Surrogate based continuous noninvasive blood pressure measurement

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Review

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Abstract: Arterial blood pressure is one of the most often measured vital parameters in clinical practice. State-of-the-art noninvasive ABP measurement technologies have noticeable limitations and are mainly based on uncomfortable techniques of complete or partial arterial occlusion by cuffs. Most commonplace devices provide only intermittent measurements, and continuous systems are bulky and difficult to apply correctly for nonprofessionals. Continuous cuffless ABP measurements are still an unmet clinical need and a topic of ongoing research, with only few commercially available devices. This paper discusses surrogate-based noninvasive blood pressure measurement techniques. It covers measurement methods of continuously and noninvasively inferring BP from surrogate signals without applying external pressures, except for reference or initialization purposes. The BP is estimated by processing signal features, so called surrogates, which are modulated by variations of BP. Discussed techniques include well-known approaches such as pulse transit time and pulse arrival time techniques, pulse wave analysis or combinations thereof. Despite a long research history, these methods have not found widespread use in clinical and ambulatory practice, in part due to technical limitations and the lack of a standardized regulatory framework. This work summarizes findings from an invited workshop of experts in the fields covering clinical expertise, engineering aspects, commercialization and standardization issues. The goal is to provide an application driven outlook, starting with clinical needs, and extending to technical actuality. It provides an outline of recommended research directions and includes a detailed overview of clinical use case scenarios for these technologies, opportunities, and limitations.

Keywords: clinical; expert; guideline; NIBP; recommendation; workshop.

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Introduction: blood pressure and blood pressure monitoring – state-of-the-art

ABP is the pressure exerted by the blood on the wall of arterial vessels. Because of the pumping action of the heart, the blood flow is pulsatile in the arteries and the BP values are usually stated in pairs: the systolic peak value and the diastolic minimum level. Most commonly, systolic and diastolic BPs in the arterial system under 120/80 mmHg are considered "normal" and values of 120–129/80–84 mmHg are considered "high normal" [1]. Hypotension is defined as a systolic pressure below 90 mmHg or mean pressure below 65 mmHg [2]. Deviations from these values in either direction can have a negative health impact, reaching as far as damaging organs by increased stress on their blood vessels in the case of hypertension-mediated organ damage or, conversely, diminished perfusion during hypotension, e.g., in the kidneys [3–5].

ABP (which sometimes also is an abbreviation of ambulatory blood pressure) does not stay constant over time, but undergoes natural fluctuations from one heartbeat to another and throughout the day in a circadian rhythm. It is modulated by respiration/ventilation and varies in response to mental and physical stress, posture changes, nutritional factors, drugs, or disease [6]. ABP is subject to a number of specific regulation mechanisms acting on different time-scales, e.g., sympathetic and parasympathetic activation. Furthermore, BP varies with the location in the arterial tree in a process called pulse pressure amplification, illustrated in Figure 1, left [7, 8]. The pulse pressure, which is the difference between systolic and diastolic BP, gradually increases towards the small arteries, then falls to values close to zero at the capillaries. For healthy persons, the SBP in the large arteries is on average 120 mmHg, while in the arterioles the pressure sharply falls to about 50–60 mmHg and in the capillaries the pressure is about 15 mmHg (Figure 1, right) [9]. Only three characteristic values from the ABP wave are typically used for clinical decision-making, which are:

- The maximal pressure, which is termed the systolic blood pressure
- The lowest pressure, which is termed the diastolic blood pressure
- The mean arterial pressure throughout one cardiac cycle

ABP results from the interplay of stroke volume, heart rate and total peripheral resistance. It is also highly sensitive to hydrostatic effects. Getting meaningful BP measurements requires not only an accurate BP reading, it is also important to specify the measurement situation and to have access to the actual context like a patient's posture, medical interventions, drugs or fluid loss.

ABP as a key hemodynamic parameter is routinely monitored across various clinical settings using invasive or noninvasive measurement approaches. An overview of measurement methods is presented in Figure 2, separated by invasiveness and applied technologies.

In high acuity settings, invasive ABP measurements using catheters are common (Figure 3, left). This approach allows the close tracking of the complete ABP wave with a very high temporal and pressure resolution. This is often a requirement during surgeries and in intensive care units. Because invasive arterial blood pressure poses the risk of infections and complications such as bleeding and perfusion deficits [10] and needs to be applied by trained personnel, it is only usable in high acuity settings. However, iABP is the "gold-standard" for BP monitoring.

As a noninvasive alternative, standard cuff-based ABP measurement using the oscillometric or auscultation method is used (Figure 3, right). Unfortunately, it provides only intermittent measurements of values for SBP, DBP, and MAP. Measurement intervals range from a few minutes in the operating rooms, typically 15 min in intensive care and up to hours in the general ward. A relatively stable hemodynamic status of the patient within the uncovered monitoring interval is presumed, which is not always the case. Therefore, cuff-based measurements can miss critical BP changes [11] and have been reported as uncomfortable and disturbing, e.g., during sleep [12].

Photoplethysmography and impedance plethysmography are, among few others, acquisition methods for BP surrogates. Applying pulse wave velocity and pulse wave analysis to these is considered a promising technology towards continuous noninvasive BP readings. Together with more direct pressure measuring approaches as radial artery applanation tonometry and vascular unloading, they aim to overcome shortcomings of the intermittent methods, in particular their low temporal resolution, reducing missed critical events and measurement discomfort.

Vascular unloading is one of the more prevalent continuous and noninvasive technologies available to medical professionals and will thus serve to exemplify the

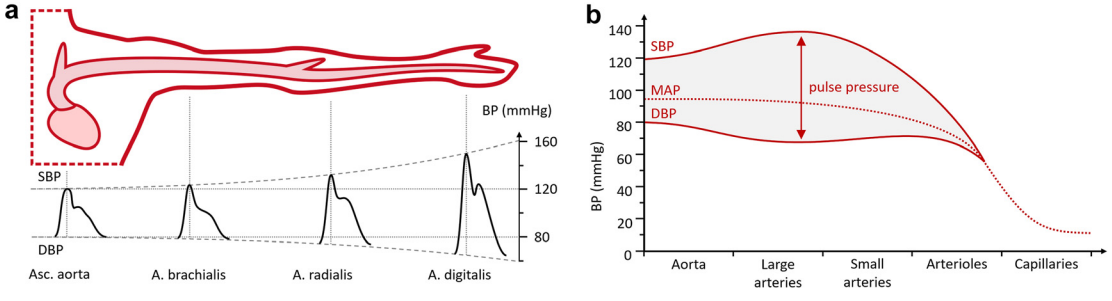

Figure 1: Blood pressure amplification and morphological changes in the pulse wave towards the periphery (left); blood pressure progression from aorta to capillaries – pressure fluctuations equalize after which overall pressure drops (right).

