measurement systems. Alternative technologies as well as locations for the measurement of the pulse wave signal should be investigated in order to improve the accuracy during calibration. Furthermore, the integration and validation of monitoring systems needs to be improved in current ambulatory blood pressure monitors.

Keywords: ambulatory blood pressure, pulse arrival time, pulse transit time

(Some figures may appear in colour only in the online journal)

1. Introduction
Abnormally high blood pressure (BP) or hypertension contributes to cardiovascular diseases (CVD) such as heart disease, stroke and kidney failure which lead to premature death and disability. With one in three adults worldwide having high BP and more people dying from CVDs, hypertension is recognized by the World Health Organization (WHO) as a global...
public health issue (World Health Organisation 2013). The morbid development of hypertension is made worse by the fact that affected people living in low- and middle-income countries have less access to effective health care services which respond to their needs. Not only is the national budget of countries drained by healthcare demands due to detection and treatment, but also the gross domestic product decreases as a result of premature deaths from CVDs.

One of the first ambulatory BP measurements (ABPM) was carried out 50 years ago (Hinman et al 1962, Sokolow et al 1966) Strong evidence has emerged in several long-term studies that mean BP levels as well as BP variations over 24 h or longer are more sensitive and reliable predictors of CV risks than conventional measurements in the presence of a physician (Pickering et al 2006), opening possibilities for more effective treatment of the disease. Threshold values (in mmHg) of hypertension from office and ambulatory BP measurements have been classified by Mancia et al (2013).

The standard method in ABPM is currently the cuff-based method employed at the brachial artery. This method is known to suffer from several limitations, namely its occlusiveness and the limited frequency of measurement (Sola et al 2011). The former reduces the accuracy of BP measurement, especially during sleep, while the latter may potentially negate short term mechanisms of BP regulation. Alternative ABPM approaches in literature to estimate BP without a cuff include arterial tonometry (Drzewiecki 2000), volume-clamp method (Drzewiecki 2000), pulse wave analysis (Millasseau et al 2006, Avolio et al 2010), and estimation of the mean BP from pressure-volume relationships of blood vessels (Shaltis et al 2008). Another method currently is based on Pulse Transit Time (PTT) or Pulse Arrival Time (PAT), which is related to pulse wave velocity (PWV). A pressure pulse is generated at the point of the aortic valve opening, which propagates along the entire arterial tree. PWV refers to the velocity of propagation with typical values ranging from 4–5 m s$^{-1}$ in larger, central and more elastic arteries, to 15 m s$^{-1}$ in peripheral, muscular arteries such as the femoral artery (Nichols et al 2005).

The development of a PTT-based BP monitor is a complex task involving sensor design, signal processing and understanding of physiology. We have conducted this literature review to identify gaps in the literature that could improve the accuracy of current ABPMs. The goal of this paper is to review developments in literature according to three aspects. An overview of how BP is estimated from PTT/PAT is given in section 2. The first aspect in section 3 is the acquisition and processing of physiological signals relevant to ambulatory blood pressure monitoring. The second aspect covers initial and period calibration methods to map PTT/PAT to BP values (section 4). The third aspect i.e. the state of the art of ambulatory blood pressure monitoring systems is then presented in section 5. A discussion on the state of the art is presented in section 6 before concluding the paper in section 7.

2. Overview

Figure 1 contains an overview on how BP is estimated based on the literature. We divide the overview into two approaches on estimating BP from PWV. Both require the simultaneous measurement of several physiological signals. The first approach requires only one pulse wave signal and may require the estimation of the pre-ejection period if the mean blood pressure (MBP) or diastolic blood pressure (DBP) is to be tracked. The second approach requires two pulse wave signals. If the MBP/DBP is to be estimated, the first approach requires the estimation of the pre-ejection period (PEP).

The first approach estimates the transit time between one signal carrying the arterial pulse wave (pulse wave signal) and another signal such as the Electrocardiogram (ECG) such as in
Chen et al (2000). The time interval between the ECG fiducial point (typically the R peak) and a fiducial point marking the pulse arrival is referred to in this paper as the PAT. The PAT example in figure 1(b) is the time difference between the ECG R-peak and the time foot of the pulse wave. The PTT is the time difference between the aortic valve opening and the pulse wave arrival. Both the PTT and PAT have been investigated for tracking changes in BP.

The second approach estimates the BP from the PTT between two pulse wave signals e.g. between the carotid and femoral arteries (Calabia et al 2011). The ECG is used to identify arrivals of the pulse wave following the QRS wave. In both approaches, BP values are estimated from the measured transit times using linear or nonlinear periodic calibration which takes time-varying properties of the arterial propagation path into account.

3. Acquisition and processing of physiological signals

Four commonly used signals in BP monitoring using PWV are identified and shown in figure 1(a). The first is the pulse wave signal, which contains a pressure or plethysmographic arterial wave. The second is the electrocardiogram. The third and the fourth signals are the phonocardiogram (PCG) and impedance cardiogram (ICG). A fifth signal (not shown in figure 1(b)), is the static and dynamic acceleration from 3D accelerometers. The signal measurement locations are shown in figure 2. ECG lead configurations are well known and therefore not shown.

3.1. Pulse wave signal

Arteries differ in their structural properties i.e. either elastic and central or peripheral and more muscular ones. Elastic arteries have a larger diameter compared to their peripheral counterparts, hence their thickness to diameter ratio is likely to vary less. Vascular tone of the peripheral arteries changes depending on surrounding tissue blood demand. which in turn affects the PWV. The arteries of the pulse wave measurement locations (figure 2(c)) are considered by us to contain a smaller muscular component (1, 2) or a larger one (3–7). In Sola et al (2011), location 1, being the internal thoracic artery is considered by the authors to be a good justification to measure ‘centrally’ as approximately 15% of the distance travelled by the
pulse wave is not in the aorta. Measurement at the external or internal carotid artery is considered by us to be more elastic than muscular given its proximity to the elastic common carotid artery. Although it is used in the gold standard of measuring aortic stiffness (Boutouyrie et al 2009), it has found little use in approach one, possibly because early wave reflection makes it difficult to identify arrival of the pulse wave using its foot (Boutouyrie et al 2009). The most popular measurement locations for the pulse wave are at the finger (4) and the radial artery (3), followed by the ear (6), probably because of their application to pulse oximetry and the fact that they are more suitable for ambulatory monitoring in current sensor designs. The toe (5) has also been investigated in the second approach (Nitzan et al 2005) with little statistical correlation between DBP and the PTT between the toe and the finger. Given its popularity as a measurement location, the finger has been widely studied for effects of vasomotion (Wong et al 2009) on PTT/PAT, limiting the ability of PAT to track SBP. Additionally, increasing contact force of the sensor against the finger has been shown increase the PTT, which can be in the order of BP changes (Teng and Zhang 2007). A varying contact force on the artery affects its pressure-volume characteristics, i.e. its compliance, which is a parameter in the Bramwell–Hill equation (Bramwell and Hill 1922). A study like Teng and Zhang’s has not been conducted for other pulse wave measurement locations.

