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**METHODS AND SYSTEMS FOR THE PULSE WAVE
VELOCITY MEASUREMENT IN A NOVEL VARIABLE
STIFFNESS ARTERIAL SIMULATOR**

Dottorando:

Federico Filippi

firma

Docente Guida/Tutor:

Prof. Salvatore Andrea Sciuto,

firma

Co-tutor:

Prof. Andrea Scorza

firma

Coordinatore:

Prof.ssa Ornella Chiavola

firma

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Abstract

Accurate assessment of Pulse Wave Velocity (PWV) is clinically relevant because it provides independent prognostic information for cardiovascular risk stratification. However, non-invasive PWV devices frequently exhibit limited accuracy and return results that are not directly comparable, highlighting the need for a metrological reference system. In this context, a prototype of a novel variable-stiffness arterial simulator has been proposed. Its operating principle is innovative and, to the best of our knowledge, it is the first of its kind to be presented in the international landscape. Once fully developed, it could support performance verification and calibration of both established and emerging technologies.

This research project aims to contribute to consolidating the operation of the novel variable-stiffness arterial simulator by developing and testing technical solutions for measuring PWV within the simulator.

The work is organized around two objectives. First, an optimal PWV estimation method was identified among three candidate approaches: full-wave cross-correlation, a wavelet-based method, and a model-based method. These approaches were applied to both simulated and experimental waveforms acquired from the simulator through structured *in silico* and *in vitro* protocols to evaluate their performance in terms of accuracy and precision.

Second, the most suitable solution for sensing pulse-wave transit within the arterial simulator was investigated by developing and metrologically characterizing innovative sensing approaches. Two options were considered: conductive-ink-based stretchable sensors and an FBG-based sensor. Tensile tests under static and dynamic loading were conducted to verify whether these solutions met the requirements imposed by the application.

Overall, the thesis identifies full-wave cross-correlation as the most promising PWV estimation approach for the simulator and conductive-ink-based sensing as the most promising transduction strategy, thereby establishing a foundation for a future reference platform for PWV device verification and calibration.

Aim of the project

This research project aims to develop and validate technical solutions for measuring Pulse Wave Velocity (PWV) within a novel variable-stiffness arterial simulator, with the long-term goal of contributing to a metrological reference platform for verifying functionality, performance, and calibration of PWV measurement devices used in clinical practice.

The scientific relevance of this objective is grounded in the fact that arterial stiffness is an independent prognostic biomarker for cardiovascular risk, and that PWV is widely regarded as the non-invasive gold-standard index for its assessment.

Despite this importance, accurate PWV measurement remains challenging: high accuracy is typically achievable only invasively, whereas non-invasive approaches often provide insufficient accuracy and precision and yield results that are not directly comparable across devices, motivating the need for controlled reference systems to support systematic performance assessment and calibration.

Within this framework, the project specifically targets to contribute to the consolidation of a simulator whose operating principle is, to the best of current knowledge, the first reported implementation capable of modulating arterial-surrogate stiffness by controlling transmural pressure, thereby enabling controlled PWV variation across a relevant range.

To make this platform metrologically meaningful, the thesis pursues two tightly coupled aims: (i) identify and validate a PWV estimation method suitable for the simulator's distinctive waveforms by testing consolidated literature approaches while explicitly accounting for experimental phenomena such as reflections, noise, and undersampling; and (ii) develop a dedicated sensing solution to detect pulse-wave transit within the surrogate, by adapting state-of-the-art biomedical strain-sensing technologies to the simulator's geometric and mechanical constraints and characterizing them from a metrological standpoint.

1) Introduction

The study of the physiological mechanisms underlying cardiovascular diseases (CVDs) has attracted sustained and growing interest within the international scientific community. This attention is well justified by reports issued by the World Health Organization, which continue to rank cardiovascular diseases among the leading causes of death worldwide [1]. In particular, an estimated 19.8 million deaths were attributed to CVDs in 2022 (approximately 32% of all global deaths), with more than 85% attributable to myocardial infarction and stroke. These figures strongly motivate the development and refinement of technologies enabling earlier diagnosis and more effective clinical management of cardiovascular conditions.

Within current biomedical practice, arterial stiffness is widely recognized as an independent cardiovascular risk factor and is therefore monitored as a predictive marker in individuals considered at risk. As discussed in Section 1.1, in clinical settings arterial stiffness is commonly assessed through the measurement of pulse wave velocity (PWV), which is currently regarded as the gold-standard index for this purpose [2]. PWV is defined as the propagation speed of the pressure wave generated by the cardiac cycle along the arterial tree.

Despite its clinical relevance, accurately measuring PWV remains challenging. In the current technical-scientific landscape, high-accuracy PWV estimation is generally achievable only through invasive approaches [3]. These methods entail substantial practical limitations, such as the need for experienced operators, longer procedure times, and higher patient-related risks, as well as increased discomfort. Conversely, as will be discussed in Sections 1.1 and 1.2, the most established non-invasive methods often fail to guarantee accuracy and precision levels sufficient to make PWV assessment fully autonomous for diagnostic purposes. As a consequence, PWV-based evaluations are frequently complemented by additional examinations to confirm the presence or severity of disease [2].

In this context, there is a clear need both (a) to systematically assess the performance of existing PWV measurement devices and (b) to establish reliable reference systems for the calibration and validation of emerging solutions intended for clinical use. Improvements in PWV measurement techniques may open new diagnostic and therapeutic perspectives, for example by supporting a more appropriate personalization of treatment strategies.

Performance assessment and calibration can be carried out using dedicated experimental setups (phantoms) designed to emulate blood vessels with controlled geometric and mechanical properties. Arterial simulators are particularly valuable tools in this regard. As described in Section 1.3, they are currently employed in a wide range of biomedical applications because they can reproduce key haemodynamic mechanisms of the cardiovascular system while isolating the phenomena of interest from confounding

physiological variability. By enabling selected parameters to be varied while others are kept constant, arterial simulators provide a controlled and highly reproducible environment for measurements that would otherwise be affected by substantial fluctuations in vivo.

To address the need for a reference device for PWV measurement systems, a prototype variable-stiffness arterial simulator has been proposed. As detailed in Section 2, its operating principle is novel and, to the best of our knowledge, represents the first implementation of its kind reported in the international literature. The simulator modulates the stiffness of an arterial surrogate by varying the transmural pressure applied across its wall. Once fully developed and validated, this system has the potential to serve as a reference platform for the assessment and calibration of PWV measurement technologies.

The work presented in this thesis was motivated by the need to consolidate the functionality and effectiveness of this simulator and is organized around two main objectives.

The first objective is the identification of a suitable PWV measurement method for waveforms generated within the arterial simulator. This investigation is both necessary and innovative. Numerous PWV estimation methods have been proposed in the literature, each based on different principles and exhibiting performance that depends on operating conditions. Given the simulator's unique and novel operating mechanism, it is essential to evaluate the accuracy and precision of the most promising methods when applied to simulator-generated waveforms, while accounting for real phenomena characteristic of the specific experimental apparatus. The criteria used to select the candidate methods are explained in Section 2 and the procedures adopted for their evaluation are described in Section 3. The corresponding results and the comparative analysis leading to the identification of the most suitable approach are presented in Section 5.

The second objective is the development of a sensor capable of detecting the transit of the pressure wave within the arterial surrogate. This component is essential for the maturity of the overall application and is also original within the international landscape. The simulator's distinctive geometric and mechanical characteristics require ad hoc sensing solutions. Accordingly, this thesis investigates technologies that are currently at the forefront of biomedical and wearable sensing research, adapting and validating them for the first time on the specific hardware of the experimental setup. The aim is to identify a solution that satisfies the application requirements in terms of measurement range (i.e., maximum detectable strain) and resolution (i.e., minimum distinguishable strain), expressed in Section 2. The criteria adopted to select the most promising technologies, as well as the design, development, and testing procedures, are described in Section 4. The resulting performance assessment and comparison of the proposed solutions are reported in Section 5.

Finally, Section 6 summarizes the achieved outcomes, the contribution of this research to the international state of the art, and the future directions enabled by the results obtained.

Overall, this thesis represents a step forward in the development and refinement of instrumentation relevant to the diagnosis of cardiovascular diseases, and it provides a solid basis for further investigations into the technical aspects required to validate both established and emerging PWV measurement technologies.

1.1) The importance of PWV in the scientific and clinical context

Arterial stiffness is a hemodynamic parameter that reflects the loss of elasticity and distensibility of large arteries [4]. The stiffening of central arteries depends on numerous risk factors. This process is intrinsically associated with aging [5], [6], [7], [8], sex [9], [10], [11], family history and genetic predisposition [12], [13], [14] and ethnicity [15], [16], [17], [18]. Moreover, it can be influenced by behavioral factors such as a sedentary lifestyle [19], [20], [21], excessive alcohol consumption and smoking [22], [23], [24], [25], unhealthy diets [26], [27], [28], psychological stress and insufficient rest [29], [30], [31], [32]. In addition, it is accelerated by several clinical conditions, including hypertension [8], [33], [34], diabetes mellitus [35], [36], and atherosclerosis [37], [38]. All these elements contribute to vascular mechanisms such as the imbalance between elastin and collagen and phenotypic changes in vascular smooth muscle cells, which ultimately lead to arterial wall stiffening [39], [40]. Physiologically, an increase in arterial wall stiffness leads to a more rapid propagation of the pressure wave (Forward Pressure Wave - fPW) generated by the contraction of the left ventricle [41] and to an earlier return of the backward pressure wave (backward Pressure Wave - bPW) generated in proximity to discontinuities in the arterial tree [42]. These hemodynamic alterations have profound consequences [43], [44], including an increase in central systolic pressure and in left ventricular afterload, a reduction in coronary perfusion during diastole and the transmission of pulsatile flow to cerebral and renal microcirculations [33]. Such effects promote the arising of cardiovascular diseases (CVDs), including ischemia, stroke and myocardial infarction [45]. A schematic overview illustrating the abovementioned cause-effect pathway linking cardiovascular risk factors to arterial stiffness and subsequent cardiovascular diseases is shown in Fig. 1.1.

For this reason, the clinical relevance of arterial stiffness is widely recognized and remains an active area of scientific investigation. Its assessment is recommended by the guidelines of the European Society of Cardiology (ESC) for stratifying patients according to their probability of arising cardiovascular events in a given time horizon to tailor prevention and therapy [46]. Arterial stiffness is acknowledged as an independent prognostic

biomarker. It is also recommended by the European Society of Hypertension (ESH) as a tool for helping to identify subclinical organ damage in hypertensive patients [47].

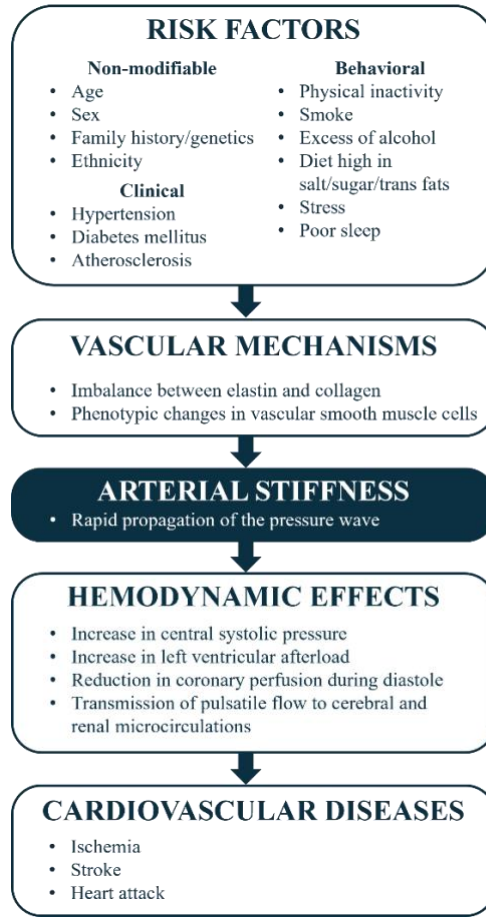


Figure 1.1. Cause-effect pathway linking cardiovascular risk factors to arterial stiffness and subsequent cardiovascular diseases.

As previously mentioned, among the various methods available for assessing arterial stiffness, the measurement of the Pulse Wave Velocity (PWV) is considered the non-invasive gold standard [48], [49], [50], [2], [51]. PWV is defined as the speed at which the pressure wave, generated by the heartbeat, propagates along the arterial tree [52]. It is considered the reference index for assessing arterial stiffness, as it is directly linked to the elasticity of the vascular walls [53]: healthy, elastic vessels slow down the wave's propagation, resulting in a lower PWV; conversely, stiffer, less compliant vessels conduct the wave more rapidly, leading to a higher PWV. The relationship between the propagation velocity of the pressure wave and the stiffness of the vessel through which it travels has been known for more than a century. A landmark contribution is represented by the work of Moens and Korteweg [54], [55], who in 1878 independently derived the following equation, which is still regarded as a fundamental reference:

$$PWV = \sqrt{\frac{E \cdot t}{\rho \cdot D}} \quad (1.1)$$

in which the PWV is related to the mechanical properties of the vessel, such as the elastic modulus E , wall thickness t , and diameter D , as well as to the properties of the internal fluid, namely its density ρ . Another step forward was made in 1922, when Bramwell and Hill conducted the first experiments to investigate the behavior of PWV in the human body. Their laboratory studies, first on isolated arteries [56] and then on living subjects [57], led to a reinterpretation of (1.1) from a medical and simplified standpoint, given that in physiological conditions the mechanical properties of the arterial wall are neither constant nor readily known:

$$PWV = \sqrt{\frac{A}{\rho} \cdot \frac{dp}{dA}} = \sqrt{\frac{1}{\rho \cdot \chi}} \quad (1.2)$$

where A is the cross-sectional area of the blood vessel and p is the internal pressure. The term χ , referred to as *distensibility* [58], represents the ability of the vessel to deform in response to changes in pressure p .

In clinical practice, PWV is most commonly assessed by detecting the passage of the pressure wave at two distinct measurement sites. In this context, regional and local approaches can be distinguished. With regional approaches, the transit of the wave is measured over an extended arterial segment, providing a comprehensive overview of the stiffness of the arterial tree. Among the most widely used segments are the carotid-femoral pathway (cfPWV) [59], which represents the clinical gold standard for PWV assessment, the brachial-ankle segment (baPWV) [60] and the finger-toe segment (ftPWV) [61]. Local approaches, on the other hand, measure PWV within a single vessel or over a short arterial segment. This enables the estimation of localized arterial stiffness or the monitoring of vascular health in the presence of plaques, aneurysms, or other site-specific abnormalities. In this case, there are no universally preferred measurement sites, as they depend on the clinical application. Examples include the aorta [62] or the carotid artery [63].

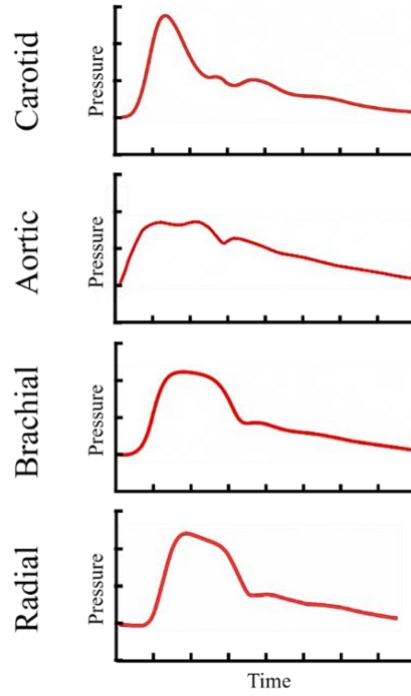


Figure 1.2. Examples of waveforms acquired at different sites of the arterial tree. Figure derived from [63].