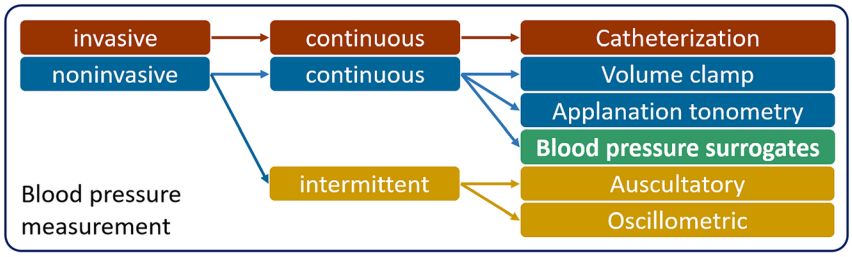

Figure 2: An overview of methods for measuring blood pressure.

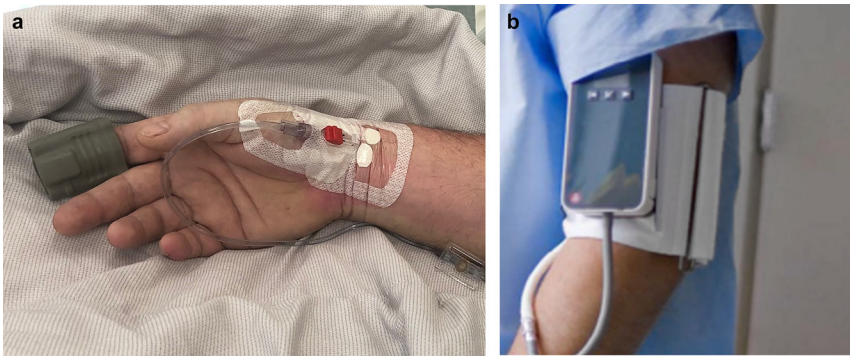

Figure 3: The two main measurement modalities in use in clinical practice: left: invasive ABP monitoring, at the radial artery, providing continuous ABP, right: cuff based inference of SBP, DBP, and MAP with intermittent measurements.

current state. With a research history of already more than 40 years [13], it is becoming an established method for cNIBP readings and is slowly gaining acceptance in the medical community. BP is inferred from a finger by pneumatically tracking ABP using a cuff while keeping the blood volume in the finger artery constant, hence the alternate volume clamp designation. As a result, the complete finger ABP curve is reconstructed, similar in shape to the invasively acquired ABP waveform. The measured pressure from the peripheral finger location needs to be transferred via a mathematical transformation procedure to brachial BP in order to be comparable with standard ABP. A couple of shortcomings have been reported: Correct placement of the finger cuff can be difficult in practice and affect the accuracy of BP readings, despite the underlying calibration scheme [14, 15]. A critical issue is its potential failure in patient conditions with peripheral shutdown, which is common for high-risk patient groups. In addition, since the applied external pressure is at about mean BP level, blood perfusion of the finger is compromised, which limits the time for application. This is solved by periodically switching the measurement between two fingers. Monitoring systems are currently relatively large and bulky requiring an additional device at the bedside.

The focus of this paper is a detailed analysis of approaches based on BP surrogates, which have been a research topic for decades. It deals with measurement methods inferring BP noninvasively and continuously without using external pressures except for reference or initialization purposes. It includes well-known approaches such as the popular PTT techniques, PWA or combinations thereof. This paper will provide a detailed view of the clinical requirements, the underlying technologies and associated opportunities and challenges.

Medical aspects of blood pressure monitoring

Clinical decision of patient-specific arterial blood pressure monitoring needs

The choice of which ABP monitoring technique to use needs careful consideration for each individual patient and his condition. The use of a particular monitoring option is therefore dependent on the situational context, e.g., for the various clinical settings ranging from emergency and intensive care units, to the intermediate care unit, the general ward and at home. A mental distinction is made between long-term trends (~hours) and short-term fluctuations. Long-term trends are supposed to be reliable indicators of true changes in patient status. Large short-term fluctuations are attributed to critical events (e.g., shock) in high acuity settings, but may also be caused by artifacts or

unimportant events (e.g., nurse interaction or situational stress). Repeating a measurement in a supervised setting is a common way of validating an abnormal single measurement result. Close tracking of ABP is also often required during clinical diagnostic procedures, e.g., CT or MRI, to assess and track interventions and treatments. It has also proven useful during sleep recording (polysomnography).

In home blood pressure monitoring, clear guidelines and ranges for measuring and diagnosing hypertension have been defined. They apply to upper arm cuff-based, (semi-) automated oscillometric devices, and specify the conditions of measurement, the monitoring schedule and the interpretation of the BP readings. A 2010 review of the European Society of Hypertension states "*Mean home systolic BP≥135* mmHg *and/or diastolic BP≥85* mmHg *should be considered as elevated. Systolic and diastolic home BP<130 and <80* mmHg, *respectively, should be considered normal in most subjects.*" [16]. A later clinical guideline of the National Institute for Health and Care Excellence increases these values to 140/90 mmHg [17].

For surgical procedures, deciding factors for the method of choice comprise the patient ASA score, procedure risk factors and tolerable measurement latency as shown in Figure 4 [18]. Arterial catheterization is mainly restricted to high acuity patients (ASA 3–5) or procedures with high mortality risks (>1–5%). Anesthetists can use the complete ABP wave to further monitor the patient, e.g., to check for vascular changes, to infer fluid status, estimate cardiac output or gain insights into the patient's depth of anesthesia and pain status [19, 20]. However, nowadays many procedures are being performed at lower mortality risks (<1%) with stable patients (ASA 1–2), where intermittent noninvasive BP seems appropriate. Typically, time intervals can be in the order of 5 min or even less often, whereas a typical ICU BP sampling interval is 15 min [5]. There is a clear trend to avoid invasive procedures due to risks and complications [21].