Figure 2. Human body with commonly used physiological measurement locations for hypertension monitoring. Figures (a) and (b) contain the ICG lead configurations according to Sherwood (Sherwood et al 1990), copyright 1990 Wiley. Figure (c) contains pulse wave, PCG and accelerometer positions from literature, as well as integrated I–V ICG electrodes from, reprinted from Sola et al (2011) copyright 2011 IEEE.
The choice of technology to measure the pulse wave signal is another aspect in its acquisition. Table 1 gives a summary of the technologies used to detect the pulse wave. The most popular technology is optical sensing (photoplethysmography), exploiting the absorption and reflection of light photos by arterial blood. The mechanical vibration from the artery propagates along tissue and can be captured by a mechanical sensor made of piezoelectric film or electromechanical film material (Alametsa et al 2012). Blood’s electrical properties have been measurable in an appropriate arrangement of electrodes to measure bioimpedance (Cho et al 2009, Lee and Cho 2013). While bioimpedance is more likely to measure blood volume changes, a Hall sensor has been shown to correlate more strongly with blood flow instead of blood volume changes using an optical sensor (Lee et al 2014). Lee’s measurements showed that a simultaneously measured photoplethysmograph lagged behind the magnetic pulse wave signal by a few milliseconds when both signals were measured on adjacent fingers. It remains unknown as whether the delay will change under ambulatory settings. Lesser investigated technologies include temperature sensing (Cuadras and Casas 2006) and measuring the magnetic field disturbance (Lee et al 2011) near the radial artery. Regardless of measurement location (figure 2) or technology, the pulse wave signal is distorted from motion artifacts. This can occur if the sensor is displaced relative to the body, changing the coupling between the sensor and the artery under measurement. Mechanical deformation of the sensor can also change its sensory properties. The sensor design may also influence the contact force on the measurement location (Teng and Zhang 2007).

There are several challenges in the acquisition of the pulse wave signal. The most significant one is the corruption of the pulse wave signal from artifacts such as motion as well as electromagnetic interference. The estimated PAT is known to vary from the true PAT by as much as 25 ms in a subject during motion (Foo 2008). In this case, the artifact not only has to be detected, but also removed in order to detect accurate arrival of the pulse wave. The origin of motion artifact (MA) is likely to depend on the type of sensor used. One possible origin is a change in the sensor-artery coupling during motion e.g. the optical path length can change if the LED or photodetector location changes with respect to the artery under illumination. Venous blood volume changes due to external pressures or gravity can also corrupt the pulse wave signal (Hayes and Smith 2001). Motion-induced forces acting by the body/medical device on the sensor can also alter the sensor’s properties e.g. resistance of a thermistor due to changes in its cross-sectional area or length. These processes can occur simultaneously or individually depending on the technology as well as motion type (Hayes and Smith 2001). The frequency content of signals from MA typically overlaps with that of the pulse wave signal.

While different sensor locations with a smaller hypothesized venous bed are being investigated (Zhang et al 2014), most of the literature on MA removal consists of a combination of sensor design as well as signal processing. Two extensive reviews by Allen (2007) and Poon et al (2011) have listed approaches ranging from neural networks to filter banks (Lee et al 2004) to frequency analysis methods such as Fast Fourier Transform (FFT) (Rusch et al 1996) and finally, time-frequency analysis using Wavelet Transform and Smoothed Wigner–Ville Transform (Yan et al 2005). Blind source separation (BSS) algorithms such as Principal and Independent Component Analysis (PCA, ICA) have also been investigated with the use of a single or two (Yao and Warren 2005, Krishnan et al 2010) pulse wave signals. Single stage adaptive filters have been investigated heavily on sensor designs which attempt to maximize the correlation between the actual MA and the simultaneously measured reference from an LED (Hayes and Smith 2001), piezoelectric sensor (Ciaccio and Drzewiecki 2008, Buxi et al 2010) or accelerometer (Sokwoo et al 2001, Relente and Sison 2002, Foo et al 2004, Wood and Asada 2006). The solutions focus on optical sensing at the finger or the wrist.
An extensive review of the pros and cons of the approaches in literature is given in Sweeney’s work (Sweeney et al 2012). Adaptive filtering is known to be computationally cheaper compared to blind source separation methods, but requires a reference signal to be measured. While BSS methods have the advantage of not requiring prior knowledge of the signal, they are computationally expensive. Another non-trivial issue is the selection of which ICA/PCA components to discard for subsequent steps in the MA reduction process (Romero et al 2011). Despite the important contributions of approaches in literature, both Allen and Poon et al concluded that MA reduction in ambulatory measurement of pulse wave signals is still an unsolved problem, with only one other investigation that quantifies the improvement in PTT/PAT estimation accuracy after MA reduction (Foo 2008).

Algorithms in recent literature propose combinations of the ones mentioned in the previous paragraphs. Krishnan et al address the problem of ICA component selection by executing ICA in the frequency domain. The results obtained were significantly better than that of the time-domain.

Table 1. Selected sensor designs from various technologies to measurement of the pulse wave. The pros and cons listed are generic to the measurement technology unless a reference is mentioned.

<table>
<thead>
<tr>
<th>Technology</th>
<th>Location</th>
<th>Pros/Cons</th>
</tr>
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<tbody>
<tr>
<td>Mechanical (Piezo PVDF)</td>
<td>2. (Almeida et al 2011, Alametsa et al 2012) 2. (Hsu and Young 2014) 3. (McLaughlin et al 2003) 4. middle finger (Baruch et al 2011)</td>
<td>Very sensitive to motion artifacts, which may partly originate inside the limb +Less sensitive to ambient light +High fidelity signal at rest (Baruch et al 2011) +Low power consumption than optical sensing</td>
</tr>
<tr>
<td>Bio-impedance</td>
<td>3. (Cho et al 2009, Lee and Cho 2013) 3. &amp; elbow (Bang et al 2009)</td>
<td>−Electrode configuration can result in bulky system +Low power consumption possible e.g. 3.9 mW (Yan et al 2011)</td>
</tr>
<tr>
<td>Temperature (NTC thermistors)</td>
<td>3. (Cuadras and Casas 2006)</td>
<td>−Less sensitive compared to optical sensing at radial artery +Small sensor, compact system</td>
</tr>
<tr>
<td>Magnetic (Hall)</td>
<td>2. (Chandrasekhar et al 2013) and (Nabeel et al 2014) 3. (Lee et al 2011) 4. (Lee et al 2014)</td>
<td>−High power consumption (1.65 W using 3.4 V supply) prevents 24h monitoring</td>
</tr>
<tr>
<td>Ultra Wide-band</td>
<td>7. (Tao et al 2007)</td>
<td>+Greater possibility of measurement of central arteries compared to optical, mechanical sensing</td>
</tr>
</tbody>
</table>

ICA approach. Peng et al use time-domain ICA with a reference template pulse wave signal to create a reference input signal to an succeeding adaptive filter (Peng et al 2014). The advantage of Peng’s approach is the same as Krishnan’s, except that the ICA algorithm is implemented in the time domain. Yousefi’s approach involves a clever combination of multiple adaptive filter stages without any additional reference signal (Yousefi et al 2014) to adaptively remove MA.

