Continuous non-invasive blood pressure monitoring via 3D force sensor and its applications in diagnostics

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Thesis of PHD dissertation

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Budapest, 2019

1 Introduction

Cardiovascular monitoring is crucial in patient monitoring, during surgeries, in the ambulance and in intensive care units. In some critical stakes, it is vital to know the blood pressure (BP) values at any moment for the practitioners to be able to take immediate actions when the condition of the patient changes suddenly. Today, the gold standard, widely used method for continuous BP measurements is the invasive arterial cannulation. So far, this method is the most accurate solution, however it has many risks such as haematoma formation, bleeding at the place of puncture and peripheral nerve injury [1].

The classic non-invasive BP measuring method was finalized by Korotkov in the early 1900s. This cuff based method is still widely used, and has not been developed much in the recent decades. The main development was the oscillometric measuring method that led to the usage of the currently most well-known and applied automatized BP measuring devices. However, this method cannot provide detailed information, only one systolic and diastolic BP value and the actual pulse rate at 40 seconds time frame.

For non-invasive continuous blood pressure measurement, there are several methods, but none of them has become frequently used yet. These methods include Peñaz principle-based method and applanation tonometry. Peñaz principle-based devices has good accuracy in beat-to-beat blood pressure measurement [2–7]. These devices has one or two finger cuffs each including a photoplethysmograph (PPG) sensor that can measure the blood oxygenation level. The finger arteries are much smaller in diameter than the radial or brachial artery, so the measured blood pressure values must be corrected. This correction can be done by precalibration with a brachial oscillometric blood pressure monitor or by a transfer function. Due to constant oppression of the finger arteries, these devices can be used safely only for 12-24 hours.

Applanation tonometry is a very promising non-invasive blood pressure monitoring method [8–12]. This method is based on the pressure fluctuations appearing between the intra-arterial pressure and the external pressure transducer. It can be supervised or unsupervised. The supervised method has a pen-like transducer that is put over the radial artery by the practitioner. This supervised method requires precalibration by an upper-arm oscillometric blood pressure monitor. By this method short periods of continuous blood pressure monitoring can be done, because it requires from the practitioner to remain still and apply the same contact pressure through the measurements. Therefore, usually the length of the measure-

ments are around 1 minute.

The unsupervised tonometry has a transducer attached to the wrist over the radial artery. The positioning of the sensor is crucial, because good quality signals can only be recorded at a strongly fluctuating position. After transducer attachment, precalibration had to be made like at the supervised method. It is a high priority to be as few patient movements as possible, because due to patient movement the transducer can change its position. If the position of the transducer is altered, it has to be attached again to the best measuring position. Therefore, this unsupervised tonometric method can be best applied on aneshetized patients. But tonometry has some promising results even in the case of morbidly obese patients [13].

The above mentioned non-invasive devices provides good tools for continuous non-invasive blood pressure monitoring, but neither of them have become widespread yet. Why are they not used in everyday practice? Could there be any other solution that can provide an easier, more robust, more accurate and comfortable option for healthcare workers? Could a non-invasive monitoring device reach the accuracy of the gold standard invasive method?

To validate the accuracy of a non-invasive blood pressure measurement device, method, there is an international criterion set by the Association for the Advancement of Medical Instrumentation (AAMI) [14, 15]. This criterion sets the maximal bias against a validated blood pressure measurement at 5 mmHg and standard deviation at 8 mmHg.

Are there other ways how the continuous blood pressure signal can be used? These signals are not only important in patient monitoring, but also in diagnostics. The shape, characteristics of the signal can provide information about cardiovascular and several internal organ diseases. This method is called pulse diagnostics. The principle of this method is that the cardiovascular system is connected to the whole body and interactions arise, and through these interactions it carries information about the whole body. This information can be learned from the pulse, more specifically from the continuous blood pressure waveform. In automatized pulse diagnostics the diagnostic information can be gained from the waveform.

A typical blood pressure waveform in the radial artery at the wrist can be seen in Figure 1. This typical waveform consists of three waves, two forward propagating wave, the percussion wave and the dicrotic wave and a backward propagating wave, the reflection wave. The percussion wave refers to the systolic event, by a fast uprise in BP amplitude. Reflection wave is a reflected wave from the peripheral arterial site. The arrival of this wave has deep impact in blood pressure waveform, so it is crucial in pulse diagnostics. The dicrotic wave (dicrotic notch) refers to the closure of the heart valves.

The closure of the heart valves creates a vacuum at the initial aorta, which causes a small back flow. During the back flow the blood collides with the closed heart valve which causes a small pressure uprise. These waves characterizes the shape of the blood pressure signal.