Looking at Figure 4, there is a large gray area for relatively unstable patients at medium procedure risks. Currently a clinician has to decide between the two main measurement modalities with their inherent shortcomings. However, in some cases, an optimal ABP monitoring would be a continuous and noninvasive methodology. Technologies like vascular unloading or tonometry are the main options nowadays, but they are often not available, since additional equipment is needed. Of course, the use of arterial catheters is indispensable if repetitive collection of arterial blood samples (in particular blood gas analyses) is necessary, e.g., in thoracic surgery or in surgery with high bleeding risk.

In practice it is also common that continuous ABP monitoring becomes unexpectedly necessary when the patient status suddenly changes, e.g., for trauma patients. Here, a clinician is in a classical dilemma to decide on the most appropriate BP monitoring approach.

Use-case scenarios for surrogate-based cNIBP include, but are not limited to:

- During diagnostic procedures such as computer tomography or magnetic resonance imaging.
- Critical phases in procedures, e.g., during induction of anesthesia.
- Cardio-vascular diagnostic procedures such as syncope diagnostic using active standing test or, in selected patients, head-up tilt table tests.
- Cardiovascular interventions without a direct need of arterial puncture (for example catheter ablation, device implantation).
- Ischemic stroke treatment, where an invasive BP monitoring is not recommended; still, close tracking of BP is imperative.

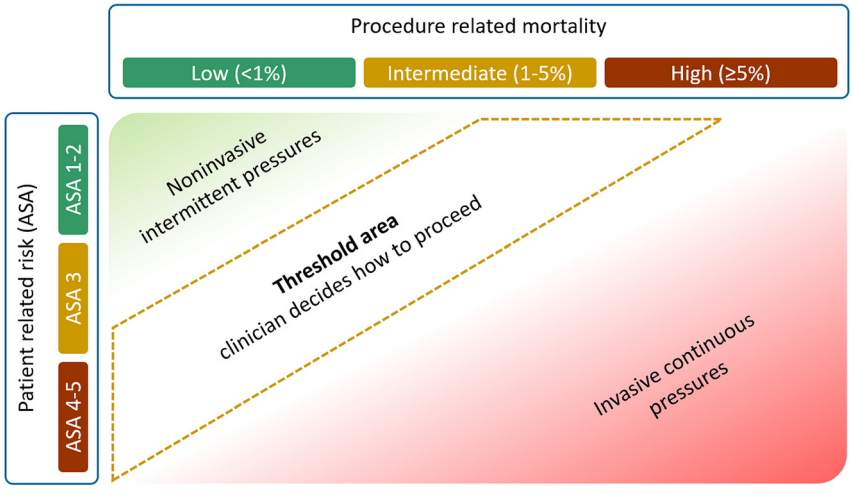

Figure 4: Chart showing the use of different BP monitoring techniques in relation to ASA score and procedure related mortality – the higher the risk, the more precise and invasive the measurement. Adapted after [18].

- In the general ward, where BP is generally measured only up to three times per day, during a nurse visit. Yet early warning scoring systems include SBP as a risk parameter.
- Diagnostic of sleep disorders by polysomnography to get undisturbed BP dynamics in relation to sleep stages and to arousal events [22].
- Daytime cardiac autonomic function testing for evaluation of therapy outcome in sleep-disordered breathing [23].
- In medical research, where continuous ABP is often highly demanded, but is not advised or even allowed due to benefit-risk assessments and ethical concerns.

Clinical decision support via arterial blood pressure monitoring

ABP monitoring is established in assessing the hemodynamic state of a patient, and is part of many clinical guidelines in the clinical decision process. Inappropriate ABP monitoring can have a major impact on patient safety and patient outcome. Underlying problems comprise the late detection of critically low or high BP, reporting a BP trajectory with insufficient sampling points or even reporting inaccurate BP. These issues are exemplified in more detail in Figure 5, where two different phases in patient SBP (black curve, invasively measured) can be easily observed. Until 17.00 h, there was a high variance of SBP, whereas afterwards SBP was almost constant. The red line indicates a reported SBP in case the measurement would have been taken non-invasively and intermittently at 15 min intervals. During the second phase, the agreement between continuous and intermittent measurement is high, making both of them viable options. However, during the first phase, the reported SBP does not represent the true underlying highly varying SBP.

Definition of a critical ABP change is highly dependent on many factors, including the monitoring context. Typically, changes below, e.g., the 5 ± 8 mmHg for oscillometric methods defined by the ISO 81060-2 norm are irrelevant, because they are within the error margin of the devices being validated in clinical trials. Another important factor is the response time for physiological changes, which a continuous monitoring system needs to be able to track, according to the upcoming ISO/Draft 81060-3. For example, hypo-perfusion caused by a hypotensive phase develops in a very short time. There are several definitions of critical events and critical BP deviations, summarized in Table 1. A percentage change related to the actual operating point can also be favorable vs. an absolute change in ABP. Typically, a minimum deviation of more than 20–30% from baseline is observed to intervene [24]. Hypotension is defined as SBP below 90 mmHg or MAP below 65 mmHg [2]. Recently the Depth-Duration-Index was proposed for patients in trauma care, where close tracking of critically BP is required [25]. The shock index combines HR and SBP for detection of a potential shock state. In the general ward, early warning scoring systems have been established, where SBP contributes to the assessment of a patient's status, focusing mainly on hypotensive phases [26].

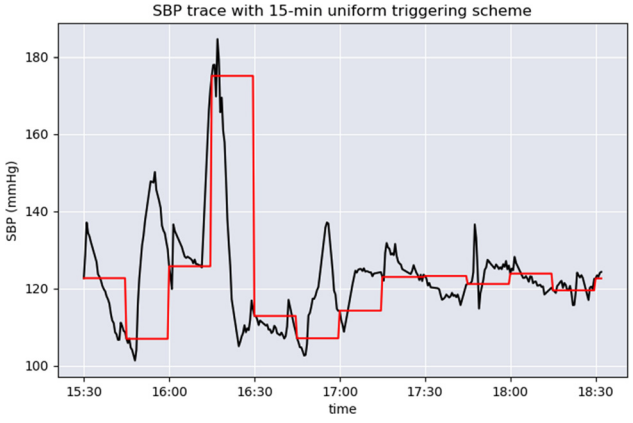

Figure 5: Illustration of missing possibly relevant blood pressure changes between intermittent measurements. The black line represents the continuous measurement. The red line indicates a reported SBP in case the measurement would have been taken non-invasively and intermittently at 15 min intervals.

Table 1: Clinical definitions of critical BP levels, changes and indices.