The second challenge is the reliable quality of the pulse wave signal during exposure of the measurement site to mildly cold temperatures. This challenge is more severe in young females. An automatic gain control in the readout circuitry (Ye et al 2011) can amplify the excitation or received signal to compensate for poor signal quality, but this can also increase the amount of electric and physiological noise. Not only can the noise contribute to errors in PAT estimation, but so can vasomotion if a peripheral artery is used as a measurement site. The PAT at the finger has been experimentally determined to vary by approximately 5ms when the temperature around the finger was varied by around 5 Kelvin (Zhang and Zhang 2006). These variations can appear minutes after the actual temperature change. In order to overcome perfusion problems, Wiener filtering has been employed to enhance the optically measured pulse wave signal (Foo and Wilson 2006), however, the effect on PAT/PTT was not measured. Another interesting approach has been to enclose the optical sensor within a temperature controlled chamber, when measuring the pulse wave at the finger (Foo 2007).

The third challenge in PAT estimation is using the right feature from the pulse wave while introducing as little error as possible. Wave reflections are present in the pulse wave measurement and can cause the PAT/PTT to be wrongly estimated if low frequency fiducial points in the pulse wave such as the maximum peak of the pulse wave signal are used (Westerhof et al 2010). Pulse waves are damped at higher frequencies. Hence, ‘sharp’ or high frequency features such as the foot of a pulse wave (figure 1(b)) are recommended. However, the wave reflection may not always be negligible at the foot. Moreover artifacts due to motion or system noise may corrupt the fiducial point. In previous investigations on PTT/PAT-BP calibration (section 4), these factors are likely contributors to scatter in PTT/PAT-BP relationships. The first algorithms in literature use the maximum of the pulse wave as well as the maximum of its first and second derivatives (Teng and Zhang 2003, Ning et al 2005). To detect the foot, the intersection between the tangents from systolic upstroke and horizontal towards the pulse wave minimum point (figure 1(b)) (Chiu et al 1991) is used. In a systematic comparison on pulse wave signals from the MIMIC database, the maximum of the first derivative shows the best agreement with a parametric estimation of the pulse wave arrival using a hyperbolic tangent function proposed by Sola et al (2009). However, the tanh function is 50% more accurate in estimating the PAT as compared to the maximum derivative method, if there is no ensemble averaging of the pulse wave signal. The parametric estimation in Sola et al (2009) is regarded by Kim et al (2012) as computationally expensive, hence a linear coordinate transformation is proposed. Table 2 summarizes the different approaches found in literature in detecting the arrival of the pulse wave. In another interesting parametric approach, a linear time invariant system is modelled using the differentiated ICG as input and pulse signal as output. The PTT is identified as the characteristic time delay of the system’s impulse response. Compared to the foot-to-foot technique used with the ECG R-peak, Xu’s method improves DBP estimation from PTT from 7.2 ± 1.8 mmHg to 4.3 ± 1.3 mmHg.

3.2. Electrocardiogram

Representing the electrical activity of the heart, the electrocardiogram (ECG) is primarily used in the computation of PAT or PTT if one pulse wave signal is measured e.g.
Chen et al (2000), Muehlsteff et al (2006) and Wong et al (2011). Although the QRS onset represents the start of ventricular depolarization, the R peak is easier to detect, especially during exercise such as running on a treadmill and biking on an exercise bike (Romero et al 2009). Using the R-peak discounts variations of the QR interval, which have been shown to decrease by up to 3 ms during exercise on a bicycle (van Lien et al 2013). Given the problem of motion artifact in physiological recordings, the R-peak is still a very popular fiducial point to segment and pre-process other signals for pulse wave arrival detection (Sola et al 2009) or PEP estimation using the PCG (Zhang et al 2008, Tang et al 2010) or ICG, where the PEP end point is estimated after noise-reducing ensemble averaging (Sola et al 2011) or time-domain processing of the ICG signal (Naidu et al 2011). One unaddressed problem in PAT/PTT estimation is the presence of ectopic beats in the ECG. Ectopic or ‘extra’ beats occur in both cardiac patients and healthy people when fibers outside the heart’s sinoatrial node stimulate a cardiac contraction. The result is usually a change in the shape or timing of the P-wave (atrial ectopic) or the QRS-wave (ventricular ectopic), the latter having the tendency to become very distorted. The frequent presence of an ectopic beat can disrupt accurate PAT measurement. Apart from ignoring ectopic beats (Pitson and Stradling 1998, Bilo et al 2014), no other literature has been found on accurately estimating PAT in the presence of an ectopic beat. A separate application of the ECG is heart rate variability measurement, which has been observed to reduce less from daytime to nighttime in patients who died from existing CV conditions (Angeli et al 2014).

There are several low-power system on chip designs in literature (Baig et al 2013) which detect the R-peak while consuming several microwatts of power (Khayatzadeh et al 2012). A very notable system reduces motion artifact in the ECG using adaptive filtering with a simultaneously measured skin-electrode impedance before A/D conversion, increasing the dynamic range of the ECG amplifier during extreme motion (Van Helleputte et al 2012).

### Table 2. Approaches for PAT computation using the pulse wave signal.

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parametric estimation</td>
<td>1. Calculate time delay between template wave and plethysmograph using least squares solution (Sola et al 2009).</td>
</tr>
<tr>
<td></td>
<td>2. Calculate time delay in cross correlation of forward and backward pressure wave, where pressure wave is decomposed using a triangular wave simulating blood flow (Qasem and Avolio 2008).</td>
</tr>
<tr>
<td></td>
<td>3. Parametric modelling of an LTI system using ICG as input and pulse signal and output, where PTT is characteristic time delay of impulse response (Xu et al 2011).</td>
</tr>
<tr>
<td>Coordinate transformation</td>
<td>1. Empirical Mode Decomposition and Hilbert Transform (Choi et al 2012) to detect wave fiducial point.</td>
</tr>
<tr>
<td></td>
<td>2. Wavelet transform using Debauchy DB6 (Sahoo et al 2001) quadratic spline wavelet (Fung et al 2004), discrete wavelet transform (Lee and Zhang 2003) to detect wave fiducial point.</td>
</tr>
<tr>
<td></td>
<td>3. Three linear transformations from continuous to sampling space, then into another euclidean space, then to 1D linear space representing PAT (Kim et al 2012).</td>
</tr>
<tr>
<td>Time domain processing</td>
<td>1. Detection of point intersected by a line tangent to the initial systolic upstroke of the pulse wave and a horizontal line through the minimum point (Chiu et al 1991).</td>
</tr>
<tr>
<td></td>
<td>2. Calculation of derivatives to detect foot of pulse signal (Ning et al 2005)</td>
</tr>
</tbody>
</table>
3.3. Phonocardiogram