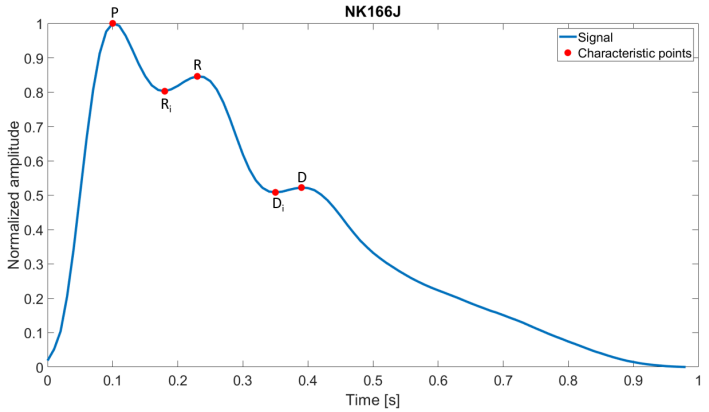


Figure 1: A typical healthy BP waveform with its characteristic points. P–peak of the percussion wave, R_i–Initial point of the reflected wave, R–peak of the reflected wave, D_i–initial point of the dicrotic wave, D–dicrotic notch.

Today, the trends show that an easy to use, compact monitoring device would be a great tool for everyday diagnostics. There are smart watches, smart phone extensions that can provide information about heart rate, blood oxygenation level and even blood pressure. The accuracy of these devices are still questionable, but by using better and better sensors, it can improve a lot. Also, if there would be a sensor, attached to a smart device, which can record the blood pressure waveform and analyze it, a new home diagnostic tool can be developed. This would be a great step forward in prevention and early diagnosis.

This dissertation tries to answer the above mentioned questions. I introduce a solution for continuous non-invasive blood pressure monitoring and prove the usability of this method.

2 Blood pressure waveform measurement using 3D force sensor

For my work, I used the OptoForce/OnRobot 3D force sensor. It can measure not only the magnitude of the force, but also the direction of it. For the recordings, I used the OMD-20-SE-40N 3 axis sensor with great resolution (2–2.5 mN [16]). The sensor has a hemispherical dome. The sensing method of the sensor is based on infrared light reflection and deformation of its dome. Due to external effects, forces on the sensor, the silicone dome deforms. This deformation causes changes in the amount of light detected on each light sensing element. The 3D force vector can be calculated based on these differences occurred on the separate sensing elements [17]. It is sensitive, able to detect a 0.01 mm deformation of its dome and it is also robust, and tolerates a 600% overload compared to its nominal capacity of 40 N. The measuring principle is based on infrared light reflection, so the sensor does not emit any harmful radiation. Moreover, the sensing surface is made of silicone rubber, which is a hypoallergenic material and feels comfortable on skin contact. Due to its material, the sensor is easy to disinfect.

First, the attachment of the 3D force sensor had to be developed. In the final version, a sensor holder was designed, using a 3D designer software, Autodesk Inventor Professional (Student version). The designed sensor holder was then printed by a 3D printer (Stratasys Objet24 3D printer). This sensor holder granted stability for the sensor and also a way to adjust the position of the sensor after the buckle was closed. My experiences suggest that this sensor attachment method can be easily learned how to use, and provides good stability and it is suitable for different size and shape of wrist. The final design is shown in Figure 2.

To measure good quality signals, the sensor has to be attached at the wrist over the radial artery. Three factors can help to find the best position and evaluate the quality of the signal. First is the 3D force vector, which is better if it is closer to 90° from the xy-plane (the basement plane of the sensor). My experiences suggest, that the optimal range of the 3D vector angle from the xy-plane is between 50° and 130°. In this range, the measurable signal can be good quality. The second factor is the difference between the minimal and the maximal amplitude. For the sensor channels (measured values for each light sensing element) it has to be at least 100 units. And the third is the characteristics of the measured waveform which is currently a visual based decision made on the site, but after well defined quality measures it can be done by a measurement software. This quality measure is still under development.

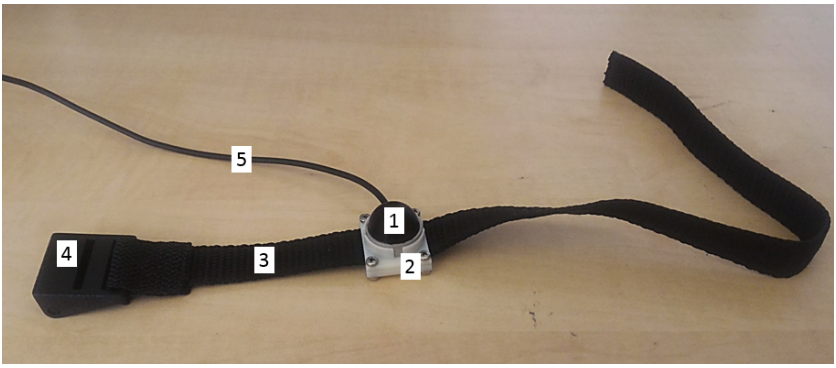


Figure 2: Final version of the sensor attachment. 1 – OptoForce OMD-20-SE-40N sensor, 2 – sensor holder, 3 – band, 4 – buckle, 5 – wire of the sensor

The protocol of the sensor attachment is described in details in the description of Thesis 1.