Fig. 1.2 shows examples of pressure waveforms acquired at different sites along the arterial tree [64]. It can be observed that the waveform morphology varies depending on the measurement site. The pressure wave recorded in the aortic segment differs substantially from that recorded in the carotid segment; this is due to the distortions experienced by the latter because of energy losses and the influence of wave reflections. Conversely, waveforms obtained at closely spaced sites, such as the brachial and radial arteries, appear more similar to one another, as they are less affected by these phenomena. Regardless of the degree of distortion between the two waveforms under examination, and thus regardless of the chosen approach, the waveform detected earlier during acquisition is conventionally referred to as the proximal wave (prPW), whereas the waveform detected later is referred to as the distal wave (diPW). In any case, for every type of approach, the calculation of PWV is based on the following relation [65]:

$$PWV = \frac{l}{PTT} \quad (1.3)$$

where l represents the distance between the two measurement sites on the arterial tree, and PTT (Pulse Transit Time) is the time taken by the pulse wave to cover that distance. Both quantities in (1.3) introduce sources of uncertainty that, as mentioned previously, make the accurate and precise determination of PWV challenging for the instruments currently used for this purpose in clinical practice. The quantity l is generally measured directly on the patient using a measuring tape. Typically, this value is multiplied by a correction coefficient

that accounts for factors such as the overestimation introduced by the superficial body path (e.g., carotid-femoral distance $\times 0.8$) [66]. An alternative approach is the subtraction method [67], in which the distances from each measurement site to a common anatomical reference are measured and then subtracted (e.g., suprasternal notch-femoral and suprasternal notch-carotid distances). Both methods have been validated using imaging techniques such as Magnetic Resonance Imaging (MRI) [68] and are widely accepted in clinical practice [59]. Some authors have proposed estimating l through mathematical formulas that incorporate patient height [69]. These formulas are also used, but only in specific contexts (e.g., in Asia, where they have been standardized [60]); however, they may overestimate the path length because of variability in physique [70] and they do not replace the previously described methods [71].

1.2) Methods for Pulse Transit Time estimation

Estimating PTT represents another significant challenge. Unfortunately, identifying the time gap is not a straightforward task and involves several difficulties. As mentioned previously, the shape of the pulse wave changes during its propagation due to dispersion, damping, and the superposition of reflected waves traveling in the opposite direction. Furthermore, during the acquisition process, factors such as temporal resolution and noise have an impact. For this reason, numerous methods have been developed over time, progressively aiming to overcome these difficulties. Currently, the solutions proposed and investigated to compute PTT can be classified into three main categories based on their underlying operating principle:

- 1) *Point-Based Methods*: These approaches rely on identifying specific and morphologically defined characteristic points (fiducial points) on both waveforms, then calculating PTT as the time difference between them.
- 2) *Wave-Based Methods*: These approaches do not rely on a single point but use a portion or the entire morphology of the wave to determine the time delay that maximizes the similarity between the two considered signals.
- 3) *Model-based Methods*: These approaches employ mathematical models to describe the dynamic behavior of the cardiovascular system and extract PTT or PWV values as inherent parameters of the model.

Over the years, several studies have compared different methods for measuring PTT. The performance of PWV estimation methods varies substantially depending on the approach employed. Different algorithms, when applied to a dataset derived from a local PWV measurement rather than a regional PWV assessment, intrinsically yield different performances and outcomes. Similarly, the same algorithm, when applied to two different

datasets, will exhibit different performance. The choice of algorithm, therefore, is not a minor technical detail but a decision with direct implications for the diagnostic and prognostic validity of the arterial stiffness estimation. Existing studies often focus on comparing a limited number of methods on specific datasets or provide primarily descriptive analyses aimed at classifying algorithms, for example, according to their operating principle.

In the context above, in this paragraph a comparative and critical approach will be adopted to enable the identification, for each application, of the PTT estimation method with the best performance in terms of accuracy, precision, and reproducibility. The aim is to provide a structured synthesis of the advantages, limitations, and available quantitative evidence, thereby guiding the selection of the most appropriate method for PWV assessment. To achieve this, the main methods currently proposed in the literature for PTT measurement and used to estimate PWV and arterial stiffness are first described. In particular, their operating principles, advantages, and disadvantages are detailed (Sections 1.2.1, 1.2.2 and 1.2.3). Then, the studies that have compared these methods to evaluate their performance are highlighted, whether applied to simulated datasets based on mathematical models (*in silico*), arterial simulators (*in vitro*), or real patients (*in vivo*) (Section 1.2.4). Subsequently, the criteria for selecting the most appropriate method are examined in detail (Section 1.2.5). Finally, the main conclusions from the analysis are drawn (Section 1.2.6).

1.2.1 Point-based Methods

The operating principle of point-based methods relies on detecting a characteristic point, i.e., fiducial point, on the pressure waveform acquired at two different measurement sites and using it as a reference to compute the temporal shift between the two waveforms. The PTT is then calculated as the difference between the time instants at which these fiducial points are detected [72].

Point-based methods were historically the first to be used for PTT identification. One of the reasons underlying their early adoption is their operational simplicity, as they can generally be applied to analog recordings without the need for computerized algorithms. The earliest documented examples of their use for PTT estimation date back to the 1920s-1930s, when PWV began to be investigated in isolated arteries [56] and *in vivo* [57], [73]. These methods became more widely established during the second half of the 20th century with the development of electronic computing systems. Indeed, this technological advancement enabled the monitoring of PWV in additional anatomical regions. Some examples are the work of Borgainer et al. in 1967, who investigated pulmonary arteries [74] and along the entire arterial tree, as exemplified by the pivotal study of McDonald et al. in 1968 [75]. Electronic calculators also facilitated the large-scale application of these methods, as reported by Avolio et al., who in 1983 conducted a population-level assessment of PWV

as a function of aging in a northern Chinese urban community [76]. With technological progress (e.g., increased bandwidth and improved resolution and sensitivity of measurement instruments), the clear trade-off between implementation simplicity and methodological robustness has become evident. The simplest algorithms are also the most vulnerable to signal artifacts, both technical (noise) and physiological (wave reflections), which necessitate specific precautions such as accurate signal pre-processing [77]. These tangible limitations have driven the continuous refinement and evolution of these techniques. For example, Asmar et al. (1995) used the systolic peak combined with a portion of the rising slope as the temporal reference [78], whereas Gaddum et al. [79] considered the interval between the diastolic minimum and the peak of the systolic upstroke. The field has progressively shifted from simple “point detection” to more complex “feature detection” in an effort to isolate the waveform component that best preserves information on propagation speed, ultimately leading to the development of wave-based methods (Section III). It is worth noting that, despite the emergence of more advanced techniques, several point-based approaches have remained in use within medical devices and continue to be considered as reference standards in clinical practice [48], [65].

The localization of the PTT based on the identification of a characteristic point on the pressure waveform can be implemented through various methods. The main ones are described below, each with its own operating principle, advantages, and limitations.

Diastolic Minimum Method

The diastolic minimum method (also known as the *foot-to-foot* method) is among the most conceptually simple solutions. It identifies the foot of the wave as the point of minimum signal amplitude within each cardiac cycle, corresponding to the diastolic pressure. This point serves as the fiducial marker used to compute the PTT, which is therefore defined as the time delay between the feet detected on the pulse waves measured at two different sites along the arterial tree [80], [81], [82].

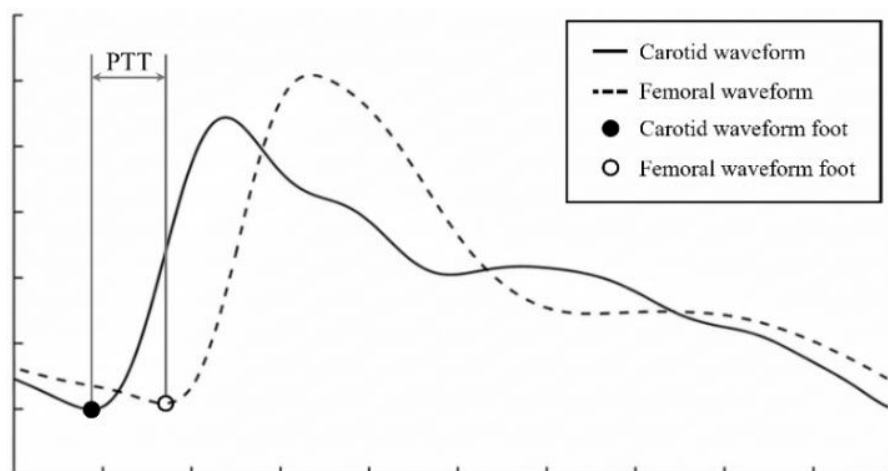


Figure 1.3. Diastolic minimum method applied to examples of carotid–femoral pulse waves. Figure inspired by [81].

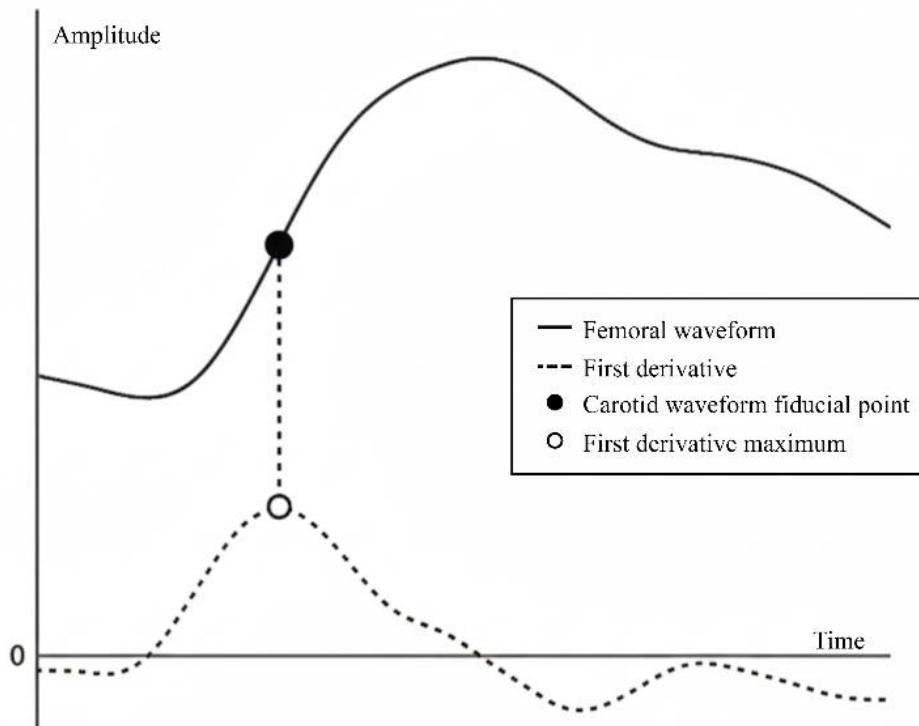
Fig. 1.3 shows the application of the method to carotid and femoral waveforms. It is likely one of the earliest techniques used for determining pulse wave transit time, owing to its simplicity [83]. A key advantage is that this point is relatively well defined and does not depend on waveform morphology changes occurring during propagation along the arterial tree. Its implementation is straightforward and computationally inexpensive, making it an easy method to apply [81].

The main limitation of this method is its high sensitivity to both low- and high-frequency noise. Baseline fluctuations or superimposed noise can easily create spurious local minima that do not correspond to the true diastolic minimum, leading to erroneous and poorly reproducible PTT estimates. In the presence of multiple closely spaced local minima, the identification of the correct point becomes ambiguous and not robust [80], [81], [84].

Maximum of First Derivative

This method identifies the point of maximum slope (or maximum rate of change) during the systolic upstroke as the fiducial point from which the PTT is calculated. Mathematically, this point corresponds to the peak of the first derivative of the pulse waveform [85].

a)



b)

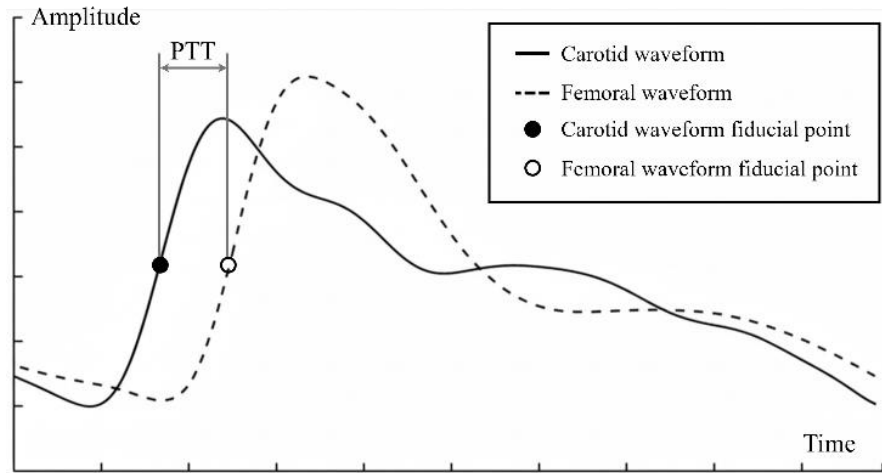


Figure 1.4. Example of the maximum of first derivative method application: (a) identification of the characteristic point on the femoral waveform using the maximum of the first derivative; (b) determination of the PTT from the fiducial points. Figure inspired by [85].

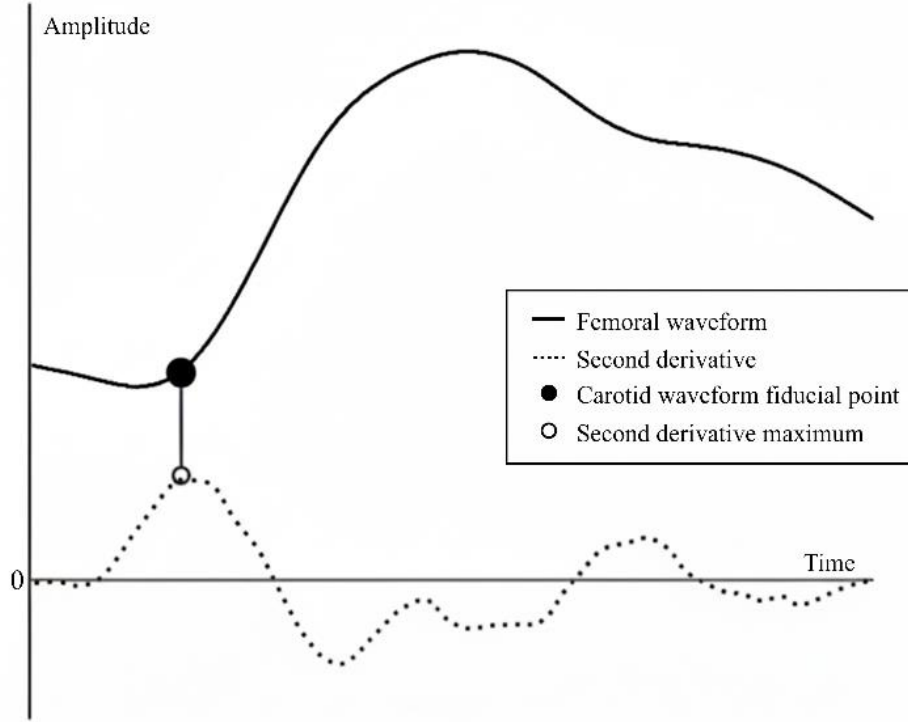
Fig. 1.4 shows an example of the application of this method to carotid–femoral waveforms. First, the fiducial point is identified on the upslope of each waveform (the point of maximum slope in Fig. 1.4a), and then the temporal shift between the two fiducial points is computed to obtain the PTT (Fig. 1.4b).