	Definition
General BP event [24]	10% or 20% change
Hypotension [2]	SBP < 90 mmHg or MAP<65 mmHg *for at least 4 min*
Sepsis [2]	SBP < baseline – {40 mmHg or 2*std(SBP)}
Orthostatic intolerance	SBP < baseline – 20 mmHg *within 3 min after posture change*
Shock index [27]	HeartRate/SBP > 0.9
Depth duration dose of hypotension [25]	$\int_{t_1}^{t_2}(90\,\text{mmHg} - SBP(t))dt$
National early warning scoring systems (EWS) [26]	SBP < 90 mmHg=3 91 … 100 mmHg=2 101 … 110 mmHg=1 111 … 210 mmHg=0 > 210 mmHg=3

A few examples show the importance of BP monitoring. A 2017 study of sedated patients during endoscopic procedures confirmed that conventional intermittent BP monitoring misses fast BP changes. MAP BP deviations between the continuous reference and the intermittent measurements appeared with a maximum increase of 30.8 ± 21.7% and a decrease of 22.4 ± 28.3 % (mean + std. dev.). cNIBP monitoring could be used to improve patient safety during such procedures [11]. The Depth-Duration-Dose (DDD) index has been shown to correlate with patient outcome in trauma patients due to prolonged hypo-perfusion of the brain caused by low SBP below 90 mmHg [25]. Here, a continuous BP monitoring technique would again significantly improve the current situation; however, only intermittent BP is available today.

Technical aspects of blood pressure monitoring

In order to gain acceptance by the medical community, an ABP monitoring method needs to fulfill certain basic requirements, listed below in no particular order:

- Accuracy in applicable settings, certified according to appropriate standards (i.e., how reliably well the ABP is tracked over time and range, e.g., during hemodynamic variation.)
- Minimum temporal resolution: continuous, quasi-continuous or intermittent
- Supplementary parameters, e.g., fully reconstructed BP waveforms, arterial compliance
- High sensitivity with low false alarm rates
- Consistency across patient populations and patient conditions
- Patient safety, e.g., low risk of infections and wrong clinical decisions
- Patient comfort, such as avoided tissue trauma due to high pressures
- Usability, suited for clinical workflows
- Cost effectiveness
- Remote monitoring and connectivity capabilities due to upcoming new use cases of telemedicine and wearable applications.

The distinction between continuous and intermittent monitoring can be subtle. Appropriate temporal resolution depends on the monitoring context and the patient BP variability. This requirement can also be expressed from an engineering perspective as upholding the Nyquist-Shannon sampling theorem. Sampling must occur with at least double the highest signal frequency of the observed underlying BP process. Sampling period and latency in the computation and displaying of the BP data should be therefore kept minimal.

Returning waveforms instead of intermittent numerical parameters only (SBP, DBP, MAP) can help with assessing the plausibility of the data, especially when and if the robustness of these automatically generated parameters is questionable. The ABP wave is often required to infer other parameters such as fluid status or CO. Furthermore, there is a need for isolating the effect of hydrostatic changes and develop appropriate compensation for the reported BP values.

Currently, patient comfort, application effort and measurement accuracy are not evenly matched. Arterial lines are highly invasive, but most accurate. The necessary cables and tubes can be disturbing during use. Because of patient compliance and safety, continuous ABP is not recorded during polysomnographic investigations, even though sleep-time BP is a better predictor of cardiovascular risk [28]. Instead, the employed cuff-based devices are obtrusive, especially in sleep research, by generating pressure and noise. Furthermore, by clamping off a certain body part, they influence the BP itself, e.g., during an arousal [12]. Vascular unloading techniques using finger cuffs are also inappropriate for application during long-term measurements. The devices are bulky, interfere with daily life activities and still impede blood flow to the measurement site.

All these constraints of the available measurement technologies ask for a novel, compliant and efficient ABP monitoring method.

Noninvasive blood pressure surrogates

Medical applications, opportunities and design choices of surrogate solutions

cNIBP measurements using BP surrogates for in-hospital and at-home use are a topic of active research. A wide variety of surrogate parameters, surrogate-use-strategies, sensor locations and combinations have been investigated and reported on in literature, though to date only a few systems have been commercialized [14, 29–32].

For practical applications, the underlying user requirements of the use-case scenario are key for system design and for the necessary performance. Important medical related choices are:

- Measuring systemic or pulmonic BP
- Measuring central or peripheral BP
- Estimation of SBP, DBP, and/or MAP value, or of the entire BP waveform
- Tracking the BP in absolute terms or relative to an initial state
- Tracking the BP quantitatively or detection of specific BP-related events

Further technical choices relate to the combination strategy of the BP surrogates with cuff-based NIBP measurements. The following scenarios can be envisioned:

(1) A conventional noninvasive cuff-based BP measurement is automatically triggered when use-case dependent significant BP changes are inferred from BP surrogates (cf. Figure 5). Only the cuff-based measurement results are shown to the user, but the surrogate is not.
(2) In-between conventional cuff-based NIBP measurements, continuous BP is inferred via the initialized BP surrogates and displayed to the user.
(3) Complete replacement of the cuff-based NIBP measurements, showing continuous SBP/MAP/DBP values to the user.
(4) Complete replacement of the cuff-based NIBP measurements, aiming to reconstruct the ABP waveform in detail.

Surrogate signals and sensors

Many approaches using various surrogate signals have been investigated. Sensing modalities comprise heart sound analysis (in particular to estimate pulmonary BP), ballisto-cardiography, ultrasound, electrocardiography, PPG, and interferometric methods (cf. Figure 6). For several of the sensing modalities, the sensor locations on the body can be chosen from a variety of positions (cf. Figure 7) [29–42]. Two examples of promising surrogates will now be described in more detail in order to illustrate the technical challenges inherent to their use.

Pulse transit time and pulse arrival time

Two of the most commonly investigated BP surrogates are the PTT and the closely related PAT. They can be derived from a variety of sensor signals, such as ECG, PPG, impedance cardiogram, and phonocardiogram, as shown in Figure 8 (left) [43]. Here, the sensor embodiments are small, lightweight and offer potentially comfortable quasi-continuous and noninvasive ABP measurements.