I tested the above defined measurement environment and sensor attachment protocol in a repeatability study. I asked one of my colleagues to participate in this test. First, I attached the sensor to her left wrist 20 times in a row, applying the defined protocol. Then, I repeated it to her right wrist, again 20 times in a row. The readable BP waveform's amplitude had to be at least 100 units and the 3D vectors angle had to be in the range of $50° - 130°$ from the xy-plane of the sensor. After the sensor was attached to the wrist, a two minutes long signal was recorded with 100 Hz sampling frequency for each trial. In the next phase, the participant was asked to make measurements on me, applying the same protocol. After a short (several minutes) practice, the same measurement procedure was repeated with 10-10 trials on each of my wrist. The correlation values between each signals were around 0.99, thus the attachment protocol is repeatable.

3 Novel non-invasive continuous blood pressure monitoring

3.1 Validation by Millar tonometer

The proposed OptoForce OMD-20-SE-40N tactile force sensor [16] based method was compared to an applanation tonometry system, the pen-shaped Millar SPT-301 non-invasive, handheld tonometer (Millar Instruments, Houston, Texas, USA) as reference measurement. The analogue output of the tonometer sampled by an ADInstruments PowerLab 4/35 data acquisition system. The sampled signals were processed, displayed and stored with a LabChart data analysis software (LabChart v.7.3, ADInstruments, Bella Vista, Australia). During the recording sessions, ECG was collected from Lead-II. Blood pressure was measured simultaneously on both arms by double-cuff, oscillometric blood pressure monitor (Microlife WatchBP Office ABI). Measurements with the Millar tonometer was conducted by dr. Tamás Horváth.

The data collection were conducted at the Faculty of Information Technology and Bionics of Pázmány Péter Catholic University (Budapest) under ethical license no. 186/2013. All participants received written and oral information about the measurements.

Our study included 30 participants: 8 women and 22 men. Table 1 shows their anthropometric characteristics.

Table 1: Characteristics of participants

	Range	Mean±std.
Age (years)	20–30	24.4±2.5
Height (cm)	155–191	175.2±8.4
Weight (kg)	44–95	69.3±11.1
BMI (kg/m^2)	18.3–28.7	22.5±2.6

Measurements were carried out in two turns. Within each turn, 3 times 1-minute long recording sessions were acquired by both the OptoForce sensor and the Millar tonometer. Before and after the sessions simultaneous, bilateral upper-arm blood pressure readings were taken. In the first turn, the OptoForce sensor was positioned above the left- and the Millar tonometer over the right radial artery. In the second turn both sensors were repositioned on the contralateral side. In the end, a total of six 1-minute long

measurements were taken with each participant. The sampling frequency of the continuous measurements was 1000 Hz.

For the comparison, the middle 70% of each minute long measurements were selected (~42 sec) in order to exclude possible noise at the beginning and at the end of the recordings. There were 12 cases where the width of the examined window had to be shortened due to significant motion artefacts.

Both continuous non-invasive blood pressure monitoring systems require calibration. I applied the same calibration method for the two signals, compensating for the linear gain and average offset values:

$$Gain = \frac{\mathrm{MAP}_{avg} - \mathrm{DIA}_{avg}}{\mathrm{U}_{avg} - \mathrm{U}_{dia}}, \tag{1}$$

$$\mathrm{CBP}(t) = Gain \cdot (\mathrm{U}(t) - \mathrm{U}_{dia}) + \mathrm{DIA}_{avg}, \tag{2}$$

$\mathrm{CBP}(t)$ is the continuous blood pressure at time (t), U_{avg} is the averaged, U_{dia} is the averaged minimum values of the raw, uncalibrated signal $\mathrm{U}(t)$ recorded by each sensor.

The average correlation between the simultaneously measured signals was 0.8933 ± 0.1307, and the average RMSE value was 7.25 ± 4.03 mmHg.

There were some outliers with significantly lower correlation (< 0.7), mostly due to motion artefacts. Excluding these (12 out of 180; 6.67%), the average correlation between the simultaneously measured signals increased to 0.9213 ± 0.063, and the average RMSE value decreased to 6.58 ± 3.08 mmHg. Figure 3 shows a highly correlated signal pair. The results of BP comparison is shown in Table 2.

Table 2: Summary of average bias and standard deviation values for systolic, diastolic, MAP and incisura pressure.

	Simultaneous [mmHg]	Same hand [mmHg]
Systolic pressure	0.35 ± 1.75	0.42 ± 1.77
Diastolic pressure	0.02 ± 0.19	0.02 ± 0.74
MAP	2.88 ± 2.42	3.02 ± 2.26
Incisura pressure	3.84 ± 3.90	3.85 ± 3.43

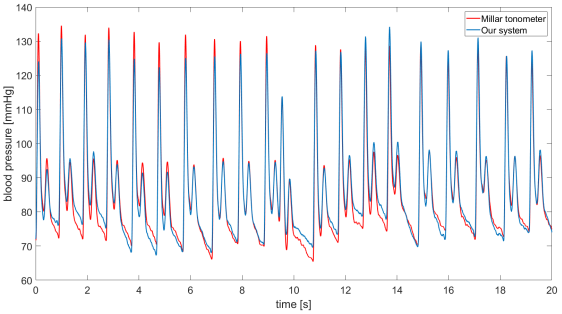


Figure 3: 20 seconds-long section of the best correlated signal pair without compensation of the blood pressure difference between the two arms (correlation coefficient is 0.9889)

3.2 Validation by invasive arterial cannula

3.2.1 Waveform similarity

The measurements were made at the Department of Vascular Surgery, Semmelweis University, Budapest under clinical license no. 186/2013. The experiment was made on those patients who had to undergo carotid surgery. All participants received written and oral information about the experiment, and after their approval, a written informed consent was obtained. In this study there were 13 patients (7 men and 6 women), but due to bad quality signal, 4 of them had to be excluded (3 men and 1 woman). The characteristics of the remaining patients can be seen in Table 3.