This method shifts the focus to the waveform’s rising slope rather than the foot, thereby mitigating the issue of spurious minima caused by noise. Moreover, by placing the fiducial point in the early portion of the waveform, it generally reduces the influence of reflected waves. However, comparisons with other methods indicate that PWV may be underestimated in certain cases [82], [86]. This occurs because waveform morphology changes during propagation, and the rising slope is one of the segments most sensitive to such alterations [77]. Despite these limitations, the method remained widely used throughout the 2000s due to its ease of implementation and was still listed among the most common techniques as of 2013 [80].

Maximum of Second Derivative

This method was developed to improve the detection of the wave foot. It first appeared in the literature in the early 1990s and became more established in the 2000s, often being compared with other point-based methods [77], [87]. In 2009, Boutouyrie et al. identified the second-derivative method as one of the standard algorithms for PTT estimation [88]. The method locates the foot of the wave at the point where the systolic upstroke changes most rapidly (the point of maximum acceleration), which corresponds to the peak of the second derivative of the signal (Fig. 1.5a) [61], [84], [85], [89]. The PTT is then calculated as the time difference between the detected wave feet (Fig. 1.5b).

a)



b)

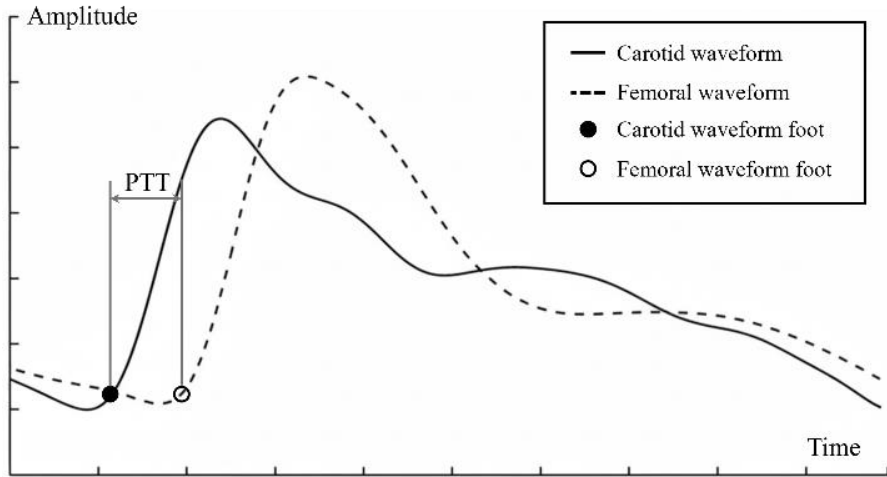


Figure 1.5. Example of the maximum second derivative method application: (a) identification of the characteristic point on the femoral waveform using the maximum of the second derivative; (b) determination of the PTT from the fiducial points. Figure inspired by [85].

By focusing on the beginning of the upstroke, this method is more likely to avoid the influence of reflected waves. Similar to the first-derivative method, the second-derivative approach is less sensitive to baseline drift and low-frequency noise. In several comparative studies, particularly for the estimation of ftPWV, the method based on the maximum of the second derivative has demonstrated the strongest correlations with cfPWV, which is considered the clinical reference for PWV assessment [61], [90]. This method is implemented in various commercial systems for PWV evaluation, including Complior [65], pOpmètre and Vicorder [91]. Its main limitation is that the differentiation operation significantly amplifies high-frequency noise in the signal. For this reason, pre-filtering and signal smoothing are

often necessary [61], [89]. Also, the shape of the second derivative, in particular, can be highly variable and may present small spurious peaks that make the unique identification of the point of interest difficult [89].

Intersecting Tangent Method

The intersecting tangent method combines the operating principle of the diastolic minimum and maximum first-derivative approaches. This technique was developed to be more reliable and robust than either of the two methods alone, as it integrates information from characteristic points located in a portion of the waveform, i.e., the onset of the systolic upstroke, that is less affected by reflections [87]. It defines the foot of the wave as the intersection point of two lines [61], [79], [85], [89], [92]: the first is the tangent line to the waveform at its point of maximum systolic slope, identified with the maximum of the first derivative. The second is a horizontal line passing through the diastolic minimum. The PTT is then computed as the temporal difference between the feet of the two waveforms obtained in this manner (Fig. 1.6).

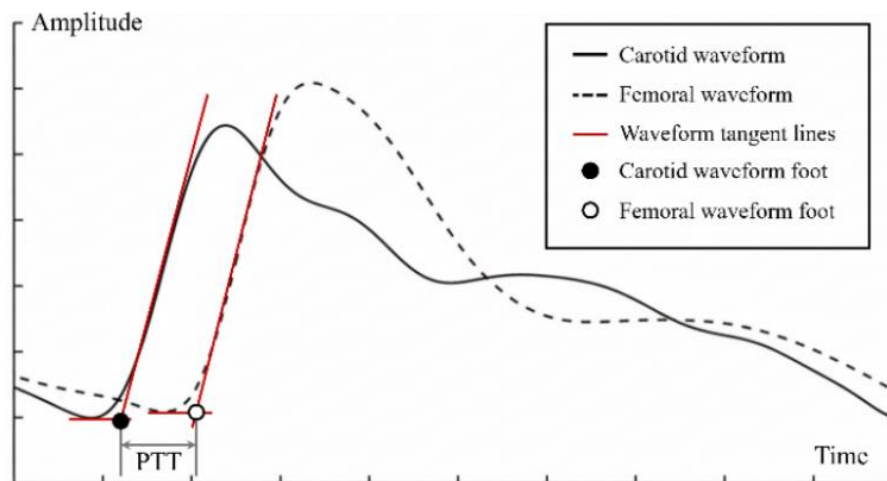


Figure 1.6. Intersecting tangent method applied to examples of carotid-femoral pulse waves. Figure inspired by [81].

The effectiveness of this method was already quantified in the 1990s [77] and was subsequently confirmed by many other authors [93]. It has demonstrated excellent repeatability and provides, among point-based methods, the most consistent results for pulse wave detection in clinical applications. To date, it is considered the gold standard in both the scientific literature and clinical practice for PWV determination [48], [59], [71]. It is also the method adopted in several widely used commercial systems for PWV measurement, such as SphygmoCor, Athos, and PulsePen [65], [91], [94]. However, a key limitation is that the method is sensitive to noise superimposed on the signals [95]. Low temporal resolution likewise causes a marked decline in performance compared with other methods [84], making it less accurate in certain contexts when benchmarked against alternative approaches [61], [81], [96], [97].

Peak-to-peak Method

This method calculates PTT as the time delay between the systolic peaks, intended as the points of maximum amplitude of the two waveforms (Fig. 1.7) [98], [99], [100].

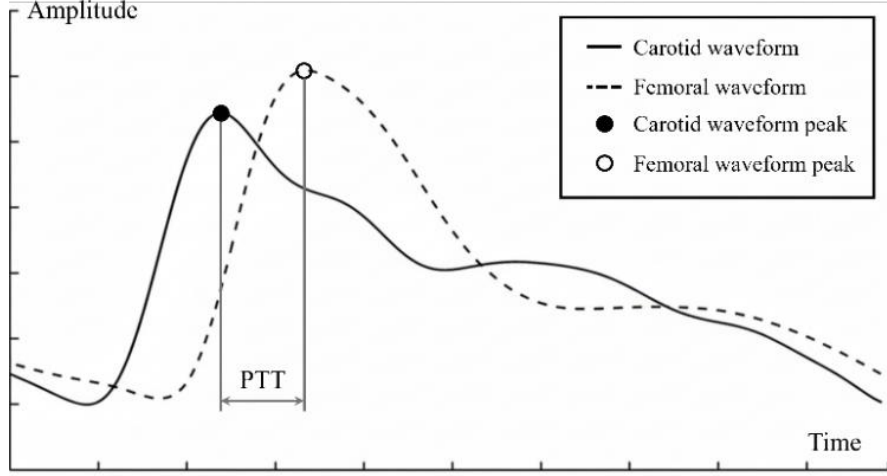


Fig. 1.7. Peak-to-peak method applied to examples of carotid-femoral pulse waves. Figured inspired by [81], [97].

Systolic peaks are often the most evident and easily detectable features in a pulse waveform. However, it is the point of the waveform most heavily influenced by many factors, among which is the superposition of the reflection waves [101], [102]. These factors prevent the peak from identifying the transit of the primary wavefront, making the method generally unsuitable for PTT estimation for the purpose of assessing arterial stiffness [99], [103].

A recent study conducted by Chen et al. in 2024 reports the use of the peak-to-peak method for PWV estimation between pressure waveforms measured at the radial styloid and the fingertip of the middle finger. The authors justify this choice by noting its lower sensitivity to noise compared with the traditional foot-to-foot approach [104]. Nevertheless, this method remains confined to very specific contexts when used for the assessment of arterial stiffness.

It is worth noting that the peak-to-peak method is used for the estimation and monitoring of blood pressure [105], [106]. The literature reports a documented relation between blood pressure and an index known as Pulse Arrival Time (PAT) [107]. It is essential to distinguish PTT from PAT, as the two are often mistakenly used interchangeably [107]. PAT is defined as the time interval between a cardiac electrical event, typically the R-peak of the electrocardiogram (ECG), and the arrival of the pulse wave at a peripheral site [108]:

$$PAT = PEP + PTT \quad (1.4)$$

As specified in (1.4), PAT includes, in addition to the PTT, the Pre-Ejection Period (PEP), which is the interval between the onset of ventricular depolarization and the opening of the aortic valve. Operationally, many authors consider the systolic peak as the arrival point

recorded at a peripheral site [109], [110], [111]. This index is often preferred over other point-based methods because it is easier to detect, more easily automated [112] and less sensitive to noise [113]. However, in some studies, PAT shows lower correlation with blood pressure compared with alternative approaches; therefore, its use must be carefully evaluated depending on the intended application and the level of accuracy required [105], [114].

Threshold Method

This method defines the fiducial point of the waveforms as the point where the signal amplitude, during the systolic upstroke, first exceeds a predefined threshold. This threshold is typically expressed as a percentage of the total pressure pulse amplitude, calculated as the difference between the systolic peak and the diastolic minimum [61], [82].

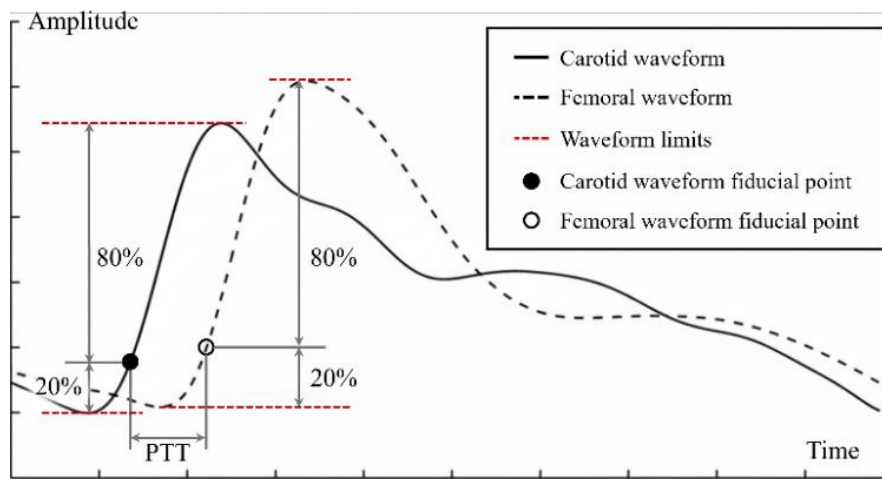


Figure 1.8. Threshold method applied to examples of carotid–femoral pulse waves. Figure inspired by [61], [81].

Fig. 1.8 illustrates the application of the method to a set of carotid–femoral waveforms. In this case, the fiducial point is identified as the value corresponding to 20% of the total upstroke, starting from the diastolic minimum. The threshold value is arbitrary and selected at the operator’s discretion. Typical values include 10% [61], [115], 20% [116] and 50% [117]. The advantages of this method are that the characteristic point is relatively easy to detect and is less sensitive to noise than other approaches, such as the second-derivative method [116]. However, the choice of threshold value is arbitrary and can significantly affect the absolute PTT value obtained [61]. Moreover, if the systolic peak amplitude is influenced by reflected waves, the two waveforms may exhibit different effective upstroke segments, leading to inconsistencies in the identified fiducial points.

1.2.2) Wave-based Methods

Wave-based methods represent the direct response to the intrinsic limitations of point-based approaches [93]. The sensibility of the latter to noise and low temporal resolution compromises their accuracy. Moreover, operator dependence in selecting fiducial points is

considerable: the choice of two different characteristic points can yield substantially different results even when applied to the same waveforms [94], [95]. For this reason, techniques capable of exploiting information derived from broader morphological segments of the waveform have become necessary.

The operating principle of wave-based methods relies on evaluating the gap between the pressure pulse acquired at two different arterial sites, assessing the similarity between the entire pressure waveform (or a selected Region of Interest, ROI) [118]. These methods are generally classified into three main categories [119]:

- 1) *Time-domain Analysis*: they evaluate the similarity between the pressure waves by comparing the proximal waveform with the time-shifted distal waveform;
- 2) *Frequency-domain Analysis*: they evaluate the phase shift, in the frequency domain, of specific harmonic components of the proximal and distal waveforms;
- 3) *Time/Frequency-domain Analysis*: they analyze the similarity of the waveforms by evaluating the phase shift in both the time and frequency domains. These methods combine the first two techniques to enable temporal localization of specific frequency components in the two waveforms.

The comparison of multiple waveform features enhances both the robustness of these methods against noise and artifacts [120] and their ability to compensate for waveform dissipation during propagation [121]. On the other hand, the implementation of such techniques requires substantial computational resources, making their integration into real-time clinical measurement systems more challenging and costly: a limitation that is only now being progressively mitigated by technological advancements [93], [122].

The following sections present and analyze the main methods described in the literature that rely on full or partial waveform analysis to estimate PTT for the determination of arterial stiffness.