Heart sounds are recorded in the Phonocardiogram (PCG) at the thorax surface (figure 2). In BP monitoring literature, the heart sounds S1 and S2 are of greatest importance. S1 occurs at the onset of ventricular systole. The reported duration and bandwidth of the S1 sound varies in literature. Abbas and Rasha mention typical duration and bandwidth values as being 100–200 ms and 10–200 hz (Abbas and Bassam 2009). Guyton states that the S1 sound is around 140 ms in duration and 3–500 hz in bandwidth (Guyton and Hall 2006) and includes the closure of the atrioventricular valves and the opening of the aortic and pulmonary valves. S2 demarcates the closure of the latter two valves at the end of systole and associated vibrations in their surroundings. The sounds have been measured at the second intercostal space along the right sternal border (Ahlstrom et al 2005) and the lower left sternal border (Abbas and Bassam 2009, Carvalho et al 2009) (demarcated by sites a and b respectively in figure 2(c)).

One application of S1 is to compute the PEP (figure 3(c)). The PAT is taken to be the sum of the PEP and the PTT from the aortic valve to the pulse wave measurement location. The PCG has been successfully used with the ECG in supine subjects to estimate the PEP in supine hemodialysis patients (Ahlstrom et al 2005), normotensives in supine position (Carvalho et al 2010), healthy subjects as well as subjects suffering from different CVDs in supine position (Paiva et al 2012) and finally in ambulatory BP monitoring (Sola et al 2011). In a second application, the time between the ECG R-peak and the maximum positive peak of S2 (RS2) was also used to directly estimate BP (Wong et al 2006) at rest in 66 normotensive and 18 hypertensive patients. Despite the results being acceptable under existing standards for a clinically accurate BP measurement device, the approach cooled down in literature. A model was subsequently developed to analyze the relationship between aortic SBP, DBP and RS2 in normotensives during and after exercise (Zhang et al 2008). A strong correlation was found between RS2 and BP values during changing peripheral resistance, heart rate and contractility of the heart.

Accurate PCG measurement has two components—transducer design to acquire the raw PCG and signal processing algorithms to segment and identify aortic valve opening within the PCG. Transducers come in two types, minimal mechanical loading of the measurement location and acoustic impedance matching (Semmlow and Rahalkar 2007). Impedance matching appears to be a popular transducer type with piezoelectric material being used due to their self-generating property and large sensitivity to mechanical strain. Piezoelectric material has been embedded onto rubber structures (Toda and Thompson 2006, Kuan-Wei et al 2012), or as a membrane in a silicone-filled chamber (Scanlon 1998) in order to match the acoustic impedance of tissue. A MEMs based cantilever accelerometer has been designed with dimensions of 35 mm × 18 mm × 7.8 mm and 5 g weight (Hu and Xu 2012). A notable ambulatory commercial sensor combines an acoustic sensor and an ECG electrode placed at V3 and V4 positions (Inovise.com 2013). The sensor has been successfully validated in a sleep study to measure the circadian rhythm in systolic durations (Dillier et al 2011). The main challenges under ambulatory conditions include automated S1 detection that is robust to sensor location, motion artifacts as well as ambient noise such as the human voice or lung sounds when placed at the chest (Schmidt et al 2012) or friction between the sensor and the skin. Large amounts of body fat can also attenuate the PCG. Kraman et al describe a setup for characterizing biomedical acoustic sensors, especially for ambient noise (Kraman et al 2006).

In signal processing, methods of detecting opening of the aortic valve opening include either peak detection in the frequency domain (Debbal and Bereksi-Reguig 2008), time domain (Ahlstrom et al 2005), Bayesian estimation using Gaussian models (Paiva et al 2012) or Principal Component Analysis using an array of sensors (De Panfilis et al 2013). While the aortic valve
opening truly reflects the end of the PEP, the AV valve closure has been reported to be easier to locate in the PCG as compared to the valve opening (Ahlstrom et al. 2005, Paiva et al. 2012). This challenge has been observed in both healthy subjects as well as subjects with various CV diseases in supine position. Ensemble averaging of as little as five cardiac cycles has been applied to successfully reduce noise assuming an additive model (Tang et al. 2010). Linear and nonlinear time-scaling was also carried out to compensate for signal length variations due to heart rate variability.

### 3.4. Impedance cardiogram

The Impedance Cardiogram (ICG) (figure 3(c)) is the first derivative of the thorax bioimpedance and can be measured in several lead configurations (figures 2(a)–(c)). As mentioned in section 3.1, the differentiated ICG signal has been used together with a pulse wave signal to estimate PTT using an LTI system (Xu et al. 2011). However, the most popular application of ICG is to estimate the PEP, which is then subtracted from the PAT in approach 1 (section 2). The actual PEP is the time interval between the onset of the ECG Q-wave and the ICG B-point, which represents the aortic valve opening. The precise identification of the B-point is an important but very difficult task because characteristic signal features around it are often indistinct or not present e.g. the start of the upstroke to the right of the B-point (Lozano et al. 2007). One likely reason is that the aorta and its blood volume contributes to about 1% to the total thorax impedance (Patterson 2010).
Algorithms for B-point detection found in literature range from a priori estimation in the time domain using the ECG R-peak (Cybulski 2011) or ensemble averaging with derivative calculation (Carvalho et al 2011, Sola et al 2011). The use of the interval between the ECG R-peak and the peak of the ICG has been proposed as an estimate of the PEP (Lozano et al 2007), however, it has been suggested that the variation between the estimated and actual PEP is significant during ambulatory conditions (van Lien et al 2013), meaning that a regression equation may not be sufficient. The lower part of the thorax accounts for very little of the total ICG signal in supine and standing positions (Patterson 2010), meaning that one half of the current injecting and voltage measurement electrode pairs might need to be placed close to the suprasternal notch. The electrode configurations (figures 2(b) and (c) (Cybulski 2011)) fulfill this requirement but these configurations may increase the obtrusion into the patient’s daily routine as compared to PCG measurement. Interestingly, the electrode configuration in figure 2(c) produces an ICG signal shown in figure 3(c), which has been used to estimate the PEP together with a simultaneously measured PCG (Sola et al 2011). The PCG sensor was dropped in a later prototype (Sola et al 2013).