Table 3: Characteristics of participants

	Range	Mean±std.
Age	57–77	65.2±7.7
Height (cm)	148–173	161.2±8.6
Weight (kg)	50–82	69.1±9.9
Heart rate (bpm)	57–90	72.4±10.1
Systolic BP (mmHg)	106–178	132.7±20.3
Diastolic BP (mmHg)	51–78	58.7±8.1

Patient monitoring was done by a GE™Dashboard 4000 patient monitor system, which recorded the invasive BP signal. During each experiment, the invasive and the non-invasive continuous BP waveforms were recorded simultaneously by a PC which was connected to the patient monitor and the 3D force sensor by USB cables. The invasive catheter was inserted in the radial artery of one arm, and our non-invasive system was put on the contralateral wrist. The measuring position on each arm was nearly the same. The measurements were 20-30-minutes long. The data from the GE patient monitor was acquired by Datex-Ohmeda S/5™Collect software. The non-invasive signal was acquired by the OptoForce Data Visualization software. The sampling frequency in both cases was 100 Hz.

During our experiment reproducibility was also tested. For 4 individuals two measurements were made consecutively by repositioning the non-invasive sensor on the wrist. Then the results of the two measurements were compared by their average correlation values.

To be able to compare the two waveforms, the same signal processing method had to be followed. For continuous arterial BP waveform's signal processing a cascaded adaptive filter was applied. It can filter the baseline wander from the signal. This signal processing method consists of two parts, a discrete Meyer wavelet decomposition filter and a spline estimation filter [18, 19]. Wavelet decomposition filters are based on signal and noise estimation on different decomposition levels. In this study the continuous BP wave was approximated by the 1st level discrete Meyer wavelet decomposition, and the noise was estimated by the 7th level, in a similar manner to [19].

To completely remove the baseline drift, the spline estimation filter was applied. This method requires the onset points of the arterial BP signals. The onset point is a local minimum point appearing at the start of the heart cycle, which was determined by the slope sum function method. In this study the cubic spline data interpolation was used. By fitting the cubic spline curve on these onset points, the baseline wander can be removed. These onset points can also be used for signal segmentation to create the single-period signals, which describe each heart cycle.

After signal processing, each single-period signal was normalized to 1 for both the invasive and non-invasive signals separately so that the waveform of the invasive and non-invasive measurements could be compared. This step was required, because the data from the invasive and non-invasive system had different units. The comparison was done by cross correlation. Those single-period signals that were corrupted by movement were excluded from the comparison if the movement could not be filtered via signal processing. To decide whether this exclusion was necessary or not,

the length of each single-period signal was considered. If the length of the non-invasive single-period signal differed by more than 20% from the corresponding length of the invasive single-period signal, the segments in question were excluded. The rate of the excluded single-period signals was always below 10% of the corresponding continuous BP signal.

The highest correlation value and the standard deviation was 0.986 ± 0.024. Most of the resulting correlation values were above 0.9. This means, most of the invasive and non-invasive single-period signals were identical in more than 90%. Figure 4. shows an example of a highly correlated signal section.

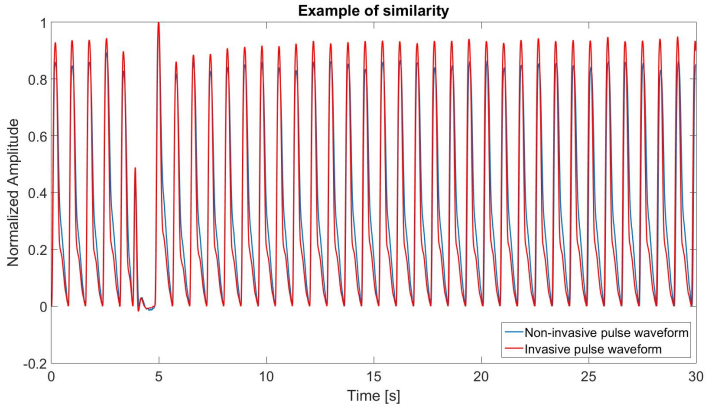


Figure 4: An example of a well correlated invasive and non-invasive continuous BP signal section. In this figure for better visibility, the normalization was made to the highest amplitude invasive signal in the presented segment.