Cross-correlation Method

Cross-correlation is a well-established mathematical technique that operates in the time domain. It quantifies the similarity between two waveforms as a function of the temporal shift of one signal relative to the other [123]. The similarity (R) is expressed as the time integral of the product of the two waveforms [94] X_p and X_d in (1.5):

$$R_{X_p, X_d}(\tau) = \frac{1}{T} \int_{-\frac{T}{2}}^{\frac{T}{2}} X_p(t) \cdot X_d(t + \tau) \cdot dt \quad (1.5)$$

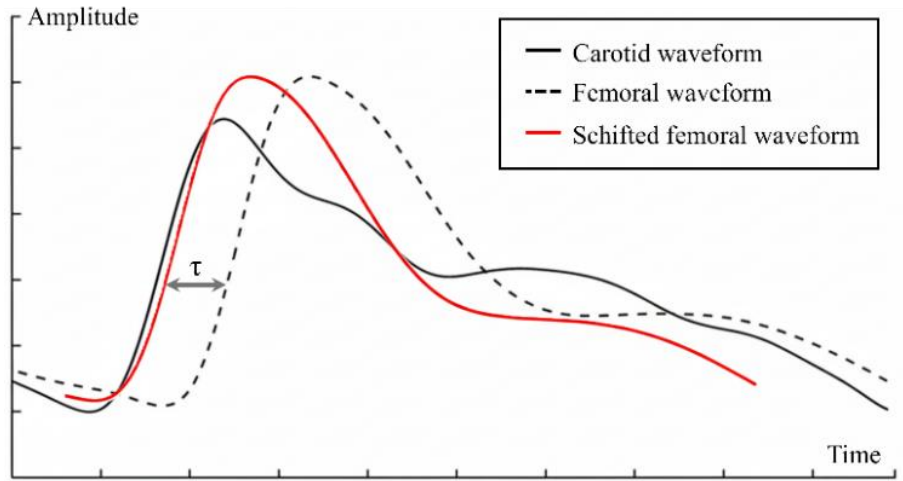
where X_p and X_d represent the time-domain signals acquired at the proximal and distal sites, respectively; t is the generic time instant, T is the number of time instants that compose the

signal and τ is the temporal shift applied to the distal waveform relative to the proximal one. The PTT is estimated as the time delay corresponding to the maximum value of the cross-correlation function (τ_{max}), that is, the point at which the similarity between the two signals is greatest [89], [97], [124], [125], [126]:

$$PTT = \tau_{max} = \arg \max_{-\frac{T}{2} \leq \tau \leq \frac{T}{2}} R_{x_p, x_d}(\tau) \quad (1.6)$$

Fig. 1.9 illustrates a graphical example of the application of the cross-correlation method to a set of carotid-femoral waveforms. The distal waveform is temporally shifted by an amount τ relative to the proximal one (Fig. 1.9a). The PTT is then identified by locating the maximum of the function R , corresponding to τ_{max} (Fig. 1.9b).

a)



b)

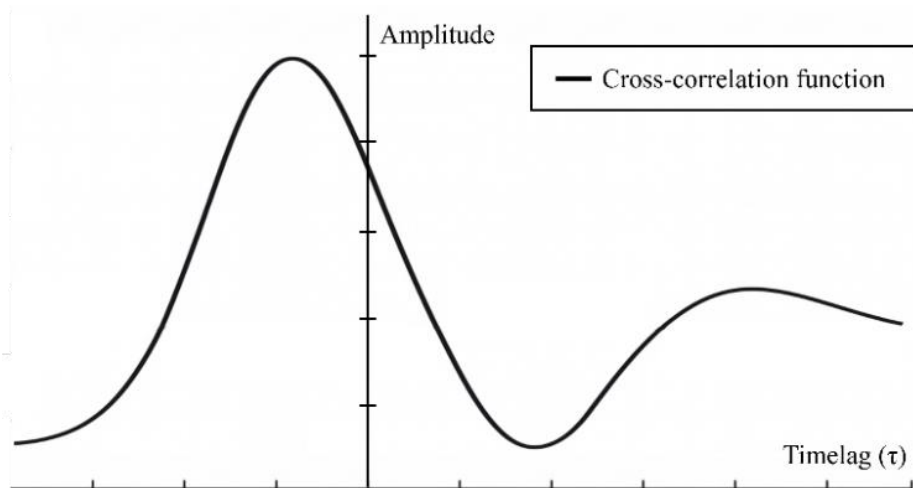


Figure 1.9. Example of application of the cross-correlation method applied to examples of carotid–femoral pulse waves: (a) temporal shifting of the femoral waveform relative to the carotid waveform; (b) determination of PTT from the maximum of the cross-correlation function. Figure inspired by [61], [81].

Widely used in various fields, including seismology [127], [128], acoustics [129], [130], neurophysiology [131], [132], fluid dynamics [133], [134] and, more generally, for time-delay

estimation [135], [136], cross-correlation has been applied to arterial stiffness assessment since the previous century [121], [137], [138]. By leveraging the information contained in the entire waveform, this method can be intrinsically more robust to random high-frequency noise than point-based methods [79], [97]. Moreover, it eliminates operator subjectivity and the ambiguity associated with defining a single fiducial point [120]. Several studies conducted on simulated waveforms [96], *in vitro* using arterial simulators [126], and *in vivo* over short vascular segments [89], [139] have identified cross-correlation as the most robust and reliable method, exhibiting the lowest standard deviation and the best reproducibility compared with fiducial point methods.

However, its strong dependence on the morphological similarity between the two waveforms represents a double-edged sword [61], [79]. The pressure wave distorts significantly during propagation along the arterial tree due to damping [82] and interactions with reflected waves [140]. When applied to long and heterogeneous arterial segments, such as in regional PWV measurements, e.g., cfPWV or even more ftPWV, the dissimilarity between the proximal and distal waveforms increases to such an extent that it compromises the accuracy of the method [61]. In this regard, a study conducted on simulated waveforms quantified the error introduced by full-waveform cross-correlation in estimating PTT in the presence of reflections. The authors found that, because reflected waves shift the location of the maximum correlation peak, the technique tends to overestimate the resulting PWV in such conditions [141]. The same concept is confirmed by both *in silico* and *in vivo* studies, which report that cross-correlation becomes inaccurate when applied to morphologically dissimilar waveforms, such as carotid and femoral signals, and exhibits a larger spread in results compared with other methods [81], [142]. Similarly, when applied to full waveforms acquired at the finger and toe, cross-correlation demonstrated the lowest correlation with the gold standard (cfPWV) compared with point-based methods [61]. To address this issue, several authors have proposed applying cross-correlation only to a portion of the pressure waveform. The principle is to focus on a signal window that is less contaminated by reflections, typically a segment of the systolic upstroke. In 2001, this technique was employed to investigate age-related changes in aortic stiffness by measuring PWV noninvasively through phase-contrast magnetic resonance imaging (PC-MRI) [143]. In that study, partial cross-correlation was restricted to the 20% - 40% interval of the systolic peak, an interval later adopted by other authors for PWV assessment in the carotid arteries [89]. However, even in this case, the choice of the interval introduces variability in determining the actual PTT value. In 2023, a study focused on identifying the most robust ROI for waveform-based PTT estimation [94]. The study confirmed the improved performance of partial over full cross-correlation but concentrated exclusively on specific waveforms (carotid and femoral signals from 75 healthy subjects), without validating the technique on waveforms with different morphologies (e.g., proximal and distal aorta).

The least squares difference method shares conceptual analogies with cross-correlation but compares waveforms by minimizing an error function rather than maximizing their similarity. It operates in the time domain by comparing proximal and distal pressure waves through least squares analysis of their differences. One of the two waves is temporarily shifted with respect to the other, and for each possible time delay, the sum of squared differences between a specific wave segment is computed. The PTT is identified as the delay that minimizes this sum [93]:

$$PTT = \arg \min_{\tau} \sum_{i=1}^n [X_p(t_i) - X_d(t_i + \tau)]^2 \quad (1.7)$$

where n represents the number of time instants contained within the selected wave segment. This approach is region-based, meaning that only a selected portion of the waveform is analyzed to exclude segments affected by perturbations such as reflected waves. In 2013, Vardoulis et al. [80] introduced a technique based on this principle, termed *diastole-patching*, which focuses on comparison of a region near the foot of the proximal wave.

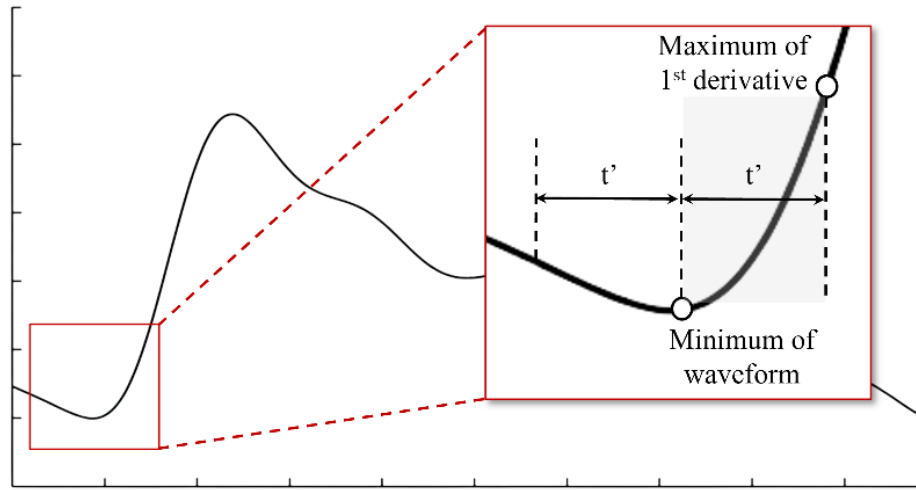


Figure 1.10. Criterion used by the diastole-patching method to extract the patch for least squares comparison, applied to an example of carotid waveform. Figure adapted from [80].

In this technique, the time interval t' between the minimum value of the waveform and the maximum of its first derivative is first determined (Fig. 1.10). A symmetric interval of equal duration is then taken to the left of the minimum. The final analyzed region, or *patch*, is the sum of these two sub-intervals ($t' + t'$). Finally, (7) is applied to identify the PTT. The method was initially validated *in silico* [80], and later verified *in vivo* on carotid-femoral acquisitions, demonstrating high accuracy and repeatability compared to the clinical gold standard [84]. Its robustness has led to further adoption by other authors [85], and in 2024, it was recommended, in addition to the intersecting-tangent method, as a reference approach for clinical PTT estimation [71]. A similar least squares-based approach was

proposed by Gaddum et al. [79], who focused instead on the systolic upstroke as the region of interest. In their implementation, the distal waveform segment between its minimum and maximum is compared to the corresponding proximal segment. This region offers good definition and low noise sensitivity compared to the foot of the wave, although it may include portions influenced by reflections. The effectiveness of least squares-based methods strongly depends on the correct segmentation of the ROI, which can be challenging in the presence of noisy signals or atypical morphologies (e.g., anacrotic pulses or poorly defined reflected waves). These factors may introduce variability in the accuracy of PTT estimation. It is important to distinguish these methods from the earlier work of Ramsey et al. [144], who also proposed comparing time-shifted wave segments centered on the foot. The key difference lies in the error function: Ramsey employed the sum of absolute differences rather than least squares. However, this method proved sensitive to small gain mismatches between acquisition channels and was developed and validated only for short inter-sensor distances (about 5 cm) using invasive catheter-based measurements.

Fourier-based Methods

The methods in this category are various, yet all are grounded in the analysis of the harmonic components of the pressure waveform. They rely on the Fourier transform and are therefore referred to as Fourier-based methods. These techniques estimate the PTT by quantifying the phase shift of the harmonics that compose the proximal and distal waveforms in the frequency domain. When the waveforms acquired at two measurement sites are compared, each harmonic exhibits a phase difference ($\Delta\phi$), which can be directly converted into a corresponding temporal delay (PTT_f) [145]:

$$PTT_f = \frac{\Delta\phi}{2\pi f} \quad (1.8)$$

where f denotes the frequency of the considered harmonic. To determine a more representative PTT value, the contributions of multiple harmonics are typically combined by using the concept of group delay (τ_g). This quantity, widely known and applied in signal and communication theory [146], [147], [148], was introduced in the context of PTT estimation as early as the late 1960s [149]. It represents the time-domain delay of a signal composed of a set of harmonics and is expressed as:

$$\tau_g = \frac{d\phi_H(\omega)}{d\omega} \quad (1.9)$$

where ω is the angular frequency. The term $d\phi_H$ represents the phase variation of the transfer function H , computed as the ratio between the distal waveform $X_D(\omega)$ and the proximal waveform $X_P(\omega)$, in the frequency domain. The group delay τ_g is then used to estimate the

PTT by incorporating it into a weighted average of the energy contributions of the considered harmonics (ω_n) [118]:

$$PTT = \frac{\sum_{\omega_n} \tau_g \cdot |X_P(\omega_n)|^2}{\sum_{\omega_n} |X_P(\omega_n)|^2} \quad (1.10)$$

The main advantage attributed to this approach is its robustness when applied to signals with low temporal resolution. In fact, the method was originally proposed in combination with Cardiovascular Magnetic Resonance (CMR) acquisitions [118], a technique that is well known for its limited temporal resolution compared to others, e.g., tonometry [93]. Subsequent studies [72] confirmed that, when the sampling interval is reduced, this method exhibits a smaller loss of correlation than time-domain approaches.

However, performing frequency decomposition on waveforms acquired over the entire cardiac cycle inevitably introduces the influence of reflected waves, whose frequency content strongly overlaps with that of forward-traveling waves, particularly at low frequencies. In this region, the energy content is dominant and dissipation is limited, thus having a major impact on (1.10). This mechanism may lead to inaccurate PTT estimates [72]. Some authors attempted to reduce the impact of reflections by dividing the signals into frequency bands and analyzing only the higher-frequency components [150]. It was already known that the arterial attenuation coefficient rapidly dissipates high-frequency energy contributions [149]. Nevertheless, the proposed technique only partially mitigated the influence of reflections, as it did not truly separate forward and backward components. As a result, the need to define the most suitable frequency window remained, introducing an additional source of variability that affects the applicability of this method.

Wavelet-based Method

The use of wavelets in biomedical signal analysis is relatively recent. Only in the 1990s, after the effectiveness of wavelets for signal decomposition had been well established in the literature [151], [152], [153], [154], did the first studies emerge focusing on the detection of characteristic points in ECG signals [155], [156], [157] or in the arterial blood pressure (ABP) waveform [153]. Subsequently, as methods for isolating transient features within the ABP waveform became more consolidated [158], [159], numerous studies began to investigate the estimation of PTT (or PAT) using wavelet-based approaches for blood pressure assessment [160], [161], [162]. Bargiotas et al. were among the first authors to employ wavelets for estimating PWV and arterial stiffness [72]. This technique allowed them to combine time-domain and frequency-domain analyses, thereby extracting multiple types of information from the examined waveforms. The method relies on generating a function known as the continuous wavelet transform $W_x(1/f, t)$, which provides a time-frequency

decomposition of the signal X through correlation with a reference function called the mother wavelet. The mother wavelet is compressed and stretched to analyze components at different frequencies and shifted along the time axis to determine their temporal localization. This makes it possible to observe how the harmonic components of the pressure waveform evolve throughout the cardiac cycle. To compare the proximal and distal pressure waveforms (generically denoted X_P and X_D) within the wavelet domain, a complex quantity known as the cross-spectrum W_{X_P, X_D} can be computed:

$$W_{X_P, X_D} = W_{X_P} \left(\frac{1}{f}, t \right) \cdot W_{X_D}^* \left(\frac{1}{f}, t \right) \quad (1.11)$$

where $W_{X_D}^*$ denotes the complex conjugate of the continuous wavelet transform of the distal waveform. From the cross-spectrum, it is possible to extract the magnitude, which indicates the extent to which two harmonic components are energetically correlated at a given time, and the phase, which represents their instantaneous phase shift. Based on this information, the PTT can be computed as:

$$PTT = \sum_{t=t_{foot}}^{t_{peak}} \sum_{f=f_1}^{f_2} \frac{W_{X_P, X_D}}{\sum |W_{X_P, X_D}|} \cdot \frac{\phi(W_{X_P, X_D})}{2\pi f} \quad (1.12)$$

considering the cross-spectrum within a selected frequency range (f_1 to f_2) and over a specific time interval, corresponding, in this case, to the systolic upstroke (t_{foot} to t_{peak}). The authors in [72] aimed to analyze PWV in the aortic arch using CMR-derived data. This approach enabled overcoming the limitations of traditional methods in terms of sensitivity to low temporal resolution, noise, and the presence of reflected waves.

The same technique was later adopted by Filippi et al. [163], who evaluated its performance on an arterial simulator capable of varying the stiffness of an arterial surrogate by modifying the applied transmural pressure. In that context as well, the method proved promising, confirming its robustness under different temporal resolutions and noise levels.

Nonetheless, wavelet-based methods present certain drawbacks, including higher computational complexity compared with more straightforward approaches and the need to properly select both the mother wavelet and the scales most suited to the waveform under analysis, factors that continue to introduce variability [162], [164].