Front ends typically consist of a current generator running at a frequency between 20 and 150 kHz and a constant amplitude of 0.5–5 mA (Cybulski 2011) and a lock-in amplifier to amplify and demodulate the AC signal. Panfili et al propose a system (Panfili et al 2006) containing a sine wave current source running at 32 kHz with 20 µA amplitude. The system consumes 2.26 mW at 3.3 V supply. Many commercial systems can be found in Cybulki’s review (Cybulski 2011). In addition, several systems measuring the thorax bioimpedance are found. Lee et al report a system measuring 4.8 cm by 3 cm by 2 cm, consuming 7.5 mW for sensing and 6.9 mW for controlling, streaming and storing so that it can be continuously used for over 30h on a 150 mAh Li-polymer battery (Lee et al 2013). A square wave current at 10 kHz provides 0.2Ω measurement resolution. Vuorela et al describe another wearable system of dimensions 51 by 83 by 15 mm and 48 g weight (Vuorela et al 2010). The system measures ECG and ICG at 130 kHz using textile electrodes as well as accelerometer data. A system on chip design is reported by Yan et al capable of measuring ECG and thorax bioimpedance at 90 kHz using a peak to peak current amplitude of 350 µA and an impedance resolution of 0.1Ω (Yan et al 2011).

3.5. 3D accelerometers

Accelerometers can be used to measure incline (DC component) as well as acceleration (AC component) of an object. In the monitoring of hypertension, accelerometers have been used for several applications. The first is to remove MA from the pulse wave signal e.g. optical sensor worn at the finger (location iv) (Wood and Asada 2007) or on the chest (location i) or back when measured with ECG signals (Raya and Sison 2002). The success seen by these approaches is dependent on the type of motion as well as the location of the accelerometer. Secondly, accelerometers have shown promise in accounting for hydrostatic BP changes due to postural changes (Jeong et al 2005, Muehlsteff et al 2006) or height differences between the heart and pulse wave measurement at the finger (Liu et al 2009). Shaltis et al measure the incline from accelerometers at the elbow and wrist (locations ii and iii) and use trigonometry to measure the height difference between the wrist and the heart (Shaltis et al 2006) or between two pulse wave measurement points (McCombie et al 2008). A tri-axial accelerometer has also been placed at the waist where the DC output is used to classify the posture between standing, sitting and lying positions (Mathie et al 2011).
4. Calibration of PAT/PTT to BP

A substantial amount of research has focused on understanding how PTT and PAT can be accurately calibrated to BP. Initial and intermittent calibration of PAT/PTT to BP values is necessary in order to track BP values continuously. A typical calibration setup involves an additional BP monitor as a reference in the initial calibration. Intermittent calibrations are needed to account for changes in the cardiovascular system, especially if the peripheral arteries are used.

The initial works by Hughes et al. (1979), Geddes et al. (1981) and Obrist et al. (1979) measured the pulse wave at the aorta, or the carotid-femoral arteries. A major assumption was that the parameters in the Moens–Korteweg equation (1)—blood density $\rho$, arterial elasticity $E_{\text{inc}}$, radius $r$ and thickness $h$—are constant throughout the arterial section travelled by the pulse wave.

$$c_o = \sqrt{\frac{E_{\text{inc}} h}{2\rho r}}$$  \hspace{1cm} (1)

A commonly used relation between BP and aortic Elastic module in anaesthesized dogs has been empirically determined by Hughes et al. (1979) as:

$$E_{\text{inc}} = E_o e^{P_{\text{MBP}}}$$  \hspace{1cm} (2)

where $P_{\text{MBP}}$ is the mean blood pressure (MBP). An important consideration is the tethering of the vessel to surrounding tissue, which can cause the measured PAT/PTT/PWV to give an inaccurate measure of the vessel’s BP-dependent elasticity (Hodis and Zamir 2011).

Table 3 gives an overview of key investigations in calibrating PAT/PTT/PWV to BP. Most calibration methods in approach one have measured the pulse wave signal at the finger while using the R-peak of the ECG as a fiducial point. Several calibration methods have been proposed so far, which include linear regressions between logarithmic and squared PAT and BP values (Poon and Zhang 2005), with a correction for heart rate (Cattivelli and Garudadri 2009) or the relative amplitudes of the main and secondary peaks in the pulse wave signal (Gu et al. 2008). Linear regression has also been used to map PTT values to MBP (Sola et al. 2013). Hydrostatic-induced changes have been used to calibrate PTT to MBP (McCombie et al. 2007) as well as PAT to SBP and DBP (Poon et al. 2006). By varying the pressure on an external cuff-based BP monitor, arterial properties have also been modeled using variations between PTT and externally controlled cuff pressure (Yan and Zhang 2006). Chen et al use the weighted sum of bandpass-filtered PAT values from previous estimations to estimate SBP (Chen et al. 2000). The bandwidth was chosen such that the linear regression between PAT and BP showed the lowest error. Recalibration was done every 5 min using the reference (invasive) BP values in order to account for changes in elasticity of the arterial wall. Finally, an empirically determined nonlinear function calibrating PWV and SBP has also been investigated (Gesche et al. 2012).

In the second approach using two pulse wave signals, the observed PWV is calibrated to DBP using an ordinary differential equation. The basis of the differential equation is the wave equation (Chen et al. 2009). In a comparison between several wave features, the SBP has been calibrated to the time difference between characteristic points on the ear and toe pulse wave signal (Chen et al. 2012). These characteristic points are the intersecting tangents between the maximum of the pulse wave signal and a point corresponding to 60% of the maximum gradient of the pulse wave signal, where 60% was the optimal value determined from the study group of 26 subjects. Finally, hydrostatic pressure changes in the MBP are calibrated to
### Table 3. Selected strategies to calibrate PAT/PTT to BP.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>What is calibrated</th>
<th>Ref BP location</th>
<th>Frequency of calibration</th>
<th>Subjects</th>
<th>Mean ± STD w.r.t. ref [mmHg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach 1</td>
<td>Weighted sum of filtered BP values from PAT &amp; reference BP (Chen et al 2000)</td>
<td>SBP</td>
<td>Invasive finger</td>
<td>5 min</td>
<td>$N = 20$ (age 4–77)</td>
</tr>
<tr>
<td></td>
<td>Weighted sum of log &amp; squared PAT with reference BP (Poon and Zhang 2005)</td>
<td>DBP, SBP</td>
<td>asc. &amp; osc. at brachial art.</td>
<td>once per session</td>
<td>$N = 78$</td>
</tr>
<tr>
<td></td>
<td>Height-induced hydrostatic BP changes (Poon et al 2006)</td>
<td>SBP</td>
<td>asc. &amp; osc. at brachial art.</td>
<td>not investigated</td>
<td>$N = 11$</td>
</tr>
<tr>
<td></td>
<td>Linear regression of ABP, PAT &amp; HR over a few seconds (Cattivelli and Garudadri 2009)</td>
<td>DBP, SBP</td>
<td>Invasive finger</td>
<td>1 h</td>
<td>$N = 25$ (MIMIC database)</td>
</tr>
<tr>
<td></td>
<td>Amplitudes of peaks in pulse wave used in PAT-BP coefficients (Gu et al 2008)</td>
<td>SBP</td>
<td>osc. at brachial art.</td>
<td>Not investigated</td>
<td>$N = 12$</td>
</tr>
<tr>
<td></td>
<td>Empirical nonlinear function fitted to BP-PWV observations (Gösele et al 2012)</td>
<td>SBP</td>
<td>asc. at brachial art.</td>
<td>Once per session</td>
<td>$N = 50$</td>
</tr>
<tr>
<td></td>
<td>Linear Regression function fitted to BP-PTT observations (Sola et al 2013)</td>
<td>MBP</td>
<td>osc. at brachial art.</td>
<td>Once per session on different days</td>
<td>$N = 15$</td>
</tr>
<tr>
<td>Approach 2</td>
<td>Diff. equation from wave equation (Chen et al 2009)</td>
<td>DBP</td>
<td>Invasive ear, toe</td>
<td>5 min</td>
<td>$N = 23$ (age 19–60)</td>
</tr>
<tr>
<td></td>
<td>Time-based features of two pulse wave signals (Chen et al 2012)</td>
<td>DBP, SBP</td>
<td>Invasive ear, toe</td>
<td>not investigated</td>
<td>$N = 26$ (age 19–60)</td>
</tr>
<tr>
<td></td>
<td>Height-induced hydrostatic BP changes (McCombie et al 2008)</td>
<td>MBP</td>
<td>Osc. radial, brachial arteries</td>
<td>radial art., finger</td>
<td>1 h</td>
</tr>
</tbody>
</table>