PTT represents the transit time of a pressure pulse propagating with the pulse wave velocity PWV through an arterial segment of length l

$$\mathrm{PTT} = \frac{l}{\mathrm{PWV}} \tag{1}$$

and it has a direct relation to BP as quantified by the Moens-Korteweg relation [43]

$$\mathrm{PWV} = \sqrt{\frac{E \cdot h}{\rho \cdot d}} \tag{2}$$

where h is the arterial wall thickness, d the arterial diameter, ρ the blood density, and E the elasticity module. The elasticity module is a function of the BP $E = f(\mathrm{BP})$. Experimental PWV and BP data [44], as well as a visualization of fitted approximation models is shown in Figure 8, right. A first exponential component and a second linear one are combined, and a constant offset is applied. Here it is clear

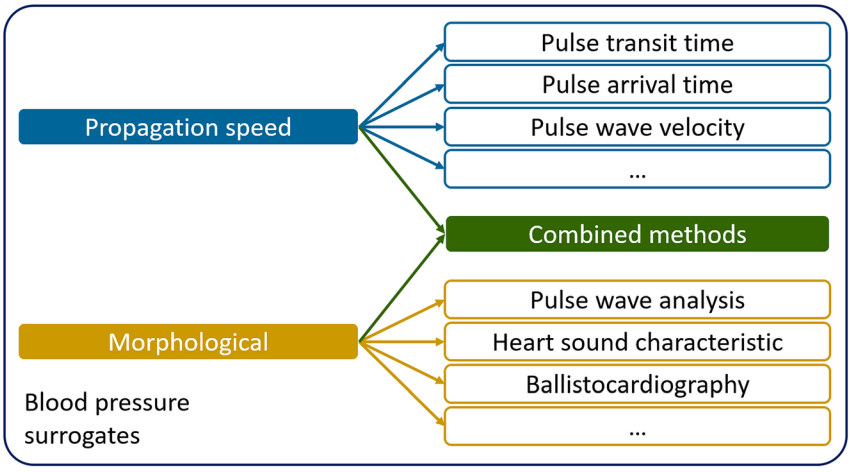

Figure 6: Non-exhaustive list of possible blood pressure surrogates.

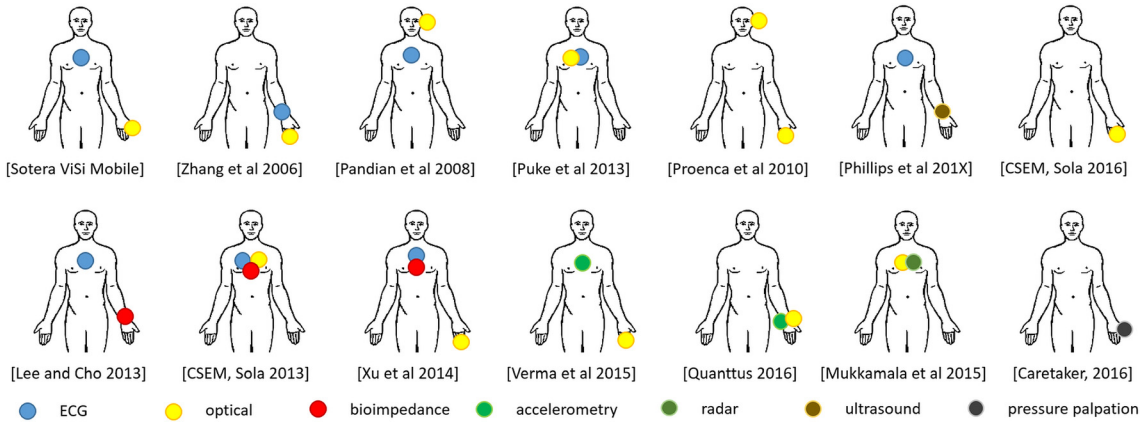

Figure 7: Non-exhaustive overview of different sensor modalities and placements employed for the acquisition of blood pressure surrogate signals.

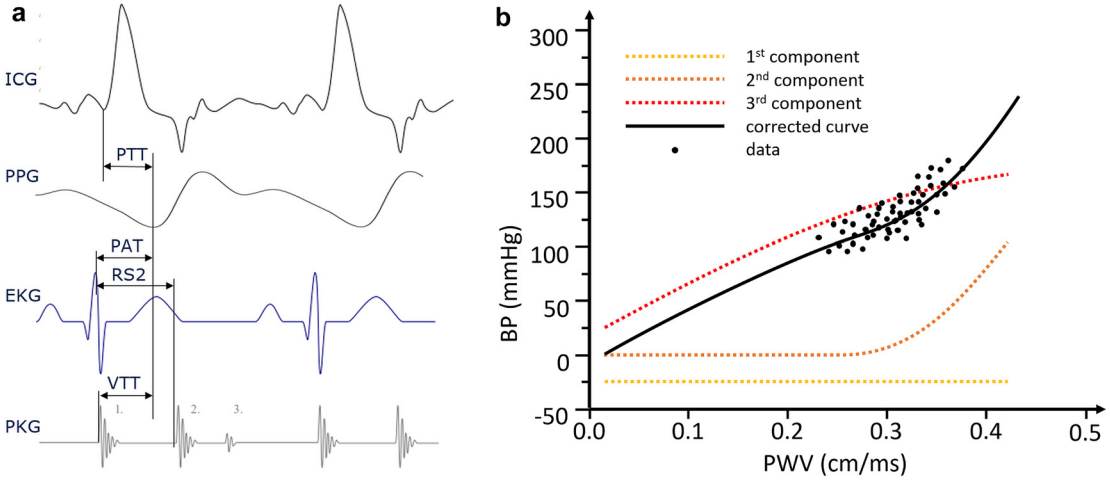

Figure 8: Left: Signals used for computing characteristic timings of the pulse wave, such as PTT and PAT, impedance cardiogram, ECG, PCG, vascular transit time, distance from R peak to second heart sound S2 (RS2)) [43]. Right: experimental PWV data and its proposed curve fit, based on [44].

that there are inherent limits to the achievable accuracy of surrogate-based BP technologies, especially when the models are extrapolated beyond the range of available data.

PAT is another well-known surrogate parameter, which is closely linked to PTT. It is defined as the time interval between the peak of the R-wave of the ECG and the onset of a peripheral pulse signal. It has been intensively investigated not only as surrogate of BP but also as a measure for vessel stiffness [45]. PAT is the sum of the pre-ejection period (PEP) and PTT. While PTT has a strong direct relation to ABP, PEP is a varying additive delay sensitive to stress, emotion and physical effort [46, 47].

A simplified mathematical model can be employed in a data driven fashion as an alternative to physically grounded models for surrogate BP, such as the Moens-Korteweg equation above. Some proposed equations for determining BP from the PTT are shown exemplarily in Table 2. These can range from simple linear models to polynomial, exponential and logarithmic ones, and are listed here for illustrative purposes. Generally, the more complex nonlinear models outperform linear ones. However, more complex models tend to overfitting if not enough data is available for training purposes.