3.2.2 Continuous blood pressure comparison study

The measurements were made at the Department of Vascular Surgery of Semmelweis University (Budapest) under ethical license no. 186/2013. All participants received written and oral information about the measurements and signed an informed consent form. 21 participants, 6 women and 15 men were measured. Table 4. shows their main anthropometric characteristics. Twelve of the participants had a carotid artery surgery, four had heart transplantation, and the other participants had stent graft surgeries.

Table 4: Characteristics of participants

	Range	Mean±std.
Age (years)	34–87	63.8±11.2
Height (cm)	148–190	169.4±27.1
Weight (kg)	50–123	78.1±14.3
BMI (kg/m^2)	23–34	27.1±3.6

The 3-axis sensor based system was attached to the arm contralateral to the arterial cannula. In 12 cases the sensor was attached to the left wrist. The duration of the measurements differed for each participant. The length of the analyzed signal depended on the presence of motion artefacts and the condition of the patient. In average, the analyzed signal length was 409.03 ± 230.31 seconds, range from 98.22 to 988 seconds. In the case of 5 participants out of the 21, there were two consecutive measurements, therefore altogether 26 simultaneously recorded invasive and non-invasive signals were processed and statistically analyzed.

To filter out the motion artefacts, a Daubechies wavelet with maximum 8 vanishing moments (db8) decomposition filter was applied. There are several examples in literature where wavelet decomposition filters were applied during noise filtering of BP waveforms, i.e. [19, 20], because the appropriate wavelet decomposition filter is an efficient tool to filter out aperiodic, low frequency noises like the motion artefact. The calibration method was the same, presented above.

The average correlation between the 26 simultaneously recorded invasive and non-invasive BP signals was 0.9001 ± 0.0588 which indicates a high similarity in the waveforms. Even the least correlating signals had a correlation value more than 0.7, which is considered as a fair similarity. The average correlation between the frequency domain of each simultaneously recorded invasive and non-invasive signals was 0.9988 ± 0.0009 that implies the identity of the frequency components.

In the case of diastolic BP the mean difference between the simultaneously recorded invasive and non-invasive signals was -0.26 ± 3.06 mmHg, which satisfies the AAMI criterion. For the studied 12160 invasive and non-invasive diastolic BP pairs, 11691 were inside the mean limits of agreement, where the mean limits of agreement ranged from -7.58 mmHg to 7.19 mmHg. 96.14% of the measured values are inside the mean limits of agreement. In the case of MAP the mean difference between the simultaneously

recorded invasive and non-invasive signals was 1.25 ± 2.26 mmHg, which also satisfies the AAMI criterion. For the 12160 invasive and non-invasive MAP pairs, 11672 were inside the mean limits of agreement, where the mean limits of agreement ranged from -3.74 mmHg to 6.23 mmHg. It means that 95.99% of the measured values are inside the mean limits of agreement. For the systolic pressures, the results show weaker similarity. The mean difference between the simultaneously recorded invasive and non-invasive systolic values was -9.53 ± 4.69 mmHg, which is out of the 5 mmHg bias range allowed by the AAMI criterion. For 8 out of 21 results of each participant satisfies the 5 mmHg bias range.

3.3 Pulse diagnostics

One major challenge facing automatized pulse diagnostics is filtering motion artefacts. For this purpose, I applied the above mentioned cascaded adaptive filter, presented by [19]. For analysis the continuous BP signal has to be segmented to single-period signals. To find the segmentation points an open source onset point detection algorithm was applied [21]. It can be parametrized, which makes it able to be accurate and deal with noisy or not common pulse waveforms. Having the onset points a spline estimation filter was applied. The spline estimation filter fits a smoothing spline curve on the onset points and subtract it from the wavelet filtered signal. This completes the cascaded adaptive filter and leads to a baseline wander free signal. Then, the signal is segmented into single-period signals according to the onset points. The last step of signal processing is the search for characteristic points, which is calculated by a derivative-based local extremum search, as the main characteristic points appears as local maximum and minimum points. The next step would be feature extraction, but to find the appropriate features of the signals, a much bigger database would be required.

Measurements were made including 175 participants, their characteristics are shown in Table 5. One aim was to have participants in each age group to be able to study the effects of aging. Also there were several participants with different kind of diseases. It is important to mention that the participants' medical history was taken as self-assessment, so this must be considered later in forming conclusion. The measurement protocol was the following:

- First, the 3D force sensor was attached to the right or left wrist.
- A cuff-based blood pressure measurement was made on the same side as the sensor.

- When the cuff is fully deflated, a 3-min-long measurement was started with the force sensor.
- After the 3 minutes, another cuff-based measurement was made.
- All the above steps were repeated on the contralateral wrist.