1.2.3) Model-based Methods

Model-based methods refer to techniques that make use of mathematical models and relationships describing the behaviour of the cardiovascular system to compute PTT and PWV. Over time, mathematical models with different levels of complexity have been developed [165], [166], [167]:

- 1) *0D models*: they provide a representation of the cardiovascular system in which each vascular segment is described by physical quantities (typically pressure, flow and volume). In such formulations, spatial variations along the vessels are neglected.
- 2) *1D models*: each arterial segment is modelled as a compliant tube in which pressure and flow vary both in time and along the vessel axis. The governing equations are derived from the conservation of mass and momentum.
- 3) *2D/3D models*: the vascular geometry is fully represented, and blood flow is governed by the general Navier-Stokes equations. As a result, velocity and pressure vary along the vessel axis, in the radial and circumferential directions. These formulations provide more detailed and physiologically accurate representations of arterial hemodynamics, albeit with substantially higher computational demands. They are generally preferred for the investigation of local hemodynamic phenomena [168] and do not provide substantial additional information beyond that obtained from 1D models with respect to PWV estimation [169]. For this reason, they will not be further discussed in the present review.

Model-based methods offer several advantages over the techniques described in the previous sections. First, they allow the full waveform to be exploited rather than relying on isolated fiducial points, thereby making PTT estimation more robust to noise and morphological distortions [167], [170], [171]. In addition, by employing a structured mathematical model, these approaches enable the simultaneous estimation of multiple hemodynamic parameters of interest, such as arterial compliance, the characteristic impedance of the arterial tree, and the magnitude of wave reflections [170], [172]. However, model-based methods also exhibit several limitations. Their accuracy is inherently dependent on the constitutive assumptions on which they are built and discrepancies between the model and actual physiology may introduce significant bias in the reconstructed pulse wave and in the resulting PTT and PWV estimates [170], [171]. Moreover, these techniques require precise signal synchronization and involve a higher computational burden than simpler methods, which limits their applicability in fast-response or real-time monitoring scenarios [80], [125].

0D Model Methods

The 0D approach was first introduced by Otto Frank in 1899 through the “Windkessel” model, which represents the cardiovascular system as an intermittent pump connected to an air chamber [173]. Owing to its promising ability to predict the decay of aortic pressure during diastole, the model was subsequently revisited and refined over time [174], [175], [176], ultimately evolving into what is now known as the lumped-parameter model [177]. In this framework, the cardiovascular system is represented by a combination of elements with electrical analogues from transmission-line theory. By arranging these parameters in

various configurations [178], it is possible to accurately reconstruct pressure wave propagation within arterial segments throughout the cardiac cycle [179], [180]. The study presented by Xu et al. [81] provides a clear example of the use of this method to derive PTT.

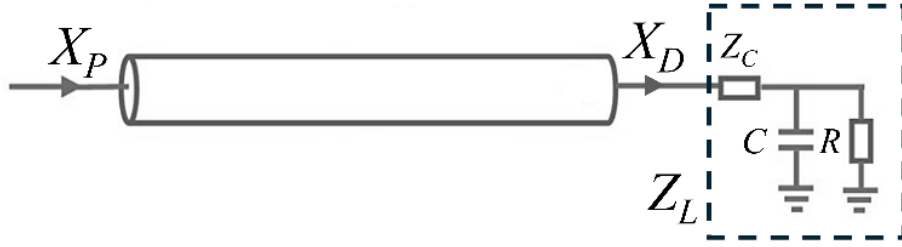


Figure 1.11. Graphical representation of the simplified tube-load model. Figure derived from [81].

The authors refer to their approach as the “tube-load model” because it is composed of two main elements (Fig. 1.11) [81]. The *tube* is a lossless conduit of length L , diameter D , and characteristic impedance Z_c [181]. The *load* instead represents the behaviour of the vascular system distal to the conduit and is modelled through C , the compliance typical of large arteries; R , the total resistance to blood flow imposed by the arterial system; and the resulting Z_L , which denotes the overall load impedance [182], [183]. In this framework, PWV estimation begins with the acquisition of generic pressure waveforms at the carotid site (X_P) and the femoral site (X_D). The model parameters are then obtained through a least-squares estimation procedure applied to a transfer function defined as:

$$H(\omega) = \frac{X_D(\omega)}{X_P(\omega)} = \frac{j\omega + \frac{1}{RC} + \frac{1}{Z_c C}}{\left(j\omega + \frac{1}{RC} + \frac{1}{2Z_c C}\right) e^{j\omega PTT} + \frac{1}{2Z_c C} e^{-j\omega PTT}} \quad (1.13)$$

The PTT is then computed from the following relationship:

$$PTT = \sqrt{\frac{\rho LC}{A}} \quad (1.14)$$

The PWV is therefore estimated as the ratio between the conduit length L and the computed PTT. The strength of this method is that it implicitly accounts for the influence of wave reflections. The model is structured so that their effect is computationally separated. Moreover, when compared with a more complex lumped-parameter formulation, the simplified version was shown to provide equally accurate and repeatable estimates of both PTT and PWV, while offering faster computation and requiring fewer parameters [81]. However, these parameters may assume non-unique values since they are obtained through interpolation. For this reason, it is essential to introduce physiological constraints and to

properly define the initialization settings [184]. Moreover, they are difficult to standardize in clinical practice due to inter-patient variability.

1D Model Methods

The 1D models describing blood flow within arterial vessels are well established and extensively documented in the literature. Beginning with the work of Bramwell and Hill [56], [57], who, as early as 1922, conducted experimental studies linking PWV to arterial stiffness, these models have progressively increased in complexity [185]. Subsequent developments introduced the effects of blood viscosity and its influence on pulsatile flow [186], [187], the viscoelastic properties of arterial walls and their implications for pressure-wave propagation [188], [189], and non-linear aspects of arterial wall deformation [190].

A wide range of PWV estimation methods is based on 1D models, each adopting different strategies to obtain the measurement. These approaches do not compute PTT; instead, they directly calculate PWV, which is derived from the constitutive relationships embedded in the models themselves. They deserve mention because several of them are used in clinical practice and are often compared with traditional techniques that assess PWV through PTT estimation.

Similar to the 0D models, some methods rely on mathematical formulations that represent the cardiovascular system as a transmission line. In 1971, Cox et al. [191] employed a distributed-parameter model based on the theory of wave propagation of a Newtonian fluid within a thick-walled viscoelastic tube under small perturbation assumptions. According to this model, wave propagation is governed by a factor known as the complex propagation constant (γ):

$$\gamma(\omega) = \alpha(\omega) + j\beta(\omega) \quad (1.15)$$

composed of a real component a , which describes the attenuation of the wave during propagation, and an imaginary component b , which represents its phase shift corresponding, in the time domain, to the delay of the wave between two measurement sites [192], [193]. By acquiring simultaneous measurements of pressure, flow, and diameter along a tube, the authors derived γ , which depends on the characteristic impedance of the system, and from this, they were able to compute the frequency-dependent PWV through the relation [191]:

$$PWV(\omega) = \frac{\omega}{\beta(\omega)} \quad (1.16)$$

The advantage of this method is that, through relationships accounting for the characteristic impedances of the system under study, Cox et al. were able to eliminate the

contribution of reflected waves. Over time, this approach was subsequently revisited, refined, and validated using laboratory experimental setups [194], [195]. The main challenge in adopting these approaches, regardless of the specific mathematical model employed [196], is the need for simultaneous measurements of multiple physical quantities. This requirement is necessary to derive all the constitutive parameters of the model and to correctly identify the contributions of backward waves [197].

Another highly promising method is the PU-loop approach [198]. It is based on the 1D form of the conservation of mass and momentum equations, which lead to the relationship describing the “water hammer” phenomenon:

$$dP = \rho \cdot c \cdot dU \quad (1.17)$$

where P is the intraluminal pressure, ρ is the blood density, c is the pressure wave speed, and U is the blood flow velocity. By acquiring pressure and velocity signals at the same site throughout the cardiac cycle, a loop is obtained as shown in Fig. 1.12.

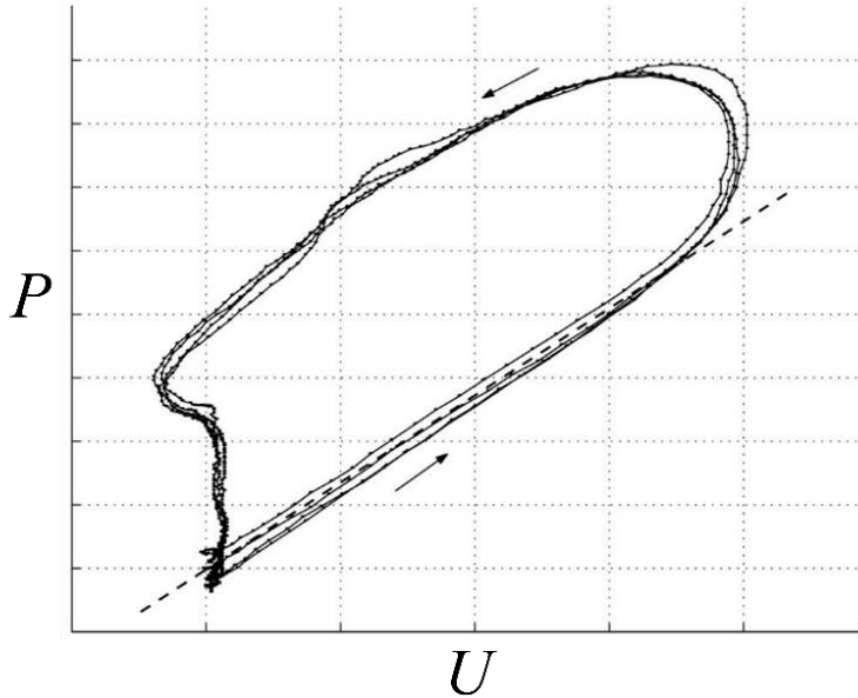


Figure 1.12. Example of a graph of blood pressure as a function of blood flow velocity. Figure taken from [198].

At the beginning of the systolic phase, before the upstroke is influenced by reflected waves, the P-U plot is nearly linear, and its slope equals ρc ; from this, the wave speed can be extracted once the fluid density is known. The PU-loop method has been tested and applied in various scenarios. *In vitro*, it demonstrated excellent agreement with the foot-to-foot method in elastic latex and silicone tubes, validating the approach under controlled conditions [199]. In animal vascular segments, specifically in anesthetized dogs, the method yielded local PWV values consistent with the regional foot-to-foot estimation and it detected

the expected increases during controlled aortic occlusions, confirming its suitability for short arterial segments [83]. In humans, during peripheral vascular surgery, the method proved sensitive to PWV changes induced by aortic clamping, confirming its physiological responsiveness in clinical applications [200]. An advantage of this technique is that it estimates local PWV without the uncertainty associated with measuring the distance between two recording sites. Moreover, it excludes the contribution of reflected waves by focusing solely on the initial portion of the systolic upstroke. The main limitation lies in the accurate identification of the linear segment unaffected by reflections, a requirement that restricts its applicability in regions with pronounced geometric discontinuities, e.g., multiple bifurcations, where reflections are more prominent. Moreover, acquiring multiple quantities simultaneously requires the use of several sensors and necessitates accurate synchronization between the signals.

1.2.4) Comparative analysis and performance evaluation

The scientific literature includes several studies that have directly compared the performance of the methods abovementioned. Analyzing these studies is crucial for understanding the strengths and weaknesses of each approach under different operating conditions.

The following paragraph provides an overview of the main studies that have compared different methods for calculating PTT. When evaluating techniques for PWV estimation, it is essential to distinguish the evidence obtained in *in vitro*, *in silico*, and *in vivo* settings, as each experimental framework introduces distinct constraints and sources of uncertainty. For each framework and testing condition, method performance will be reported in terms of accuracy, precision, and repeatability. Accordingly, when provided in the respective scientific study, the following metrics, cited in their general form, will be reported [201].

The *bias* represents the difference between the mean value of the results returned by a method ($\bar{x}$) and a reference value (x_{ref}):

$$bias = \bar{x} - x_{ref} \quad (1.18)$$

The *Root Mean Square Error (RMSE)* is a metric that quantifies the average deviation of the n values returned by a method (x_i) from their mean value ($\bar{x}$):

$$RMSE = \sqrt{\frac{1}{n} \sum_{i=1}^n (x_i - \bar{x})^2} \quad (1.19)$$

The *Coefficient of Variation (CoV)* is a dimensionless metric that measures the relative variability of a dataset with mean value $\bar{x}$ and standard deviation SD :

$$CoV = \frac{SD}{\bar{x}} \quad (1.20)$$

The *Intraclass Correlation Coefficient* (ICC) is an index used to assess reliability, repeatability, and agreement among different measurement methods:

$$ICC = \frac{\sigma_b^2}{\sigma_b^2 + \sigma_w^2} \quad (1.21)$$

where σ_b^2 represents the variance between data obtained from different methods, and σ_w^2 is the variance of data obtained from the same method (often the reference method).

Table 1.1 summarizes the main outcomes of the studies, which will be further detailed in the following subsections, in terms of the performance metrics mentioned above. For each study, the dataset, the methods under comparison, and the method or value adopted as the reference are reported. It should be noted that Table 1.1 does not include all the results presented in each work, as each author conducted an independent investigation and often focused on additional metrics not considered here. Readers are therefore referred to the original publications for a comprehensive understanding.

Table 1.1. Main Methods' Outcomes as a Function of the Dataset and Reference Value. Results in Terms of Performance Metrics

Study	Dataset	Reference value	Compared methods	Bias	RMSE	CoV	ICC	r	Reference
<i>In Vitro</i>	Signals from arterial simulator (applying different filters)	Reference value from intersecting tangent method	Second derivative	2.96 % (1 st filter) 2.52 % (2 nd filter) 1.27 % (3 th filter)	N.R.	0.45 % (1 st filter) 10.45 % (2 nd filter) 2.20 % (3 th filter)	N.R.	N.R.	Hermeling et al. [116]
			Intersecting tangent	1.65 % (1 st filter) 0.50 % (2 nd filter) 0.25 % (3 th filter)	N.R.	0.66 % (1 st filter) 2.36 % (2 nd filter) 1.18 % (3 th filter)	N.R.	N.R.	
			Threshold (20%)	1.73 % (1 st filter) 0.86 % (2 nd filter) 1.15 % (3 th filter)	N.R.	0.68 % (1 st filter) 1.43 % (2 nd filter) 0.93 % (3 th filter)	N.R.	N.R.	
<i>In Silico</i>	Simulated waveforms using mathematical model (aoPWV and cfPWV)	Theoretical PWV value from a mathematical model	Diastole-patching	0.261 m/s (aoPWV) -0.400 m/s (cfPWV)	0.315 m/s (aoPWV) 0.467 m/s (cfPWV)	2.844 % (aoPWV) 4.160 % (cfPWV)	0.977 (aoPWV) 0.959 (cfPWV)	N.R.	Vardoulis et al. [80]
			Diastolic minimum	0.834 m/s (aoPWV) 0.387 m/s (cfPWV)	0.904 m/s (aoPWV) 0.472 m/s (cfPWV)	8.376 % (aoPWV) 3.642 % (cfPWV)	0.864 (aoPWV) 0.963 (cfPWV)	N.R.	
			Intersecting tangent	-0.919 m/s (aoPWV) -0.936 m/s (cfPWV)	0.978 m/s (aoPWV) 0.991 m/s (cfPWV)	10.366 % (aoPWV) 9.771 % (cfPWV)	0.786 (aoPWV) 0.820 (cfPWV)	N.R.	
			First derivative	-1.743 m/s (aoPWV)	1.845 m/s (aoPWV)	21.155 % (aoPWV) 17.371 % (cfPWV)	0.445 (aoPWV) 0.548 (cfPWV)	N.R.	