*art., artery; asc., auscultatory; diff., differential; osc., oscillometric; ref., reference; w.r.t., with respect to.*
changes in PTT using the radial artery and the finger as measurement locations (McCombie et al. 2008).

In a typical algorithm where the logarithm of the PAT is linearly proportional to SBP, Poon et al. found that recalibration after a minimum of 60 beats from the finger was already insufficient to achieve an accuracy acceptable by the AAMI SP10 limits (8 mmHg standard deviation) (Poon et al. 2008). Most of the calibration routines summarized in table 3 use the finger, ear or toe as pulse wave measurement locations. The only calibration routine that does not need to account for changing vascular tone, is reported in Sola et al. (2013). The pulse wave signal is measured on the internal thoracic artery, which according to the authors, is very close to the central arteries. Recalibration on different days required only an offset correction from subject-specific calibration data from a regression analysis from the first day.

While the results from initial investigations have been positive, the calibrated relationship between BP and PWV/PTT/PAT has limitations due to factors such as vasomotion (Payne et al. 2006, Zhang and Zhang 2006, Wong et al. 2009), pre-ejection period (Foo and Chu Sing Lim 2006), which can be affected by exercise (Muehlsteff et al. 2006), changes in posture at nearly constant BP levels e.g. 40 ms from sitting to lying (Muehlsteff et al. 2008) or by 10–20% when changing posture from sitting to standing (Parry and McFetridge-Durdle 2006) or by about 12–35% when administering vasoactive drugs (Ahlstrom et al. 2005, Payne et al. 2006). The combination of PEP and PTT at the finger has been found to be most suitable for tracking systolic blood pressure (SBP), but the effects of various vascular states still need to be studied (Wong et al. 2011). The accuracy of PAT to track SBP is found to be worse at higher SBP values during exercise (Poon and Zhang 2005, Muehlsteff et al. 2006). Conversely, the accuracy is found to be better during sleep (Bilo et al. 2014, Zheng et al. 2014), likely due to less vasomotion. The Somnotouch device in Bilo et al. (2014) (table 4), which measures the pulse wave signal at the finger, passed the European Society of Hypertension's accuracy requirements. Currently, most of the results presented in an review of BP-PAT/PTT/PWV relationships (Hennig and Patzak 2013) are likely to result in a Grade C/D according to the BHS standards (O’Brien et al. 1993) i.e. their clinical use is not recommended.

5. BP monitoring systems

In the previous sections, calibration methods of PAT/PTT to BP as well as acquisition and processing methods of physiological signals were described. This section describes integrated systems from literature containing signals, processing and calibration methods. It is known that the integration of these systems is a very complex task, requiring attention to the design of individual sensors, their networking. The embodiment of these devices e.g. patch or t-shirt or watch is a critical detail as it can influence the position, size and shape of the sensor and processing units. Multiple signal acquisition from several locations requires networking between the sensors. A wireless body sensor network (BSN) or intra body communication are alternatives to wires. Their properties are discussed in greater detail in Teng et al. (2008).

One of the earliest examples of system integration is a t-shirt with ECG electrodes at the wrists is designed by Zhang et al. (2006). Textile ECG electrodes are placed on the wrists to maintain the required contacting force between the electrodes and skin without inducing a sense of unease on the subject. The placement also reduces motion artifacts in the ECG induced by breathing. A hydrostatic calibration method is proposed instead of an oscillometric method. In an evaluation study of the system, mean differences of 11.29 mmHg (SBP) and 7.15 mmHg (DBP) with respect to a volume-clamp BP monitor are reported (Chan and Zhang 2008). Another example of a vest is by Pandian et al. (2008) with an architecture similar to
that by Zhang et al except that processing is done on a remote base station instead of in a wrist watch. The integration of wires into the T-shirt means that no wireless network is used. Guo et al report a chest belt containing dry micromachined ECG electrodes and a pulse oximeter sensor worn at the earlobe (Guo et al 2008). A Zigbee unit connects the system to a PDA phone, where the PTT-based BP is estimated and displayed. Its accuracy after calibration was not reported. Yoon et al have described a wired system which reports moderate correlations with an oscillometric device (Yoon et al 2008).

Other systems focus on the implementation of a body sensor network (BSN) e.g. Weder et al (2011), comprising of a finger PPG and chest ECG readout linked together in a body sensor network. Using a beacon mode in the IEEE 802.15.4 standard allows a wireless time synchronization of ± 1 ms between the ECG and PPG sensor. A similar system with the IEEE 802.15.4 standard is reported in Espina et al (2006) with a 100 µs synchronization error. Another prototype by Lee et al uses intra body communication instead of using a BSN (Lee and Cho 2013). Integrated circuits measuring the ECG on the chest and the pulse wave using bioimpedance are reported. A noise-shaped body-channel communication method using analog frequency modulation at 5–10 MHz is proposed to transmit the pulse wave to the ECG sensor mote.

Other notable examples include a wrist watch designed by Xu et al (2008) does not allow continuous monitoring as both ECG electrodes are on a single wrist watch. Finally, a complete system based on Zhang et al (2006) is validated on ten subject over 24 h in Zheng et al (2014). Finally, the system that comes closest to overcoming the problem of changing vascular tone is reported in Sola et al (2011, 2013). Under controlled conditions, it is shown that calibration with an oscillometric device may only be necessary on the first day that the system is worn by an individual.

Table 4 contains a list of systems reported in the literature. No integrated systems were found from approach 2, although plenty of literature was found on estimating BP from PTT. We have managed to find two commercial systems during in our literature search.