Table 5: Characteristics of the participants

	Total	Men	Women
Number of participants	175	67	108
Age (years)	45.12 ± 12.04	42.64 ± 12.43	46.66 ± 11.59
Height (cm)	170.34 ± 9.74	179.9 ± 6.81	164.4 ± 5.73
Weight (kg)	76.18 ± 16.11	87.07 ± 15.23	69.42 ± 12.6
BMI (kg/m^2)	26.15 ± 4.63	26.49 ± 5.81	25.67 ± 4.48

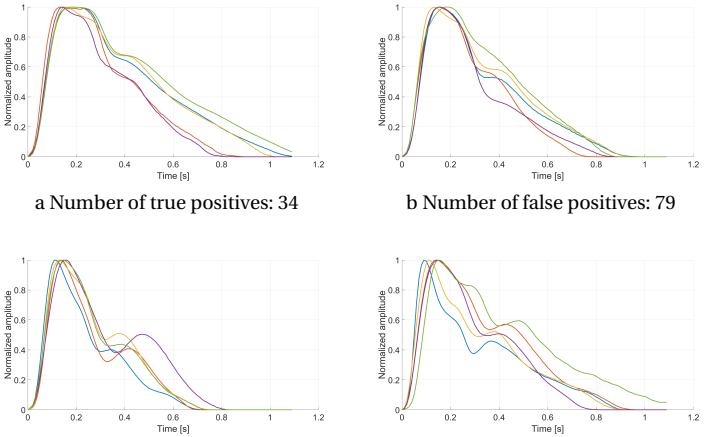
The presented database is too small to create a classification algorithm. Also, its size is not enough to create many clusters to separate different conditions. So, I concentrated only on the healthy and hypertensive signals and I tried to separate them by clustering using only the information gained from the waveform. The evaluation is based on the database information. To validate the results, I applied two different algorithms, a k-means algorithm and a competitive neural network.

For this clustering the number of features should be minimal to make the dimension of the problem low, thus making it easier for the algorithms to identify differences how to separate the two groups. One feature is based on the knowledge about the signal shape in different health conditions. In the case of hypertensive signals, the width of the percussion wave is usually much longer, as the reflected waves arrive earlier and merge with the end of the percussion wave. This feature can be described more precisely by taking the numeric integral of the upper 10% of the signal, because the amplitude decreases slowly in a typical hypertensive signal. The other feature was selected from the absolute features, which was the height of the dicrotic peak.

For the clustering 104 healthy participant's signal (44 men and 60 women) and 24 participants (8 men and 16 women) with only hypertension disease was selected according to database information. Overall this means 256 single-period pulse signals.

The results of clustering, shown in Figure 5., are the following: the sensitivity is 0.7083, the specificity is 0.6202 and the precision is 0.3009. Although

at first glance these numbers do not look promising further clarification and discussion are required to evaluate these results. First, there are a great number of healthy signals in the hypertensive cluster. By visual inspection most of these signal would belong to the hypertensive cluster. As the database contains self assessed information, it has a relatively high chance that the given participant does not know about his/her disease. Considering the hypertensive signals clustered as healthy, it is important to know that almost all the hypertensive participants was on medication except one participant. This means that for those participants whose disease was diagnosed and treated in an early stage, the condition of their arteries could remain healthy, thus the shape of their signal can be healthy too.



a Number of true positives: 34

b Number of false positives: 79

c Number of false negatives: 14

d Number of true negatives: 129

Figure 5: Results of the clustering algorithms with several example signals in each group.

4 Summary of the new scientific results

4.1 Thesis group 1.

Thesis 1. *I have created a novel measurement method which can record non-invasive blood pressure characteristics from the radial artery using a 3D force sensor. I have defined the sensor attachment protocol to record non-invasive blood pressure characteristics. The designed wrist band and this protocol provides an easy to learn method with high repeatability. Signals from repetitive measurements by the same operator showed high* (≈ 0.99) *correlation. This novel method also has the advantage that it can measure approximately same quality signals on its surface in the* $50°$–$130°$ *angle range from the 3D force sensor's base plane.*

I have designed a wrist band, which can be used to attach the sensor to the wrist. It consist of a 3D printed sensor holder, its position can be adjusted on the band. An important design property is its adjustability, but still remaining fixed during the measurements (robust). This means that it was able to resist most of the patient's movements or other effects on the wrist band and hold the sensor in its initial position over the radial artery. My experiments proved that this sensor attachment solution has the above properties.

The protocol contains the following steps:

- The radial artery is attempted to be found at the wrist by palpation.
- At a strongly pulsating point the sensor is attempted to be attached. The tip of the sensor's dome is put over the strongest pulsating point, then the band is fixed using the buckle.
- A check should be done whether the amplitude of the signal is over 100 units for every channel and the 3D force vector is close to the $90°$, if so, the sensor placement is completed. Otherwise, the position of the sensor has to be adjusted by moving the sensor holder on the band or the band must be tightened. If the strongest pulsating point cannot be found the initial position of the sensor has to be changed, using palpation again to find the strongest pulsating point and trying to position the sensor over it.

The presented repeatability study proved that using the defined protocol the measurements are repeatable. Also, it is easy to learn, requires only several minutes of training.

Publication partially connected to this thesis: [I].