				-1.577 m/s (cfPWV)	1.753 m/s (cfPWV)				
			Second derivative	-1.205 m/s (aoPWV) -1.166 m/s (cfPWV)	1.280 m/s (aoPWV) 1.241 m/s (cfPWV)	13.999 % (aoPWV) 12.201 % (cfPWV)	0.666 (aoPWV) 0.724 (cfPWV)	N.R.	
	Simulated waveforms using mathematical model	Theoretical PWV value from a mathematical model	Tube-load model (simplified)	-0.13 m/s	N.R.	N.R.	N.R.	N.R.	Xu et al. [81]
			Diastole- patching	-0.98 m/s	N.R.	N.R.	N.R.	N.R.	
			Cross- correlation	1.76 m/s	N.R.	N.R.	N.R.	N.R.	
			Intersecting tangent	-1.15 m/s	N.R.	N.R.	N.R.	N.R.	
	Simulated waveforms based on arterial simulator behaviour.	Reference value	Cross- correlation	< 0.1%	N.R.	N.R.	N.R.	N.R.	Filippi et al. [96]
			Peak-to- Peak	0.2 %	N.R.	N.R.	N.R.	N.R.	
			Intersecting tangent	0.7 %	N.R.	N.R.	N.R.	N.R.	
<i>In Vivo</i> (Animals)	Waveforms acquired from 11 anesthetized dogs	Foot-to-foot (McDonald et al. in 1968) (local PWV)	PU-loop	≈2%	N.R.	23.6 %	N.R.	N.R.	Khair et al. [83]
		Foot-to-foot (McDonald et al. in 1968) (regional PWV)	PU-loop	≈ 20%	N.R.	23.6 %	N.R.	N.R.	
	Waveforms acquired from 11 anesthetized animals	Blood pressure (assuming linear correlation with PWV)	Tube-load model	N.R.	3.4 mmHg	N.R.	N.R.	0.83	Mingwu Gao et al. [171]
			Intersecting tangent	N.R.	5.2 mmHg	N.R.	N.R.	0.94	
<i>In Vivo</i> (Humans)	26 patients and 11 volunteers (invasive aoPWV + non-invasive brPWV)	Comparison between tested methods (r is given with respect to intersecting tangent method)	Diastolic minimum	N.R.	N.R.	2.5 % (aoPWV) 4.4 % (aoPWV) 22 % (brPWV)	N.R.	0.95 (aoPWV) 0.97 (aoPWV) 0.23 (brPWV)	Chiu et al. [77]
			First derivative	N.R.	N.R.	3.2 % (aoPWV) 3.7 % (aoPWV)	N.R.	0.77 (aoPWV) 0.81 (aoPWV)	

						7 % (brPWV)		0.79 (brPWV)	
			Second derivative	N.R.	N.R.	3.2 % (aoPWV) 3.7 % (aoPWV) 7 % (brPWV)	N.R.	0.99 (aoPWV) 0.99 (aoPWV) 0.90 (brPWV)	
			Intersecting tangent	N.R.	N.R.	2.9 % (aoPWV) 4.0 % (aoPWV) 5 % (brPWV)	N.R.	-	
	64 volunteers	Comparison between tested methods	Second derivative	1.7 ± 0.8 m/s	N.R.	4.8 %	N.R.	N.R.	Millasseau et al. [87]
			Intersecting tangent		N.R.	5.7 %	N.R.	N.R.	
	50 patients and 6 volunteers	Comparison between tested methods (results given with respect to intersecting tangent method)	Intersecting tangent	-	N.R.	N.R.	N.R.	-	Ibrahim et al. [139]
			Cross-correlation	-0.1 ± 1.0 m/s	N.R.	N.R.	N.R.	0.95	
			QA-loop	0.8 ± 1.7 m/s	N.R.	N.R.	N.R.	0.87	
	340 subjects	Intersecting tangent	Diastole-patching	-0.1 m/s	0.804	4.210 %	0.930	0.934	Papaioannou et al. [84]
	81 patients and 10 volunteers	Manually identified value	WFMA	-0.161 m/s	0.351 m/s	N.R.	0.992	0.995	Hu et al. [86]
			Diastole-patching	-0.265 m/s	0.588 m/s	N.R.	0.978	0.988	
			Intersecting tangent	0.286 m/s	0.795 m/s	N.R.	0.948	0.971	
			Second derivative	0.449 m/s	0.932 m/s	N.R.	0.928	0.963	
			First derivative	0.751 m/s	1.243 m/s	N.R.	0.891	0.929	
			Diastole minimum	-1.951 m/s	1.861 m/s	N.R.	0.591	0.793	
	16 volunteers	Comparison between tested methods (results given with respect to intersecting tangent method)	Intersecting tangent	-	N.R.	30 %	N.R.	N.R.	Darwich et al. [89]
			Second derivative	-0.21 m/s	N.R.	34 %	N.R.	N.R.	
			Partial cross-correlation	-0.31 m/s	N.R.	23 %	N.R.	N.R.	

	47 healthy subjects	Clinical reference (cfPWV)	Wavelet-based	[-0.5, 0.5] m/s	N.R.	N.R.	N.R.	[0.48-0.62]	Houriez-Gombaudo-Saintonge et al. [202]
			Cross-correlation	[-2.3, -0.9] m/s	N.R.	N.R.	N.R.	[0.30-0.55]	
			Fourier-based	[-1.8, -1.2] m/s	N.R.	N.R.	N.R.	[0.30-0.61]	
	75 subjects	Intersecting-tangent (SphygmoCor)	Intersecting-tangent (Athos)	-0.07 m/s	0.519 m/s	N.R.	N.R.	0.965	Valerio et al. (2023) [94]
			Full cross-correlation	-1.04	2.435	N.R.	N.R.	0.820	
			Partial cross-correlation	0.16	0.573	N.R.	N.R.	0.960	

N.R.: The authors did not provide any considerations regarding the value.

Testing PTT estimation methods under simulated conditions is essential because it allows researchers to assess performance in a controlled environment [53]. *In silico* experiments make it possible to fix a well-defined PWV value, derived from the mathematical model, thereby providing a reliable reference against which the methods can be compared. In addition, generating waveforms mathematically enables robustness testing by varying the signal to noise ratio (SNR) and selecting the sampling interval. Experiments performed within arterial simulators, on the other hand, offer repeatable measurements. They also allow the physiological reference parameters to be specified with high precision, e.g., the pressure within the vessel. Below, several key studies used as benchmarks for the selection and development of PTT estimation methods are summarized.

- Hermeling et al. (2007) [116] tested three point-based methods on an arterial simulator to evaluate their performance in estimating local PWV. The aim was to assess the applicability of these techniques to signals acquired with an ultrasound system. The compared methods included the maximum second derivative, the intersecting tangent method, and a 20% threshold approach. The reference PWV was obtained by applying the intersecting tangent method to impedance signals measured using sensors placed directly on the conduit. All methods performed well when a more selective filter was applied (eighth-order, 2 Hz cut-off frequency). Under these conditions, all methods reported a CoV $< 0.7\%$, with the second derivative method exhibiting a higher percentage bias ($\approx 3\%$) compared with the others. When a less selective filter was used (second-order, 2 Hz cut-off frequency), the performance of the second derivative method deteriorated markedly (CoV $\approx 10.5\%$), whereas the intersecting tangent and threshold methods remained robust (CoV $< 2.5\%$) with a relative error $< 1\%$.
- Vardoulis et al. (2013) [80] compared several commonly used point-based methods (diastolic minimum, intersecting tangent, maximum of first derivative, maximum of second derivative) and validated the diastole-patching method by applying them to waveforms representing an aortic segment and the carotid-femoral pathway, generated using a validated 1D arterial model. A total of 2000 cases were simulated under different hemodynamic conditions. The reference PWV was computed analytically from the model. The diastole-patching method outperformed the others. For the aortic segment, it reported a bias of 0.26 m/s, an RMSE of 0.32 m/s, and an ICC of 0.977 compared with the theoretical PWV values of the model. For the carotid-femoral pathway, diastole-patching again demonstrated excellent performance, although in this case it performed on par with the diastolic-minimum method (for both: bias 0.4 m/s, RMSE 0.47 m/s, and ICC 0.96).

- Xu et al. (2022) [81] compared four methods (diastole-patching, intersecting tangent, cross-correlation, and the simplified tube-load model) applied to carotid and femoral pressure waveforms generated by a 1D model, while varying vessel radius and length by $\pm 20\%$. The reference PWV was the value specified within the model. The tube-load model exhibited the highest performance, followed by diastole-patching, cross-correlation, and the intersecting tangent method. With respect to the reference values of the model, it maintained a bias within 0.13 ± 0.06 m/s. Even in the presence of noise (SNR ranging from 20 to 5 dB), the tube-load model remained the most accurate, with a bias of 0.07 ± 0.05 m/s. In this scenario, the diastole-patching method proved less robust, showing a marked deterioration in performance.
- Filippi et al. (2023) [96] compared three methods, peak-to-peak, intersecting tangent (denoted by the authors as tangent-secant), and cross-correlation, using simulated signals generated in MATLAB, reproducing the characteristic waveforms of a variable stiffness arterial simulator [203] under reflection-free conditions. The simulated waves were shifted by a known amount, used as the reference PTT. The cross-correlation method showed the best performance, exhibiting a bias of less than 0.1% with respect to the reference values, thereby highlighting the superior repeatability of cross-correlation compared with point-based approaches.

In Vivo Studies: Animals

Testing PTT estimation methods in animal models offers several advantages. First, the acquired waveforms are generated by a real biological system with all its inherent complexities; therefore, the resulting measurements more closely reflect the performance that these methods would exhibit in the human body [53]. In addition, tests can be conducted under different hemodynamic conditions. Historically, various procedures have been used to perturb blood pressure over a wide range, which is useful for evaluating method performance across different physiological states [99]. Finally, in such studies, it was not uncommon to employ invasive measurement techniques, which are considered more accurate for waveform acquisition [93].

- Khir et al. (2004) [83] compared the PU-loop method with a point-based foot-detection technique similar to the one proposed in [75]. For this purpose, they used waveforms acquired along different aortic segments in 11 anesthetized dogs. Pressure and flow measurements (required for the PU-loop method) were always obtained at the aortic root. In contrast, for the point-based method, pressure was recorded at four approximately equidistant sites, from the ascending aorta to the iliac segment. The results show that the two methods provide comparable estimates when a local measurement is considered. The average PWV values differed by only 2% when computed from the foot-to-foot

method in the ascending-proximal thoracic segment. However, when PWV was evaluated along the entire aorta (ascending-iliac segment), the discrepancy increased to approximately 20%. In both cases, the foot-to-foot method exhibited a CoV of about 14%, whereas the PU-loop method showed a CoV of approximately 24% (as calculated by the authors). The authors attributed this discrepancy to the fact that, in the second scenario, the two methods quantified different quantities (local PWV versus regional PWV), thus supporting the use of the PU-loop method as a valid approach for estimating local PWV.

- Mingwu Gao et al. (2014) [171] evaluated the effectiveness of the tube-load method in 11 anesthetized animals, in which blood pressure was acutely varied through the administration of vasoactive drugs. The tangent secant method was used as a comparator. Based on the assumption that, under controlled short-term conditions, arterial pressure is the primary determinant of PWV variation, the blood pressure was adopted as the reference metric. Assuming a linear relationship between PWV and BP, the method with the best performance should associate each PWV value with a corresponding BP value, yielding lower error and a higher correlation coefficient. Consistent with this expectation, the tube-load method demonstrated, across multiple testing conditions, a reduction in RMSE ranging from 35% to 43% and an increase in the correlation coefficient r between 11% and 53%.

In Vivo Studies: Humans

Although *in vitro* and *in silico* tests allow verification of a method's accuracy against a known reference value, and *in vivo* animal studies can be used to assess the method's sensitivity to physiological parameter variations, *in vivo* testing in humans is essential and represents a mandatory step before clinical implementation. This stage makes it possible to evaluate the variability in PTT values introduced by practical application in a clinical setting [79]. These studies primarily focus on reproducibility, agreement, and clinical applicability of the methods, often comparing them with a designated "gold standard":

- Chiu et al. (1991) [77] compared four point-based methods (diastolic minimum, first derivative, second derivative, and intersecting tangent) in 26 patients and 11 healthy volunteers. Pressure waveforms were acquired invasively along the aortic segment and non-invasively between the brachial and radial arteries. No external reference was used; instead, the methods were compared with each other. The first derivative method yielded results that were systematically different from the other three techniques under all testing conditions. In contrast, the second derivative and intersecting tangent methods showed consistent agreement across all conditions. For the aortic measurements, these two methods demonstrated the highest correlation ($r = 0.99$) with a CoV of approximately 4%. In the non-invasive recordings, they maintained excellent correlation ($r = 0.98$) and

exhibited a CoV of about 5-7%. The greater dispersion observed in the non-invasive data was attributed to increased noise and more pronounced wave reflections during acquisition. Overall, the authors concluded that these two methods were the most effective and robust for PWV estimation [76].

- Millasseau et al. (2005) [87] compared two devices that, at the time, were already used in clinical practice for measuring cfPWV: the Complior system (which employs the second derivative method) and the SphygmoCor system (which uses the intersecting tangent method). Tests were conducted both at rest and during acute interventions designed to increase heart rate. The results showed that different timing techniques lead to systematically different PWV values, regardless of other factors such as the waveform acquisition method. At rest, the two systems exhibited a difference of 1.7 ± 0.8 m/s, with an intra-subject CoV of 5-6% for both devices. During tests performed under increased heart rate, the discrepancy between the two methods remained significant. The authors concluded that the intersecting tangent method used by SphygmoCor was more accurate, as its results were more consistent with the expected clinical values for the measured subjects.
- Ibrahim et al. (2010) [139] compared three PWV measurement methods, tangent-secant, cross-correlation, and a model-based approach (i.e., QA-loop method) that estimates PWV from flow and arterial cross-sectional area at a single site, in 50 patients and 6 healthy volunteers. CMR images of an aortic segment were analyzed. From these images, mean velocity curves at two measurement sites were extracted for the tangent-secant and cross-correlation methods, while flow and cross-sectional area waveforms at a single site were obtained for the QA method. The results showed that the tangent-secant and cross-correlation methods were in better agreement with one another, exhibiting the highest inter-method correlation ($r = 0.95$). They were more reproducible and showed less observer-dependent variability compared with the QA method. Specifically, the inter-observer correlation was 0.94 and 0.88 for the tangent-secant and cross-correlation methods, respectively.
- Papaioannou et al. (2015) [84] evaluated the performance of the diastole-patching method by comparing it with the intersecting tangent technique. Both methods were applied to carotid-femoral pressure waveforms acquired in 340 subjects, each of whom underwent two consecutive PWV measurements. The diastole-patching method provided more precise and reproducible estimates, yielding a bias between repeated measurements of 0.04 ± 1.16 m/s, a CoV of 6.7%, and an ICC of 0.85. Even in a subgroup of 81 subjects in whom the intersecting tangent method produced a difference > 1 m/s between two

consecutive PWV measurements (CoV 14.2%), the diastole-patching method maintained a more limited dispersion (CoV 9.8%).