Because the Moens-Korteweg relation includes vessel properties like arterial stiffness and geometry, as well as hydrostatic effects, it is subject-specific, likely time varying

Table 2: Equations used for modeling the PTT into a blood pressure estimate. Systolic, mean and diastolic BP require different models.

$\mathrm{SBP} = A - B*\Delta\mathrm{PTT}$
$\mathrm{SBP} = A + B*\ln(\mathrm{PTT})$
$\mathrm{BP} = A + B*\mathrm{PTT}^{-2}$
$\mathrm{BP} = A*\ln(B*\mathrm{PTT}^{-2} - 1)$
$\mathrm{DBP} = A*\exp(-B*\mathrm{PTT})$
$\mathrm{DBP} = \frac{A}{3} + \frac{2B}{3} + C*\ln(D*\mathrm{PTT}^{-1}) - \frac{A-B}{3}*C*\mathrm{PTT}^{-2}$
$\mathrm{SBP} = \mathrm{DBP} + (A - B)*C*\mathrm{PTT}^{-2}$

and context sensitive. Therefore, a (cyclic re-) initialization procedure is needed in practice to ensure consistent BP estimation behavior [48]. It should be noted that data driven models (cf. Table 2) also have, in principle, subject and time dependent coefficients requiring reinitialization.

Pulse wave analysis and pulse decomposition analysis

PWA, also known as pulse contour analysis, refers to a class of techniques which aim to estimate the transfer function from a noninvasively acquired pulse waveform signal to the ABP waveform, e.g., from PPG or laser spectroscopy. A particular approach is the pulse decomposition analysis, which has been applied for BP inference with some success [29, 49].

The sensed pulse wave is assumed to contain the superposition of reflections of the pulse generated by the incipient systolic ejection (cf. Figure 9). These occur at big branches in the arterial tree, analogous to the impedance changes in electrical wave propagation models on wires. In turn, the BP modulates the propagation speed of these reflected waves. Consequently, the reflections arrive at the sensor with different amplitudes and PTTs, modulating the acquired pulse signals. The PDA method estimates the BP from the amplitude and time relationship thereof.

In practice, however, the reliable detection of pulse signal characteristics is often difficult, since they are dependent on sensor contact pressure, respiration and other environmental conditions [50]. This makes a robust BP estimation problematic. Nonetheless, these drawbacks are counterbalanced by the fact that only a single sensor is necessary for BP inference with this approach.

Initialization of BP surrogates

As discussed above, the estimation of the time-varying blood pressure $\mathrm{BP}(t)$ of a patient from a surrogate signal $S(t)$ is enabled by a functional mapping $f(\bullet)$

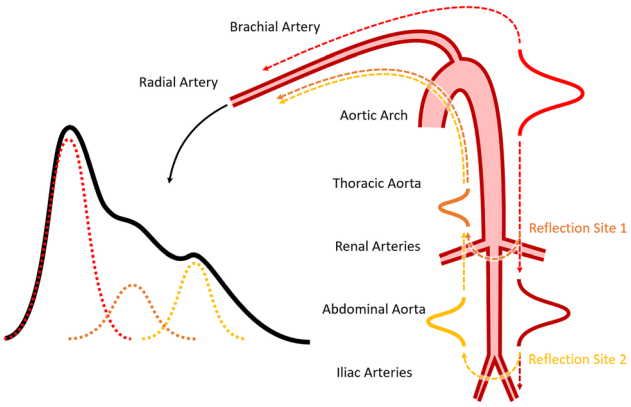

Figure 9: The form of the pulse wave is related to a superposition of reflections, amplitude and phase modulated by the ABP. Analyzing the pulse wave shape therefore allows estimating the BP, based on [49].

$$\mathrm{BP}(t) = f(S(t), \theta), \tag{3}$$

where the mapping $f(\bullet)$ is characterized by one or more parameters θ. As an example, one may consider a linear relationship.

$$f(S(t), \theta) = \text{sensitivity} \cdot S(t) + \text{offset}, \tag{4}$$

where the parameter set θ consists of two scalars $\{\text{sensitivity}, \text{offset}\}$. However, more complex, non-linear, higher-order mappings are possible (cf. Table 2).

Depending on the surrogate type and the mapping model, the parameters θ can be either fixed, population-based, patient-specific, or a combination of those. For example, a population-based parameter could be related to the age group, or gender of the patient.

The initial determination of the parameters is called "initialization". The initialization process is also often referred to as "calibration" in the literature. More correctly, however, calibration is the comparison of the device output to a calibration standard, usually one emitted by a national metrological body. Since the correct parameter value may change over time, e.g., because of medication or hemodynamic status changes of the patient, more or less frequent adjustments of one or more parameters may be required. These adjustments are referred to as "(re-)initialization." They can occur periodically at fixed time intervals, or they may be triggered by a change-point detection of one or more tracked auxiliary parameters, e.g., HR, body posture, etc.

The knowledge of fixed and population-based parameters for particular patient groups generally originates from preceding off-line analyses of sufficiently large data sets, and it is stored in the surrogate BP device. In practice, the medical staff then enters the particular patient's

personal data and the correct initialization parameters are automatically retrieved. While some implementations of surrogate-based methods exist which employ only constant and/or population-based parameters, it is generally observed that such devices mostly produce trustworthy BP trends rather than correct absolute values. At times even implausible values can appear in the estimate [15].

The determination of patient-specific parameters, on the other hand, is much more challenging, since they must be obtained on-site from the patient, possibly even repeatedly for multiple reinitializations. In practice, it is therefore desired that the reinitialization procedures should be minimally invasive, require little to no patient cooperation, do not pose a significant extra workload for the medical staff, and yield values that are valid indefinitely. The latter aspect is strongly linked to the fundamental stability properties of the chosen surrogate type. After all, it is undesirable that overly frequent reinitializations undermine the advantages of using the unobtrusive surrogate.

A practical option to determine an offset parameter of a mapping $f(\bullet)$ is the conventional oscillometric BP measurement with an air-filled cuff. This measurement can be fully automated and, if it can be ensured that the cuff remains applied to the patient, e.g., in an ICU or OR setting, it is even suitable for automated periodic reinitializations.

Clearly, the accuracy of the BP oscillometry sets inherent bounds on the achievable accuracy from the BP surrogate. Therefore, it is imperative that the oscillometric procedure is implemented sufficiently robustly, and that it automatically recognizes and handles failed or inaccurate measurements, e.g., due to motion artifacts.