There are a few commercial available ambulatory BP monitors. Together with a simultaneously measured ECG, the Novacor device uses the ascutulatory method to measure the PAT at the brachial artery (O’Brien et al 1991). The Arteriograph looks at the timing of the reflected component of the pulse wave signal at the brachial artery (Rajzer et al 2008). These devices have the end goal of estimating PWV instead of BP and should be hence be mentioned in this review. Probably the most mature prototype of PAT/PTT-based BP measurement is the Somnotouch by Somnomedics Gmbh. of Germany (Bilo et al 2014). This device has undergone a clinical trial for its suitability to tracking BP during sleep, achieving a pass according to the European Society of Hypertension criterion for both SBP and DBP estimation. The system is similar in architecture to the research prototypes in table 4, in the sense that it measures traditional lead ECG and an optical pulse wave signal at the wrist. Visi Mobile by Sotera Wireless Inc (USA) is slightly different from the Somnotouch (Zhang et al 2014) in the sense that the pulse wave signal is measured at the base of the thumb with the hypothesis that there will be less motion artifact due to the a smaller venous bloodstream. This is currently under investigation. Although Samsung refrains from calling its latest prototype, the Simband a commercial product, this wearable device deserves mention for its ability to measure PAT with an external proprietary ECG device (Samsung 2014).

6. Discussion

The plethora of work done so far is an important foundation to continue on the path to a truly cuffless BP monitor. In this section, existing research problems in the literature are discussed.
Table 4. List of systems estimating BP from PAT/PTT in literature, where all systems belong to approach 1.

<table>
<thead>
<tr>
<th>System architecture</th>
<th>Acquired signals (meas. location)</th>
<th>Initial calibration</th>
<th>Recalibration method</th>
<th>Processing done in</th>
<th>Accuracy $N =$ no. of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-shirt with wrist watch (Zhang et al 2006)</td>
<td>ECG (wrists) optical (finger)</td>
<td>Nonlinear PAT-BP (Poon and Zhang 2005)</td>
<td>Hydrostatic changes from arm elevation (Poon et al 2006)</td>
<td>Wrist watch</td>
<td>SBP $5.3 \pm 10.1 \text{ mmHg}$ DBP $2.0 \pm 8.4 \text{ mmHg}$ ($N = 10$)</td>
</tr>
<tr>
<td>Vest with wireless unit (Pandian et al 2008)</td>
<td>ECG(chest) optical(finger/ear)</td>
<td>Nonlinear PAT-BP</td>
<td>Not investigated</td>
<td>Remote PC</td>
<td>SBP $0.5 \pm 8 \text{ mmHg}$ DBP $0.6 \pm 6 \text{ mmHg}$ ($N = 10$)</td>
</tr>
<tr>
<td>Chest belt using BSN (Guo et al 2008)</td>
<td>ECG(chest) optical(ear)</td>
<td>(Fung et al 2004)</td>
<td>Not investigated</td>
<td>PDA Phone</td>
<td>Not investigated</td>
</tr>
<tr>
<td>Wrist, finger (Yoon et al 2008)</td>
<td>ECG (wrists) optical (finger)</td>
<td>Linear Regression</td>
<td>PAT w.r.t. osc. BP device</td>
<td>PC</td>
<td>Corr. coeff. ($N = 5$) SBP $(R = 0.71)$ DBP $(R = 0.76)$</td>
</tr>
<tr>
<td>Chest strap &amp; PPG sensor in BSN (Weder et al 2011)</td>
<td>ECG (chest) optical (finger)</td>
<td>Not investigated</td>
<td>Not investigated</td>
<td>Only PAT was investigated</td>
<td></td>
</tr>
<tr>
<td>2 ICs with intrabody communication (Lee and Cho 2013)</td>
<td>ECG (chest) Bioimpedance (wrist)</td>
<td>Not investigated</td>
<td>Not investigated</td>
<td>Not investigated</td>
<td></td>
</tr>
<tr>
<td>Wrist straps (Zheng et al 2014)</td>
<td>ECG(wrists) optical(finger/ear)</td>
<td>Nonlinear PAT-BP (Poon and Zhang 2005)</td>
<td>Smoothed PTT every $\sim 12$ h</td>
<td>PC (Matlab)</td>
<td>SBP $2.4 \pm 5.7 \text{ mmHg}$ ($N = 10$)</td>
</tr>
<tr>
<td>Chest belt (Sola et al 2013)</td>
<td>ECG, optical ICG (all chest)</td>
<td>PTT-MAP with linear regression</td>
<td>Not stated</td>
<td>MAP</td>
<td>$0.7 \pm 5.1 \text{ mmHg}$ ($N = 15$)</td>
</tr>
<tr>
<td>Chest patch (Puke et al 2013)</td>
<td>ECG (chest) optical (chest)</td>
<td>PAT-SBP with linear regression</td>
<td>Not stated</td>
<td>Not stated</td>
<td>SBP $6.91 \pm 4.23 \text{ mmHg}$ ($N = 4$)</td>
</tr>
<tr>
<td>Bandage vest (Xu et al 2014)</td>
<td>ECG (chest) optical (finger) Bioimpedance (chest)</td>
<td>Not stated</td>
<td>hydrostatic method</td>
<td>ARM Cortex-M4 32 bit MCU</td>
<td>Not stated</td>
</tr>
<tr>
<td>Somnotouch (Bilo et al 2014)</td>
<td>ECG (chest) optical (finger)</td>
<td>Non-linear PTT-PWV-BP mapping (Gesche et al 2012)</td>
<td>One-time</td>
<td>Not stated</td>
<td>SBP $0.45 \pm 6.1 \text{ mmHg}$ DBP $0.3 \pm 3.4 \text{ mmHg}$ ($N = 33$) Under investigation</td>
</tr>
<tr>
<td>Visi Mobile (Zhang et al 2014)</td>
<td>ECG (chest) optical (thumb)</td>
<td>PAT-MAP with Linear regression</td>
<td>Not investigated</td>
<td>PC</td>
<td>Under investigation</td>
</tr>
</tbody>
</table>

Note: System architecture in bold indicates a commercial device.
BP estimation using PTT/PAT involves the acquisition of multiple signals. Since it is shown that the foot-to-foot algorithm can show less reliable results without ensemble averaging (Sola et al. 2009), the algorithms proposed in later works (Sola et al. 2009, Xu et al. 2011) show promise in improving PAT accuracy. The development of real-time, embedded versions of these algorithms will be significant contributions to the integration of BP monitoring systems. Motion artifact is also an unsolved problem, especially in pulse wave measurement despite significant research effort. Future systems could detect and discard measurements containing motion artifact or ectopic beats.