- Hu et al. (2015) [86] compared established methods (diastole minimum, first and second derivative, intersecting tangent, and diastole-patching) with a novel wave-based approach proposed by the authors, based on the least square difference method, i.e., WaveForm Matching Algorithm (WFMA). Tests were performed on carotid-femoral pressure waveforms derived from clinical data of 81 subjects, using a manually identified PTT value as the reference. The WFMA method demonstrated the best performance, followed by the diastole-patching method; both complied with the ARTERY guidelines [201] for clinical cfPWV measurement and were classified as “excellent”. Specifically, the WFMA method exhibited a bias of 0.16 m/s, an RMSE of 0.35, and an ICC of 0.99 against the reference. Repeatability was also assessed by measuring PWV on 10 volunteers with a one-hour interval, yielding an inter-measurement ICC of 0.96.
- Darwich et al. (2015) [89] compared the inter-subject and intra-subject reproducibility of three methods: intersecting tangent, second derivative, and partial cross-correlation. The methods were applied to waveforms representing vessel distension collected from 16 healthy volunteers at two different measurement sites. These waveforms were derived from carotid images acquired via MRI and segmented by selecting two ROIs. In the intra-subject test, the robustness of the methods was evaluated by assessing result variations using different ROIs and time windows on the waveforms. Partial cross-correlation yielded the most stable values, exhibiting a CoV of approximately 12%. Inter-subject tests assessed the reproducibility of the methods; in this case, as well, cross-correlation demonstrated better performance, with a CoV of 23%.
- Houriez-Gombaudo-Saintonge et al. (2019) [202] compared three methods for estimating aortic PWV from 4D flow CMR data acquired from 47 healthy subjects. The methods were based on cross-correlation, Wavelet, and Fourier analysis. The Wavelet-based method outperformed the others, demonstrating superior inter-operator reproducibility with an ICC of 0.99. Furthermore, it proved more robust even with lower temporal resolution, presenting an ICC of 0.97. Additionally, it yielded values that were more consistent with reference values derived from clinical cfPWV measurements and the Bramwell-Hill formula compared to the other methods.
- Valerio et al. (2023) [94] compared a method based on partial cross-correlation for cfPWV calculation in 75 subjects against the total cross-correlation. Data were acquired using the Athos system, while the SphygmoCor system was employed to derive reference values. Partial cross-correlation yielded results comparable to the tangent-secant method ($r = 0.96$ vs. $r = 0.965$; bias 0.16 m/s vs. -0.07 m/s; RMSE 0.57 m/s vs. 0.52 m/s). Both methods meet

the ARTERY criteria [204]. However, the partial cross-correlation proved more robust to noise, exhibiting the lowest mean absolute error compared to “noise-free” values. Conversely, total cross-correlation produced the poorest results ($r = 0.82$; bias -1.04 m/s; RMSE 2.4 m/s), confirming that unprocessed cross-correlation is limited to local PWV estimation.

1.2.5) Practical considerations for method selection

As can be inferred from the previous paragraph, there is no single method that is universally superior to the others; the optimal choice strictly depends on the specific application, as each entails unique requirements and constraints [79], [93]. The following discussion analyzes the primary applications (regional and local measurements) currently addressed in clinical practice for PWV assessment, highlighting their specific needs and identifying the most effective methods for obtaining accurate and reproducible PWV measurements, as validated by *in silico* and *in vitro* studies. The selected techniques are summarized in Table 1.2, along with their respective advantages and limitations, and are described in detail below. Techniques relying on invasive acquisition methods (e.g., catheters, occasionally used as a reference for validation) are excluded, given the current trend towards non-invasive assessment.

Table 1.2. Main advantages and limitations of the methods selected in the literature as a function of the application.

Application	Method	Advantages	Limitations	Ref.
Regional PWV measurement	Diastole-patching	Robustness to noise	Sensitivity to waveform similarity	[79]
	Waveform matching algorithm	- Region-of-interest analysis/exclusion of reflections - Robustness to noise and undersampling	ROI-selection dependence	[85]
	Region-based cross-correlation	- Region-of-interest analysis/exclusion of reflections - Robustness to noise and undersampling	ROI-selection dependence	[93]
	Simplified tube-load model	computational elimination of reflected waves	Computational and optimization complexity	[80]
Local PWV measurement	Wavelet-based method	- Robustness to undersampling - Reflection exclusion	- Dependence on the mother wavelet choice - Complexity of computation and implementation	[71]
	Group Delay	Repeatable at low temporal resolution	Reflections not fully isolated	[117]
	Partial cross-correlation	- Region-of-interest analysis/exclusion of reflections - Robustness to noise and undersampling	ROI-selection dependence	[92]
	PU-loop	local measurement (one measurement site)	Simultaneous acquisition of multiple quantities	[197]

As pointed out in Section 1.1, regional PWV measurement (e.g., cfPWV) is currently the most widely used clinical approach for assessing arterial stiffness. Typically, the transit of the pressure wave is recorded non-invasively using applanation tonometry at two sites separated by a known distance. In many cases, the measurement is performed sequentially at each site, and the traces are synchronized using the ECG as a reference [93]. The aim is to obtain a reliable estimate of PWV over a long arterial segment.

Assuming that the errors associated with estimating the distance between the two measurement sites and with synchronizing the acquired traces are negligible (limitations that are nonetheless present in real-world applications), the main challenge of this approach lies in the distortion of the acquired waveforms due to dissipative effects along the arterial tree. For this reason, the most effective methods for regional PWV estimation are those that analyze the similarity of a waveform portion, focusing on the initial part of the systolic upstroke, or those based on mathematical models capable of predicting or accounting for waveform distortion and reflected waves.

In silico studies have shown that the diastole-patching method provides more accurate PWV values than traditional point-based techniques, and that it maintains good repeatability while remaining robust in the presence of noise [80]. *In vivo*, it demonstrated higher reproducibility than the intersecting tangent method implemented in SphygmoCor [84]. Thanks to its performance, it has recently been included among the recommended methods for PWV assessment alongside the intersecting tangent approach [71].

The WFMA has also proven effective. *In vivo* studies have shown that it exhibits the lowest bias and the highest accuracy compared with the used reference method, and it demonstrated the best repeatability among all tested point-based and wave-based techniques [86]. The region-based cross-correlation method can thus be included among the methods considered suitable for this purpose, since it has shown greater robustness than the intersecting tangent approach in the presence of noise [142].

It is important to note that, despite the performance of the more recent methods described above, the intersecting tangent method remains one of the most consistent and widely applicable techniques. It is recommended in the *consensus* document [81] and it is, in fact, the standard implemented in leading clinical devices such as SphygmoCor and Athos [94], [204].

The simplified tube-load model, which incorporates both wave propagation and reflection, has emerged as a highly promising approach. *In silico* studies have shown it to be more accurate than the intersecting tangent and cross-correlation methods, and *in vivo*, it demonstrates greater repeatability compared with these techniques [81].

Local PWV assessment is a rapidly evolving practice that offers distinct advantages over regional PWV measurement. It aims to quantify arterial stiffness at a specific anatomical location, thereby providing information on the local biomechanical properties of the vessel [89]. This enables a more detailed and site-specific characterization of vascular damage, which can serve as both an indicator and a potential risk factor for cardiovascular disease and stroke [93]. One advantage is that the estimation of the distance between measurement sites is more accurate, and the acquired waveforms are not affected by distortion or by the multiple reflections generated across the numerous bifurcations present inside long segments of the arterial tree.

One of the main challenges in this type of acquisition is that the measurement sites are very close to each other (10–50 cm), and therefore, the delay between the two waveforms is only a few milliseconds [93]. For these reasons, surface sensors (PPG and tonometry) are generally avoided to eliminate inter-channel hardware delays and to exclude the influence of tissue transit time, that is the time required for the wave to travel from the artery to the skin surface, which is comparable to the PTT. Both effects may introduce systematic errors in transit-time estimation [93].

Non-invasive imaging techniques, such as 4D-flow CMR and high-frequency ultrasound (PWI), are therefore preferred, as they allow multiple measurement sites to be analyzed within a single acquisition, thereby resolving the issue of signal synchronization. The limitation is that these techniques typically offer lower spatial and temporal resolution than other measurement systems. Consequently, the most effective methods for local PWV assessment are those that have demonstrated strong robustness when applied to undersampled signals.

In *in vivo* studies, the *wavelet cross-spectrum* method has proven to be a robust solution [72]. It shows a higher correlation with age and with cfPWV compared with time-domain techniques, and together with the Fourier-based *group-delay* method, it is among the most robust approaches under undersampling conditions. In the presence of noisy signals, however, the wavelet method outperforms even the group-delay technique.

Partial cross-correlation has also proven to be an accurate and reproducible technique compared with other tested algorithms [126]. In *in vivo* studies, it exhibited superior inter-test reproducibility relative to point-based methods [89], although its *in vivo* variability remains substantially higher than that observed in *in vitro* phantom experiments [116]. With regard to *full cross-correlation*, the literature confirms that although it is more sensitive to reflected waves [141], this issue is generally less problematic when analyzing local arterial segments [120], [205].

In contexts where pressure and blood-flow measurements can be obtained non-invasively, e.g., in superficial peripheral arteries [83], the *PU-loop* method represents an excellent solution. Owing to its operating principle, it requires measurements at a single site, thereby drastically reducing the uncertainty associated with the inter-site distance that affects other methods [93]. In *in vitro* tests, the method yielded results comparable to the traditional foot-to-foot approach [199], whereas in *in vivo* experiments, it proved sensitive and reliable in detecting stiffness changes induced by acute pressure manipulations [83].

1.2.6) Final conclusions

The estimation of Pulse Wave Velocity (PWV) for the evaluation of arterial stiffness depends on the accurate and reproducible calculation of the Pulse Transit Time (PTT) of the pressure waveform inside arterial vessels.

This comparative analysis of the literature highlights that there is no single "best" PTT estimation method. Rather, the optimal choice must be carefully evaluated based on the specific application context. Specifically, the distinction between measuring regional PWV (e.g., carotid-femoral) and local PWV (e.g., carotid or aortic) imposes specific requirements in terms of acquisition modality, expected signal quality, and the arterial segment under examination.

Point-based methods, particularly the Intersecting Tangent and second derivative approaches, perform best for regional PWV measurements over long arterial segments. By focusing on the waveform foot, they are only minimally affected by distortion accumulated over long propagation distances due to reflections within the arterial tree. Their simplicity and low computational cost have enabled their integration into devices that are currently used in clinical practice. However, they are susceptible to noise and require signals with a high sampling frequency.

Wave-based methods, such as diastole-patching and region-based cross-correlation, often outperform point-based approaches for regional PWV estimation and, even more markedly, for local PWV assessment, where the distance between sensors is short. In these scenarios, the uncertainty associated with distance measurement and signal synchronization is reduced thanks to imaging-based acquisition. Within this context, wave-based methods offer strong robustness in the presence of noise and undersampled signals, albeit at the cost of higher computational demands. However, they remain sensitive to the contribution of reflected waves, which may lead to overestimation or underestimation of the calculated PWV.

Model-based methods have the potential to overcome several limitations of traditional approaches. These techniques can, in principle, separate the contribution of backward-traveling waves and estimate multiple hemodynamic quantities from single-site or sequential measurements. Several studies have reported that, under specific conditions,

these methods show improved agreement with reference techniques and superior performance compared with conventional PWV estimation approaches. Nevertheless, their use remains largely confined to research settings. The model parameters required are highly subject-specific, as they must be derived from the individual being assessed. Moreover, validation studies to date have involved relatively small cohorts.

Future Directions

The future of arterial stiffness assessment using PWV measurement is moving toward more accessible and automated methods that can extract information from simple peripheral signals, including those obtainable with wearable devices [206], [207]. Recent studies have shown that machine-learning models can infer cfPWV directly from a single waveform, instead of relying on PTT calculations [206], and can maintain good performance even when the signals are noisy, which makes them promising candidates for out-of-hospital or home monitoring scenarios [207]. These results were also enabled by the adoption of wave-based approaches that decompose blood pressure signals into time-frequency representations, which are then used as inputs to learning algorithms. Such strategies further highlight the potential for robust and operator-independent PWV estimation [208]. This trend again underscores the importance of cardiovascular simulators, which in this context are already being used to generate large databases of virtual subjects for training models that link raw pulse-wave acquisitions to PWV [209], [210].

However, to translate these computational advances into clinical practice, several critical challenges must be addressed. First, rigorous validation on *in vivo* data, including independent, external clinical cohorts, is required to ensure reproducibility across diverse biological populations [209]. Additionally, improving robustness in ambulatory settings is essential, so that algorithms can reliably handle motion artefacts and environmental noise inherent to wearable devices and smartwatches [206]. Finally, because these models are highly dependent on their training data, transparent reporting of model architecture, training datasets, and evaluation procedures is crucial to ensure that results remain interpretable and comparable across studies, devices, and populations [210].

1.3) Arterial simulators: role and usefulness in biomedical applications

The cardiovascular system is among the most complex fluid-dynamic networks in biology, governed by tightly coupled interactions between pulsatile flow, blood rheology (including non-Newtonian effects), and the viscoelastic mechanics of vessel walls. In the effort to understand hemodynamic phenomena, researchers have historically relied on *in vivo* studies. However, experimentation in living organisms presents substantial limitations. Physiological variability, such as fluctuations in heart rate, blood pressure, and vasomotor tone, often masks the intrinsic mechanical behaviour of the arterial tree, making it difficult

to isolate specific independent variables. In addition, ethical constraints and the potential invasiveness of many protocols restrict the scope of *in vivo* investigations, particularly when evaluating novel medical devices or probing extreme pathological scenarios [211].

To address these limitations, biomedical engineering has developed *in vitro* arterial simulators, often referred to as Mock Circulatory Systems (MCS). These platforms are electromechanical and hydraulic systems designed to reproduce physiological and pathophysiological cardiovascular conditions within a controlled laboratory environment. By acting as surrogates for living systems, they enable precise and repeatable manipulation of hemodynamic parameters. Moreover, they provide an intermediate validation layer between computational models (e.g., *in vitro* approaches) and *in vivo* studies, offering a practical “ground truth” for testing mathematical hypotheses and calibrating diagnostic instrumentation [212].

The following sections briefly outline the typical structure of arterial simulators (Sections 1.3.1 and 1.3.2). Then, their relevance across key biomedical applications will be summarized (Section 1.3.3) and their possible suitability for a PWV measurement system reference will be discussed (Section 1.3.4).

1.3.1) Composition and Design of Arterial Simulators

Although the architecture of an arterial simulator is strongly dependent on its intended use, most systems share a common topology composed of four main subsystems [212]:

- *Pumping unit (heart surrogate)*: this subsystem reproduces cardiac output and is responsible for generating the desired flow and pressure waveforms. The fidelity of the pulsatile signal depends on both pump design and the associated control strategy. Common implementations include piston pumps, gear and centrifugal pumps, and programmable artificial-heart units.
- *Vascular surrogate (arterial surrogate)*: the conduit connecting the pump to the periphery is the most critical element for studies focused on arterial stiffness and wave propagation. The selected material should exhibit mechanical and viscoelastic behaviour comparable to that of human arteries. Common materials include latex, silicone and 3D-printed scaffolds.
- *Working fluid (blood surrogate)*: the circulating fluid determines, among other aspects, wall shear stress and the damping of pressure waves. Frequently adopted fluids include Newtonian surrogates (e.g., water or water-glycerol mixtures) and more complex blood analogues containing microparticles to better reproduce non-Newtonian behaviour.
- *Peripheral load (peripheral vascular surrogate)*: to replicate the impedance of systemic circulation, simulators incorporate afterload modules that introduce controlled resistance

and compliance. Typical elements include compliance chambers (e.g., air-filled reservoirs) and resistive components (e.g., clamps, porous media, or tubes with smaller diameter than the main arterial surrogate).

1.3.2) Measurement sensors for hemodynamic quantities assessment

Accurate measurement of the quantities generated by dynamic phenomena within arterial simulators is essential both to verify correct simulator operation and to ensure that the apparatus reproduces the target mechanisms for which it was designed. Sensor selection depends closely on the simulator's purpose and on its geometric and functional characteristics. The most commonly measured quantities include [212]:

- *Pressure*: pressure is a primary variable in hemodynamic analysis, and the choice of sensor directly affects waveform fidelity. Common solutions include catheter-tip manometers and differential pressure transducers.
- *Flow*: flow-rate quantification is required to compute quantities such as circuit impedance and wall shear stress. Widely used technologies include ultrasonic flowmeters, electromagnetic flowmeters, and optical flow methods (e.g., PIV/LDV).
- *Displacement*: surrogate wall displacement measurements can be used to quantify vessel compliance and, in some configurations, to indirectly detect pressure-wave transit along the conduit. Typical sensors include piezoelectric probes, capacitive sensors, strain gauges, sonomicrometry (ultrasound crystals), and optical/video dimension analyzers (VDA).