The determination of the sensitivity parameters of $f(\bullet)$ is more challenging than that of the offset, as illustrated in Figure 10. To derive the sensitivity parameter robustly, it is beneficial to observe a suitably large number of surrogate- and blood-pressure data points that span a sizeable pressure range. Here, the main practical problem is that large intrinsic BP swings may not be naturally present in the patient during the times of initialization. A further problem is the accurate measurement of the patient's BP at those multiple time points. One solution are multiple oscillometric measurements, which negatively influence patient comfort and are themselves not free from errors.

The problem of safely inducing systemic BP changes in a patient on demand for the purpose of surrogate calibration and initialization is still an active area of research. A multitude of procedures has been used to this end, mainly in research settings. Some examples are the application of vasoactive substances such as Nitroglycerin, the tilt table test, the Valsalva maneuver, posture changes, physical and mental exercise, paced breathing and the application of lower body negative pressure, to name a few. Other technical approaches [51, 52] aim to employ local BP perturbations, for instance at the upper arm using an air cuff, but they are specific to a particular surrogate type and sensor location, e.g., PAT and PPG at the finger.

To date it is still an open question to what extent many of these methods truly only affect the BP and do not have side effects on other vital parameters, which could obstruct the surrogate initialization.

Performance visualization and metrics

The following list gives an overview of common error metrics. However, it is non-exhaustive.

– **Mean and standard deviation** are the most straightforward used metrics, exemplified here by the accuracy of sphygmomanometric devices: 5 ± 8 mmHg. The 5 mmHg offset are the difference between the averages of the reference and estimation, and the 8 mmHg

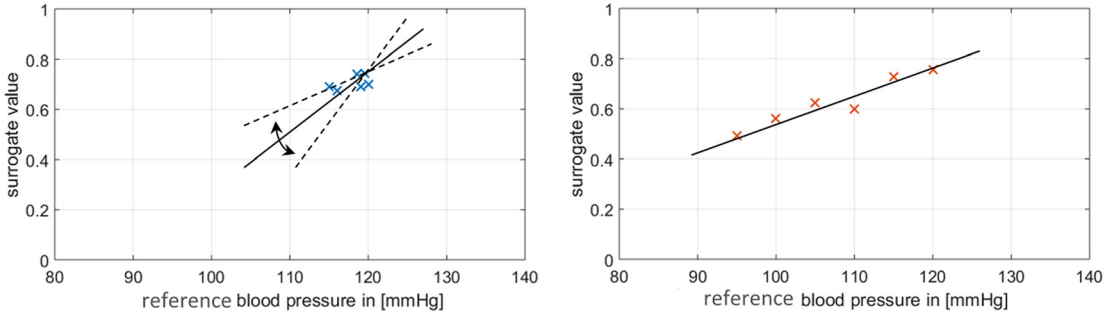

Figure 10: The robust initialization and (re-)calibration of the sensitivity parameter for a surrogate requires a sufficiently large range of surrogate and blood pressure values. A small range of blood pressure values (left) leads to a less certain estimate of the sensitivity than a large range of values (right).

represent the standard deviation of that error. This offers a compact, tangible and easily interpretable result, at the cost of no information about the used operation point.

- **Root-mean-square error** or **deviation (RMSE/RMSD)** is a basic metric used in most model performance evaluations and is computed as the square root of the average squared error residuals. A value of zero indicates a perfect fit, however, non-zero values (as is always the case) are scale dependent, and no normalization is universally accepted. Additionally, because the RMS computed from squared error residuals, it is sensitive to outliers.
- **Bland-Altman plots** were popularized by J. M. Bland and D. G. Altman (1986 and 1999) and are frequently employed for medical data visualization. They are a type of scatter plot which displays the differences between the points in two data sets against the mean value of the same points. Typically, for BP data, the differences are plotted against the "gold standard" and not against the mean of both sets. This representation makes trends and offsets in the data quickly visible – to aid with the interpretability, horizontal lines indicate the mean difference and the agreement limits of the differences (±1.96 SD).
- **Four quadrant plots** are, analogously to the Bland-Altman visualization, scatter plots. Measured data is plotted against the reference data, creating a cloud of points which span one or more of the four quadrants. It is therefore most suited for offset-free data. Usually a line can be interpolated through the point cloud, indicating the main correlation relationship. Bounds indicating relevant deviation thresholds can be superimposed as well. With this kind of plot one can quickly see data trends and the correlation sign, assess the (non-) linearity of the correlation and the divergence.
- **Correlation coefficients**, such as those proposed by Spearman, Kendall or Pearson, indicate how well the estimated values align with and track the reference data. They are of great use when performing trend estimation, without particular interest in the absolute values. These coefficients differ from each other through the type of relation they allow between the two datasets, be it strictly linear or a more relaxed monotonic one. The p-value is always computed along with these correlation coefficients in order to gauge their statistical significance.
- **Median** or **Mean Absolute Percent Deviation (MAPD)** is employed to describe the prediction accuracy of a model, in percentage form. It is particularly intuitive, which is why it is often used. Some of its drawbacks include the fact that it cannot be used for zero values and is biased toward choosing models which underestimate the target value. The Mean Arctangent Absolute Percentage Error (MAAPE) is a possible yet more complex solution to these problems.

Regulations

Commercial widespread use of any technology demands agreements of minimally required performance in well-defined test procedures via standardization. Otherwise, the acceptance of new technologies by the medical community is impaired by the lack of knowledge about basic performance including potential harm in patient safety. For the established BP monitoring technologies, such standardization has been in place for many decades. An overview of the ISO standards for non-invasive sphygmomanometers is shown in Figure 11, where for non-automated (ISO 81060-1) and automated/intermittent measurements (ISO 810601-2) the standards have been defined, accepted and implemented by the medical industry. However, for the

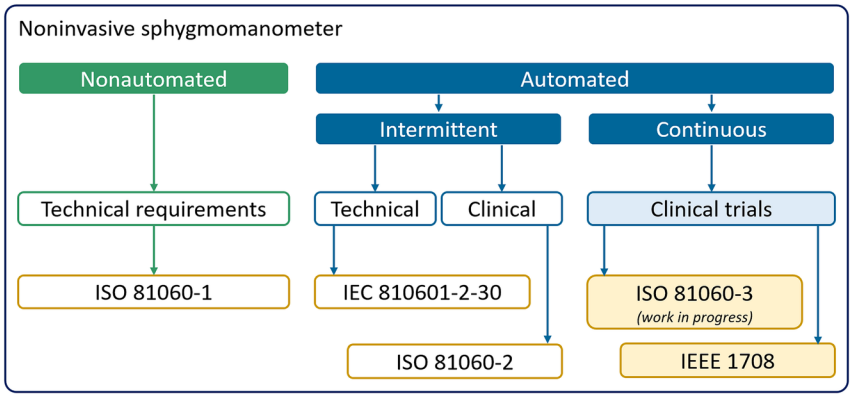

Figure 11: Standards for blood pressure measurements of various device classes.

continuous measurements including BP inferences from surrogate measures as covered in this paper, there is ongoing effort in the definition of a new standard as ISO 81060-3; a published first draft should be available in 2020. In an earlier attempt by the IEEE, the standard 1708 was developed, which hasn't found widespread acceptance yet.