Where pulse wave measurement locations are concerned, most investigations focus on the finger or radial artery or at the earlobe. Especially in females or people of small build, poor perfusion at these measurement locations or sudden vasoconstriction due to cold and emotional stimuli (Raynaud’s phenomenon) can prevent reliable pulse wave acquisition. This problem is also valid for non-invasive blood pressure measurements with peripherally placed cuffs (e.g., Finapres). Central, elastic arteries have only recently become the focus of this research, likely because the pulse wave arrival is difficult to detect using existing technologies. The aortic pulse wave is too deep within the thorax to be detected using mechanical, optical and temperature sensing. The carotid pulse wave is difficult to detect without applying pressure at the neck, making long term monitoring difficult. RF radar technologies in the form of Continuous Wave Doppler (Aardal et al. 2013) and Ultra Wideband (Tao et al. 2007) have already been proven to extract heart movements or brachial arterial pulsations respectively. Bioimpedance for pulse wave detection has been explored only at the radial artery and elbow. Given the encouraging PTT-BP accuracy when measuring at the internal thoracic artery (Sola et al. 2013), the aforementioned technologies should be investigated to measure the pulse wave close to or from the central arteries.

Regardless of the pulse wave measurement location, the contact force of the sensor at locations other than the finger (Teng and Zhang 2007) should be taken into account in designing and evaluating the sensor’s performance in accurately estimating PTT. The measurement of heart sounds in ambulatory conditions is a very challenging topic. In supine subjects, the estimated PEP from a commercial PCG sensor and ICG using several algorithms from literature were compared to the echocardiography gold standard (Carvalho et al. 2010). The mean estimated errors by the PCG and ICG were 0.7 ms and 5.8 ms respectively. We surmise that despite its accuracy, ambulatory PCG measurement is not used in any of the systems (table 4) because of issues with ambient noise, motion artifacts and friction between the sensor and the skin. Even though the ICG lead configuration results in a more bulky system (figures 2(a) and (b)) with accuracy challenges in B-point detection, it is still preferred to a PCG sensor. Hence, the development of PCG sensors which are resistant to the described problems may result in more accurate and compact systems. The application of ICG to model PTT in Xu’s work (Xu et al. 2011) should be investigated for conditions other than hypovolemia as well as for measurement locations other than the finger. As an alternative to ICG, Xu’s approach could also be tried with PCG sensors. Finally, even though posture was shown to affect PEP and therefore PAT (Jeong et al. 2005, Muehlsteff et al. 2008), real-time integration of posture has not yet become a standard part of PAT/PTT-BP calibration. The chest, neck and ear are likely to be better than the finger in terms of accounting for posture.

The major limitation on accurate intermittent calibration using a peripheral artery such as the finger is the changing vascular tone as well as the PEP. Tracking BP may be nearly impossible if recalibration is needed as often as 15 beats (Poon et al. 2008) in order to achieve acceptable clinical accuracy. However, several investigations which discovered this limitation measured the pulse wave at the finger. Although the works by Sola et al. (2011, 2013) indicate that measuring the pulse wave at a conduit artery close to the aorta may overcome this
limitation, only MBP estimation is investigated. These findings suggest strongly that accurate and less frequent recalibration can be achieved by detecting the pulse wave at locations at or closer to the elastic arteries such as the carotid artery or the aorta itself.

Given the stronger correlations of PAT with SBP in the investigations such as Payne et al. (2006), Poon and Zhang (2005) and Muehlsteff et al. (2006), the estimation of SBP still requires the inclusion of the PEP. If the PEP is used to track SBP changes, posture measurement should be accounted for in real-time PEP changes. It may be possible, however, that PTT/PAT is only accurate to track MBP according to clinical standards. If more efforts are devoted to measuring the PTT/PAT at elastic instead of peripheral arteries. Finally, regardless of the pulse arrival algorithm used, ensemble averaging over at least 2 beats is known to improve accurate estimation of PTT (Sola et al. 2009). At the same time, using a small number of beats before recalibration improves the accuracy of BP estimation (Poon et al. 2008). This result was obtained without any ensemble averaging. Intuitively, the combination of both techniques may give more insight into the optimal recalibration period.

The scatter reported in PTT/PAT-BP calibration especially at higher SBP can arise from several sources e.g. sampling frequency, algorithm inaccuracy in estimating fiducial points, contact force of the sensor, network synchronization error if a BSN is used, motion artifacts and wave reflection from arterial bifurcations/terminations. The accuracy of BP estimation [mmHg] is considered in a hypothetical system, which acquires the ECG, one pulse wave and the ICG sampled at 500Hz. The accuracy is also considered for the maximum derivative algorithm to detect pulse wave arrival and an algorithm for ICG B-point detection (Carvalho et al. 2011). the scatter from sampling three signals is already 3*± 1 ms. The scatter from the pulse wave detection algorithm using ensemble averaging of 5 beats is approximately 15 ms (Sola et al. 2009). The mean estimation error of the PEP using ICG is taken to be 5.8 ms (Carvalho et al. 2010). The accuracy of the ECG R-peak detection algorithm is assumed to be less than 1 ms and can hence be ignored. Assuming a linear regression of MAP = − 0.61*PTT[ms] + 154.5 (Sola et al. 2013), the scatter in mmHg is estimated to be ± (3*1 + 7.5 + 2.8)*0.61 = ± 8.1 mm Hg. According to the AAMI SP10 standard, this would be 0.1 mmHg more than the acceptable clinical standard deviation of 8 mmHg. Even though the values are taken from separate investigations, the estimated inaccuracy highlights the fact that the clinically unacceptable accuracy in BP estimation does not include effects from sensor contact force or motion artifacts. The accuracy of 8.1 mmHg demonstrates the importance of the design and choice of sensors and signal processing in a BP monitor.

In section 5, we managed to list only eleven integrated systems, out of which six have been validated with calibration. We surmise that the small number of systems are due to a wide span of knowledge and facilities ranging from IC and embedded system design to signal processing as well as biomedical engineering and wearable system design. More intense collaboration between research groups will result in many more systems being developed. Not only is the design a huge challenge, but so is its evaluation.

7. Summary

The goal of this survey was to summarize developments and gaps in the literature on ambulatory blood pressure monitoring using PAT/PTT. We have classified two approaches to estimating BP, which require the measurement of one or two pulse wave signals. The findings from literature have been sorted into PAT/PTT-BP calibration methods, the acquisition and processing of physiological systems and prototypes of BP monitors integrating calibration as well as signal acquisition and processing.
There are three main gaps in the literature. Firstly, sensor designs for measurement of the pulse wave at locations closer to central arteries should be investigated for more accurate and less frequent PAT/PTT-BP calibration. Besides focusing on obtaining a distinguishable waveform, while suppressing motion artifact, attention should be paid to the contact force against the artery, such that the PAT/PTT is not affected. Integration of postural changes should also be done. Secondly, factors that affect the PTT/PAT-BP calibration should be investigated further in order to quantitatively modify the calibration algorithms. These are obviously dependent on the pulse wave sensor location. Thirdly, more inter-disciplinary collaboration is needed to integrate components into wearable, compact systems. Scatter between PTT/PAT and BP should be considered with respect to several system designs as discussed in the previous section. The evaluation of BP estimation accuracy under controlled as well as ambulatory conditions should also be included.

The results of this paper are intended to enable the design of more prototypes which could enable BP to be monitored in ways that patients will find more convenient.

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