4.2 Thesis group 2.

Thesis 2.1. *I have compared this 3D force sensor-based method with another non-invasive continuous blood pressure monitoring method. Using a Millar tonometer as the validation device and making measurements in a young, healthy group, my results showed that the 3D force sensor-based method is within the AAMI criterion, which requires a bias within 5 mmHg and a standard deviation within 8 mmHg. After the calibration of both sensors by cuff BP measurement, for systolic, diastolic, incisura pressures and MAP the difference between the two methods were* 0.35 ± 1.75 *mmHg,* 0.02 ± 0.19 *mmHg,* 3.84 ± 3.90 *mmHg and* 2.88 ± 2.42 *mmHg, respectively.*

The Millar tonometer method is a validated and approved, commercially available continuous blood pressure waveform measurement method. A trained personal is required for the conduction of these measurements. The comparison of the 3D force sensor-based method and the Millar tonometer for continuously available BP values and also the continuous wave's shape was conducted. Both devices can measure relative BP changes, therefore they require calibration by a cuff BP measurement.

Publication related to this thesis: [I].

Thesis 2.2. *I have carried out validation measurements by an invasive arterial cannula to check the waveform similarity between the two methods. In this study the invasive and the non-invasive continuous blood pressure waveforms were compared. Simultaneous measurements were carried out on 9 participants with altogether 13 measurements. After signal processing for the waveforms the average correlation was* 0.9527 ± 0.0917. *To prove the repeatability, for 4 participants two consecutive measurements were conducted. The correlation values for each pair of measurements were: (*0.939 ± 0.142, 0.971 ± 0.096*); (*0.968 ± 0.055, 0.977 ± 0.022*); (*0.986 ± 0.024, 0.969 ± 0.076*); (*0.935 ± 0.073, 0.954 ± 0.032*)*

It was crucial to compare the measurable continuous BP signal to the real BP waveform. For pulse diagnostics, the shape of the continuous BP signal is more important than the nominal BP values. Therefore, this study aims to compare the waveform of the invasive arterial cannula's signal and the non-invasive signal. Before comparison, the same signal processing steps were applied for each signal.

Publication related to this thesis: [IV].

Thesis 2.3. *I have compared the 3D force sensor-based method with an invasive arterial cannula studying the blood pressure values. The invasive system measured the absolute BP, the non-invasive system was calibrated to measure the relative BP changes. This validation study included 21 participants with altogether 26 simultaneously recorded non-invasive and invasive continuous blood pressure measurements. The average difference between the simultaneously recorded invasive and non-invasive systolic, diastolic and mean arterial pressure was* -9.53 ± 4.69, -0.26 ± 3.06 *and* 1.25 ± 2.26 *mmHg, respectively.*

The best practice to validate a continuous BP monitoring device is to compare with the gold standard invasive arterial cannula measurement that can measure the absolute BP. In this validation, the continuous BP signals from the two different devices were compared, so both the actual BP value and the continuous waveform were taken into consideration. The participants involved in this study were mainly elderly patients (the average age was 63.8 ± 11.2) who all underwent a serious cardiovascular system connected surgery.

The non-invasive system had to be calibrated to be able to measure the relative BP changes. The systolic and diastolic values of the invasive and non-invasive signals were contrasted. The diastolic values are equivalent to the momentary values of the continuous BP signal at each onset point. Similarly, the systolic values are equivalent of each single-period signal's global maxima point (between the current and the next onset points). The waveform similarity is taken into consideration by calculating the MAP using the integral of the waveform signal.

Publication related to this thesis: [II].

4.3 Thesis group 3.

Thesis 3. *A database was created by measuring on both arms of 175 people with the novel, 3D force sensor-based method and collecting data on the participants health condition. The measured signals showed agreement with common pulse waveforms presented in the literature of the related field. Using the presented database and the widely accepted observations of the related literature, I could demonstrate the frequently discussed signal types for the healthy and hypertensive group of the recorded signals. The effect of aging in healthy people was also observable in the measured signals. I applied a k-means and a competitive neural network clustering method to separate the pulse waveforms into two groups, healthy and hypertensive, based on the waveform. The presented methods had the same result: 0.71 sensitivity, 0.62*

specificity and 0.30 precision.

The basic step of developing a pulse diagnostic device is to prove its capability of recording single-period signals commonly described in the literature of the related field. In the absence of online annotated database, we created a database with our measurements. These measurements included 175 people, 350 signals (measurements on both hands). Each signal was 3 minutes long. The database was recorded anonymously, it included antropometric characteristics of each participant, like age, height, weight, BMI, gender. For all participant it was noted, if he or she had an internal organ or cardiovascular disease and the smoking habits. All the data on the participants were self-assessment. The measurements included oscillometric blood pressure measurement before and after each pulse signal recorded. In data collection and database systematization, Flóra Zieger provided me a great help.

According to the database, there were 104 participants, 208 signals, who had not have any known disease at the time of the measurement and 24 hypertensive participants, 48 signals. For clustering two features were selected. The first feature is the numeric integral of the normalized averaged single-period pulse signal above the 0.9 line of its amplitude. The other feature is the amplitude of the dicrotic peak of the normalized averaged single-period pulse signal. To cluster the signals I used two different methods, the k-means clustering algorithm using the Euclidean distance and a competitive neural network based clustering method built-in in the Matlab R2019a software. Both algorithms concluded the same result. In the hypertensive cluster, there were 34 signals from participants with hypertension and 79 signals from healthy participants. In the healthy cluster, there were 14 signals from participants with hypertension and 129 signals from healthy participants. This means 0.7083 sensitivity, 0.6202 specificity and 0.3009 precision.