Given the preliminary status of ISO 81060-3, only the basic concept is mentioned, where essentially two different device performance classes have been defined, each of them with precisely specified tolerances:

- Type 1
  - Displays absolute P values
  - Does track BP changes
- Type 2
  - Does track BP changes

It is expected that the standard will be published in 2021 or 2022.

Opportunities for future research and recommendations

ABP is one of the most prominent ubiquitous parameters in patient monitoring, and is key in many clinical decisions. CO and the perfusion index are also clinical markers, which, depending on context, are equally representative of organ perfusion and general cardiovascular state [53]. When acquiring surrogate cardiovascular parameters, the target parameter estimated therewith should be based on clinical relevance/need and achievable estimation quality, e.g., should a highly relevant parameter be estimated with low accuracy, or a less relevant one with high accuracy. Given that ABP is a well-researched and universally accepted diagnostic tool, efforts toward cNIBP acquisition are well substantiated.

The accuracy of surrogate-based cNIBP estimation methods has not yet been conclusively proven, with some studies suggesting that especially systolic BP tracking is problematic [14]. One of the reasons are the difficult and oftentimes inconsistent validation, since no unified procedures are in place, as well as the inconsistent reporting of bias and error in some studies [15]. Certifications are achieved by regulations not meant for such devices, such as *"AAMI SP10: 2002 Manual, electronic, or automated sphygmomanometers"* or the already withdrawn *"ISO 81060-2:2009 Non-invasive sphygmomanometers – Part 2: Clinical validation of automated measurement type"* [27]. Developers and manufacturers should consistently disclose their internal validation methods in detail, thus assuring comparability and reproducibility of results. State of the art results still suffer from high variance in estimating correlations to the reference. Many studies typically include less than 50 patients in a coherent cohort, which is reasonable for basic feasibility research but not sufficient and meaningful for conclusions on real-life performance. For comparison, standards for oscillometric methods require 85 patients (ISO 81060-2). A good spread of subjects and measured parameters is essential for validation, which requires the inclusion of different demographics covering realistic measurement scenarios for the intended use cases. Furthermore, the operating point (e.g., the subject is at rest or mobile) for which most devices are calibrated is often not disclosed clearly. As a result, unknowingly using the devices outside of their intended operating parameters yields implausible results. Stricter specifications of operating points for the envisioned use scenarios are advisable.

Another important aspect is the lack of a satisfactory physiological justification behind many of the proposed models, i.e., the inclusion of the parameters assumed by the model and their mathematical relations are not clearly motivated. Assumptions, which are often made to simplify the actual physiological complexity, are hardly justified, such as the use of constants in the Moens-Korteweg equation. Whilst the impact of arterial stiffness changes might be handled in principle by initialization procedures, the ratio of arterial diameter to wall thickness along the arterial tree is typically assumed constant. Most of the employed models rely heavily on empirical findings and correlations, which raises doubt about their broader applicability. However, the well-established oscillometric method is also empirically founded. It is a broadly accepted technique based on long-term experience of its clinical value. Similar arguments can be expected for surrogated-based NIBP, which need to be underpinned by large samples for clinical validation in the future.

The requirement for these larger sample sizes can be further supported by the need to avoid misleadingly high correlations of the surrogate features to the estimated BP. Confounding variables are problematic, as they are hard to control and compensate for. A typical example is a high correlation of HR with PAT during physical exercises. Also, the signal quality from the required sensors often depends on measurement boundary conditions (sensor contact pressure, hydrostatic pressures, body location), which is difficult to control in many scenarios. This can make implementations complex and hardly viable for practical use. In addition, more insights are needed in the interactions of surrogate parameters with variables such as movement, ventilation, body temperature, psychological state, and medications, which is a topic of further research.

Estimations for fringe ABP regions (i.e., unusually high or low BP compared to the initiation/calibration sample values)

are expected to be prone to large errors, as extrapolations for those regions are based on insufficient, if any, data points. Furthermore, the basic assumptions of the used model vs. the true underlying physical situation could not be valid, because its simplifications may not be justified anymore. Here, safe and reliable models including test methods need to be researched and developed.

For applications in high acuity settings, a major challenge for peripherally attached sensors is the case of centralization, as it can be observed e.g., in shock states. Also, local vasomotor activity has a significant impact on measurement accuracy. Measuring near drug injection areas has also proven problematic. Whether or not the pick-up sensors for the surrogates can be realistically moved to a less interference-prone location is unclear. In general, the sensor locations have significant impact on the overall measurement performance.

The innovation in the field of continuous unobtrusive BP measurements has been driven by three main stakeholders, which can be identified as academic research institutions, healthcare providers, and industry. Each of the parties offers unique capabilities. Universities to date largely engage in frontline research and concept development but often lack the means to conduct large-scale medical validation trials and are limited to relatively small-sized studies. Healthcare providers, on the other hand, have access to large amounts of data and could be able to address the existing need for sizable, well-acquired, annotated, and curated datasets, which are suitable even for modern data-driven Artificial Intelligence methods. Lastly, the industry has the capability to create commercially viable implementations, which meet applicable standards. These parties need to cooperate more closely to align efforts.

An essential aspect to consider in the development is that any solution needs to fit into the clinical workflow, does not add issues in alarm management and provides useful additional information on the patient condition beyond NIBP. These solutions need to improve clinical decisions by offering clear and tangible clinical benefits. A key learning from this workshop was that the progress in the field historically appears to be predominantly caused by a technology push, rather than a pull through medical needs. However, a holistic application-driven approach, which considers both technology and medical use case, is the necessary pre-condition for successful innovations.

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