In the evaluation of these results several assumptions should be considered. The information on participants' condition was self-assessment, therefore it can be noisy. 23 of the 24 participants were taking medication for hypertension which could improve their condition. In the case of healthy participants, it is possible that they have hypertension, but they did not know about it at the time of the measurements. And finally, the size of the database is low, much more data would be required to make more confident statement. However, the results showed that there is quantitatively describable difference between the healthy and the hypertensive pulse signals, which proves the potential of this novel method in pulse diagnostics.

Publication related to this thesis: [V, VI, VIII].

5 Application areas

The obvious application area is in clinical and ambulance monitoring, where arterial blood test are not required. Also in ambulance it would be very important, because today, there is not any continuous blood pressure monitoring option in the ambulance car, only the intermittent oscillometric cuff-based blood pressure monitor.

Due to its ease and safety of use, the non-invasive continuous blood pressure monitoring can be also used at home as a mobile device. Continuous BP signals measured at home in different day times would give a valuable tool for practitioners to conclude a diagnosis. Also, it would provide a great database that can be used for study (effects of diseases, drugs, events during the day cycle).

This non-invasive continuous blood pressure measurement method can be used as an additional parameter measuring system for another diagnostic method, like ECG, CT, where continuous blood pressure waveform can give an important additional information, parameter or can be used to calculate crucial parameters, like blood flow velocity or augmentation index of the artery.

Using the continuous waveform, this measurement method can be a useful diagnostic device for several inner-organ or cardiovascular diseases. It has also potential in medicine development, it can be a tool to follow the effects of several medicine, i.e. antihypertensive drugs.

Extending the measurement with an ECG system, the Pulse Transit Time can be calculated. By Pulse Transit Time, the Pulse Wave Velocity can be determined, which is proportional to the blood pressure, therefore it is able to estimate the blood pressure non-invasively without a cuff-based measurement. This can lead to a cuffless calibration method for our non-invasive continuous blood pressure monitor.

This continuous blood pressure monitoring device has also some potential in ankle-brachial index (ABI) measurement. It can provide extended information by the continuous signal. Also, using the PTT-based blood pressure estimation, the accuracy of ankle blood pressure can be better than the cuff-based measurements.

As a potential commercial application, non-invasive continuous blood pressure monitoring can be applied in fitness devices, like smart watches, fitness bracelets. By the continuous signal, it can give also a wider range of parameters, like blood flow velocity, augmentation index and estimation of arterial stiffness. It can also provide more information about the effects of the exercises on the body. It can support a training plan to be fit on each

individual.

A business plan was created based on the presented non-invasive continuous blood pressure measuring system by Flóra Zieger. This was a part of a combined project presented to the European Union's SME competition, where it reached over the threshold title.

6 Acknowledgements

I thank to my supervisors, Dr. György Cserey and Dr. Péter Sótonyi, for their guidance and help both in my work and in my personal development. It was an honour to work with them.

I thank Professor Tamás Roska and Professor Péter Szolgay, former and present heads of the Doctoral School, for providing all the equipment an environment for my work. I am grateful for the support of the Roska Tamás Doctoral School of Science and Technology at the Faculty of Information Technology and Bionics (ITK - Research Faculty) of Pázmány Péter Catholic University (PPCU - University of National Excellence) as well as the technical assistance provided by OptoForce Ltd. and OnRobot Ltd.

I thank Katinka Tivadarné Vida for her kind help in the administrative tasks. Also, the work of the Dean's Office, the Financial Department and the IT Department is appreciated.

I am grateful to Dr. Zsuzsanna Vágó for her kindness and guidance in fulfilling my teaching tasks. It was a very good experience for me to teach functional analysis as one of her teaching assistant. I also thank to all the students I have thought during my PhD. I could say that all of my former practice groups were great, and was a privilege to work with them.

The help of Tamás Horváth in the validation measurements with the Millar tonometer is gratefully acknowledged, along with the other advices and guidance he provided during my work.

Very special thanks to Flóra Zieger for the privilege of working together for many years on this project. It was a real honour for me.

I thank to Miklós Koller, Márton Bese Naszlady, Kinga Tihanyi, Anna Csörgő, Ákos Tar, József Veres, Ákos Godó, Bianka Huberth, Erzsébet Fodor, Dániel Hajtó, Andrś Bakó, Anna Ignácz and all the other former and present members of the robotics laboratory for the opportunity to work together.

I would like to thank my fellow PhD. students and friends, Márton Hartdégen and Gergely Csány for their support.

The help of Dr. Dorottya Kis, Éva Rigó and Anita Bogdán during measurements is gratefully acknowledged.

Most of all, I thank to my Family, especially my Mother and my wife, Kati, for all the support and care they provided me during my work.

The research has been partially supported by the European Union, co-financed by the European Social Fund (EFOP-3.6.2-16-2017-00013 and 3.6.3-VEKOP-16-2017-00002).

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