1.3.3) Biomedical applications of arterial simulators

Given the advantages outlined above, arterial simulators are employed in a broad range of biomedical applications [211], [212]:

- *Studying the relationship between hemodynamics and pathology*: arterial simulators enable mechanistic investigation of arterial disease by isolating variables and supporting causal inference between hemodynamic behaviours and pathological progression. Representative applications include studies of structural failure in arterial bifurcations associated with atherosclerosis, stenosis and plaque biomechanics and microvascular/backward-flow investigations.
- *Medical device testing and validation*: before clinical deployment, devices such as stents, valves, and pumps must be evaluated in controlled conditions to assess safety and performance. Arterial simulators provide a standardized “test bench”. Examples include ventricular assist devices (VADs) and artificial hearts.

- *Validation of in silico (computational) models:* computational simulations (e.g., CFD) can be efficient and cost-effective but rely on assumptions that require experimental validation. Arterial simulators are therefore used to validate mathematical models and relationships among hemodynamic variables or, as described in Section 1.2, to validate PWV estimation methods.
- *Clinical training and surgical simulation:* beyond research, simulators support medical education by enabling clinicians to practice invasive procedures without risk to patients, such as catheterization and microvascular anastomosis.
- *Calibration of cuffless blood-pressure monitors:* wearable cuffless devices can be evaluated using simulators because pressure and arterial-wall properties can be controlled independently and known a priori. For example, a device can be tested on a tube with constant stiffness while pressure is increased in steps. If the device reports stiffness variations driven solely by pressure, the behaviour of its algorithm can be assessed and validated.

1.3.4) Suitability as a reference platform for PWV assessment

Arterial simulators have become essential infrastructure in biomedical engineering because they allow hemodynamic variables to be isolated and controlled, separating the effects of geometry, fluid viscosity, and wall stiffness in a way that is generally infeasible in clinical studies. As noted above, these systems are already used for calibrating medical devices (e.g., cuffless blood-pressure monitors) and for verifying methods used to estimate hemodynamic indices, including PWV.

On this basis, it is reasonable to consider arterial simulators as strong candidates for establishing a metrological reference for the verification and validation of devices currently adopted for clinical PWV assessment, as well as for the calibration of emerging solutions aimed at improving the reliability of these measurements in clinical practice.

2) The novel variable-stiffness arterial simulator

As previously mentioned in Section 1, a variety of instruments are currently used in clinical practice to measure PWV. However, these devices are often characterized by limited accuracy [93] and, more importantly, they frequently provide results that are not directly comparable [212]. This highlights the need for a reference system capable of verifying the performance and calibrating both devices already in clinical use and emerging technologies for PWV measurement.

To this end, an innovative arterial simulator prototype has been introduced recently [213] and represents a first step toward the development of a device capable of addressing this need. Its key strength lies in the ability to modulate PWV within an arterial surrogate. This feature enables the assessment of an instrument's capability to detect PWV variations across the physiological range, to evaluate its sensitivity and to quantify its accuracy.

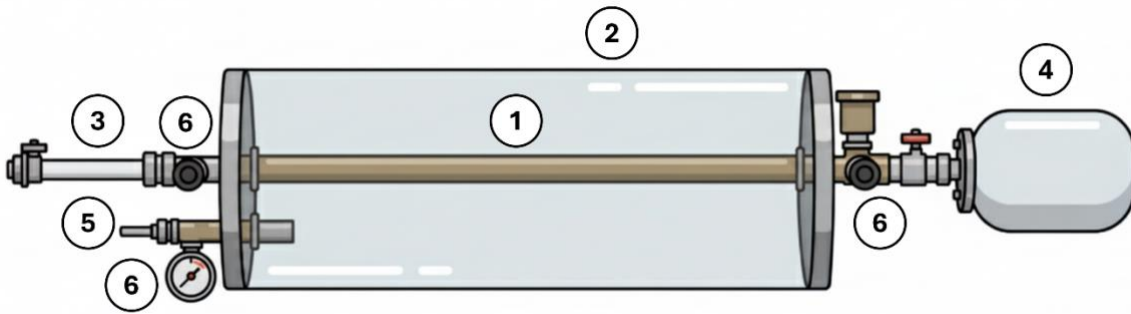


Figure 2.1. Schematic of the arterial simulator main components: arterial surrogate (1), PMMA chamber (2), piston (3), hydropneumatic accumulator (4), external chamber valve (5), pressure transducers (6).

The novel variable-stiffness arterial simulator is illustrated in Figure 2.1. It consists primarily of a silicone rubber vessel, representing the arterial surrogate, enclosed within a polymethyl methacrylate (PMMA) case. Hydraulic fittings connect the surrogate to a piston that reproduces the pressure pulses generated by the heart. Distilled water is used as the working fluid inside the conduit. The system includes a hydropneumatic accumulator that allows adjustment of the internal pressure of the conduit p_i , as well as a valve to regulate the pressure within the external chamber p_o . Pressure transducers are installed to continuously monitor both pressure levels.

2.1) Operating principle

As described in [213], its distinctive structural configuration enables a continuous modulation of the PWV within the arterial surrogate. The presence of the external chamber

makes it possible to independently adjust the internal and external pressures applied to the walls of the arterial surrogate (Fig. 2.2).

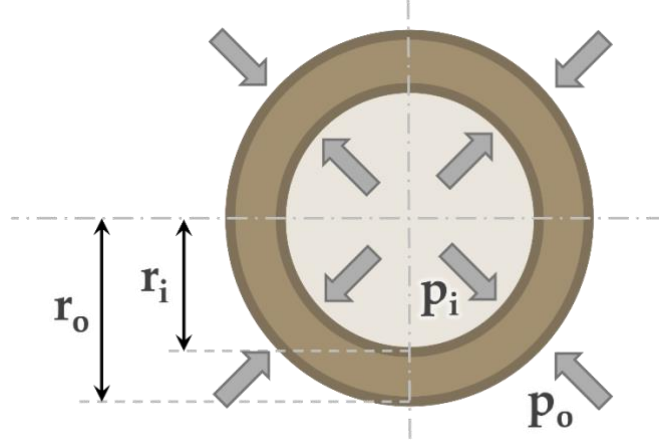


Figure 2.2. Cross-sectional representation of the arterial surrogate. The inner radius r_i and outer radius r_o are indicated. The internal pressure p_i and the external pressure p_o acting on the conduit walls can be adjusted through the valves and components within the simulator.

In this way, the transmural pressure ΔP can be adjusted, defined as follows:

$$\Delta P = p_i - p_o \quad (2.1)$$

Referring to a cylindrical coordinate system, the application of a transmural pressure generates a plane stress condition. In particular, the stresses imposed by the transmural pressure can be described by Lamé's equations [214]:

$$\sigma_t = \frac{p_i r_i^2 - p_o r_o^2}{r_o^2 - r_i^2} + \frac{r_i^2 r_o^2 (p_i - p_o)}{r^2 (r_o^2 - r_i^2)} \quad (2.2)$$

$$\sigma_r = \frac{p_i r_i^2 - p_o r_o^2}{r_o^2 - r_i^2} - \frac{r_i^2 r_o^2 (p_i - p_o)}{r^2 (r_o^2 - r_i^2)} \quad (2.3)$$

where σ_t and σ_r represent the tangential and radial stress of the conduit walls, respectively, as a function of the radius r , of p_i and p_o . Specifically, r_i and r_o are the internal and external radius of the conduit (Fig. 2.2). On the assumption that the material constituting the surrogate is isotropic, the stress state can be related to the strain state using the following constitutive equations [214]:

$$\varepsilon_t = \frac{1}{E} (\sigma_t - \nu \sigma_a - \nu \sigma_r) \quad (2.4)$$

$$\varepsilon_r = \frac{1}{E} (\sigma_r - \nu \sigma_a - \nu \sigma_t) \quad (2.5)$$

$$\varepsilon_a = \frac{1}{E}(\sigma_a - \nu\sigma_r - \nu\sigma_t) \quad (2.6)$$

where ε_t , ε_r , and ε_a are the tangential, radial, and axial strains, respectively, and ν is the Poisson's ratio of the material. In addition, the axial stress σ_a depends on the pre-tensioning of the surrogate applied during its installation inside the case [214].

A distinctive feature of elastomeric materials is that, within the elastic regime, their Young's modulus is not constant but depends on the deformation state [215].

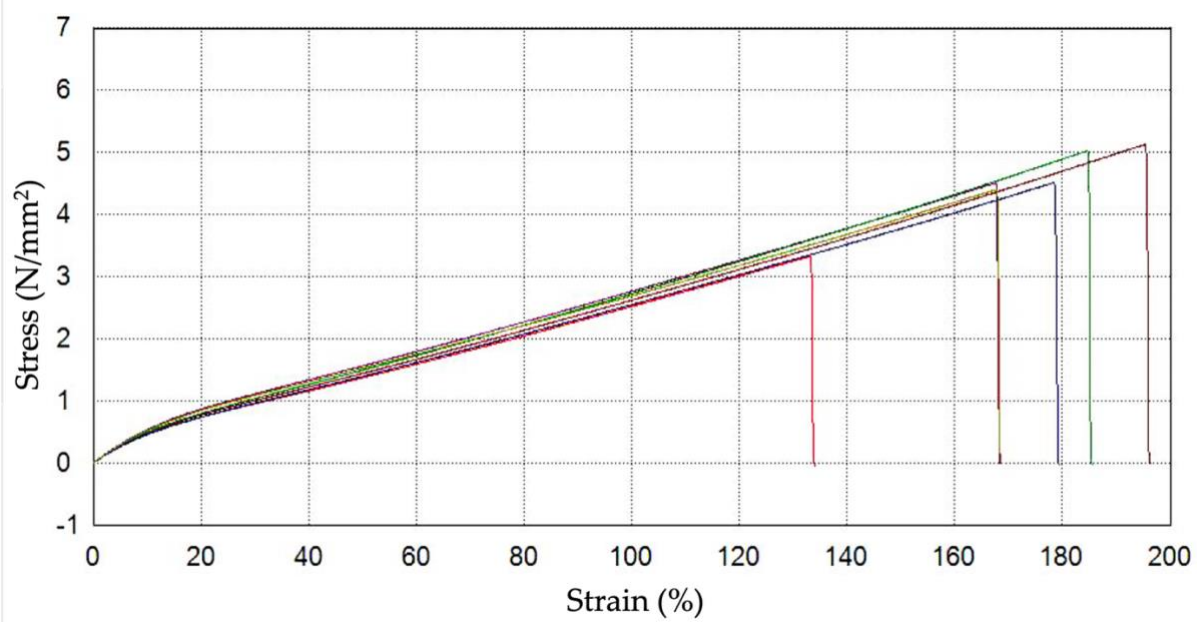


Figure 2.3. Stress-strain curve of six specimens made of silicon rubber. Behaviour deriving from uniaxial stress-strain test.

Fig. 2.3 shows an example of a stress-strain curve obtained from a tensile test performed on six specimens made of the same material as the arterial surrogates used in this work. The plot clearly illustrates how the slope of the curve, representing the Young's modulus, varies as the strain increases.

By adjusting ΔP , therefore, the resulting effect is a variation in the PWV according to the Moens-Korteweg equation [216]:

$$PWV = \sqrt{\frac{Eh}{\rho d}} \quad (2.7)$$

where E , h and d are the Young's modulus, the thickness and the inner diameter of the surrogate, respectively, while ρ is the density of the inner fluid.

2.2) Circuit components

To ensure the optimal operation of the entire system, each component was properly dimensioned. The setup shown in Fig. 2.1 is described in detail below.

Arterial Surrogate

The arterial surrogate used in the arterial simulator is made of silicone rubber (Fig. 2.4).



Figure 2.4. Arterial surrogate used within the variable-stiffness simulator during the installation of the sensing instrumentation for detecting the passage of the pressure wave.

Its main geometric and mechanical properties are listed in Table 2.1.

Table 2.1. Main characteristics of the silicon rubber hose used as arterial surrogate. Values are expressed as mean $\pm$ standard deviation (SD). In this case, the SD represents the contribution from repeated measurements.

Characteristic	Value
Length (cm)	42.0 ± 0.1
Inner diameter (mm)	16.0 ± 0.4
Thickness (mm)	2.0 ± 0.1
Young's modulus (MPa)	$\approx [2 \div 8]$

In this initial experimental phase, the design of this component was not intended to faithfully reproduce the characteristics of living arterial tissue, which is considerably more complex in both structure and composition, but rather to satisfy specific construction constraints imposed by the other elements of the system, whose geometries follow commercially available standards, while remaining broadly consistent with the intended application. For example, the selected diameter is close to that of a large artery but was chosen among standard commercial dimensions. Similarly, the Young's modulus is close to that of a blood vessel, although it is slightly higher to ensure that the vessel can support its own weight and avoid sagging when mounted in suspension inside the simulator.

External case

The external case is a sealed container made of polymethylmethacrylate (PMMA), represented in Fig. 2.5.

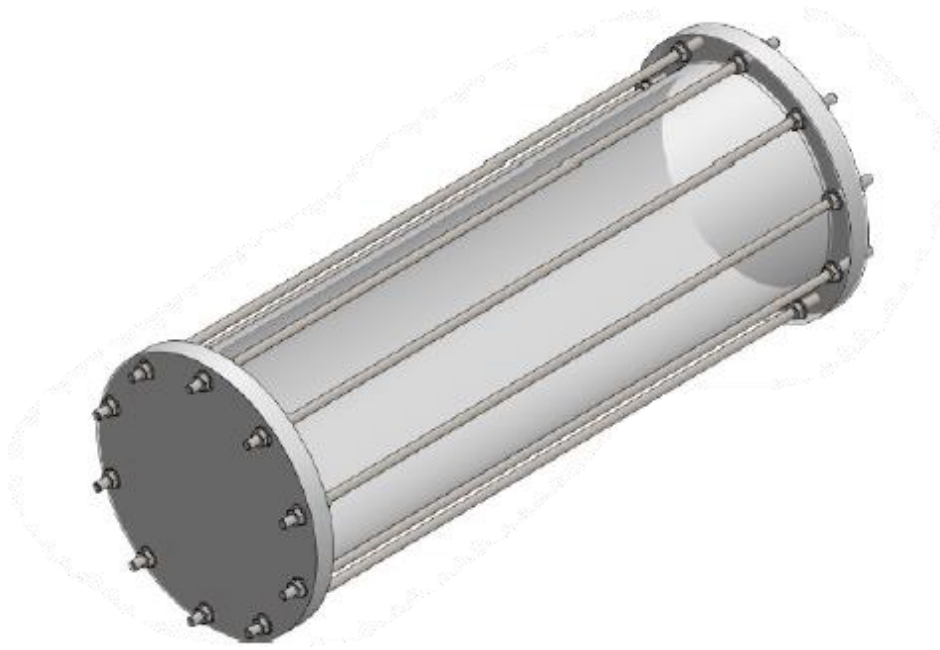


Figure 2.5. External container with two caps that seal the environment using gaskets. Threaded bars and nuts hold the caps in place.

The main geometrical and mechanical characteristics are illustrated in Table 2.2.

Table 2.2. Main geometrical and mechanical characteristics of the external case.

Characteristics	Value
Length (cm)	60
Inner diameter (cm)	19
Thickness (mm)	5
Specific weight (g/cm ³)	1.19
Tensile strength at break (N/mm ²)	72
Elastic modulus of traction (N/mm ²)	3200

The external case is designed to withstand up to 3 atm (gauge), allowing the behavior of the arterial surrogate to be explored across a wide range of stress-strain states. Two circular caps, each 20 mm thick, together with rubber gaskets, ensure an airtight internal environment. These components are secured in place using threaded rods with nuts and locknuts. Holes on the caps accommodate sleeves that allow connections between the inside and outside of the chamber (Fig. 2.6).

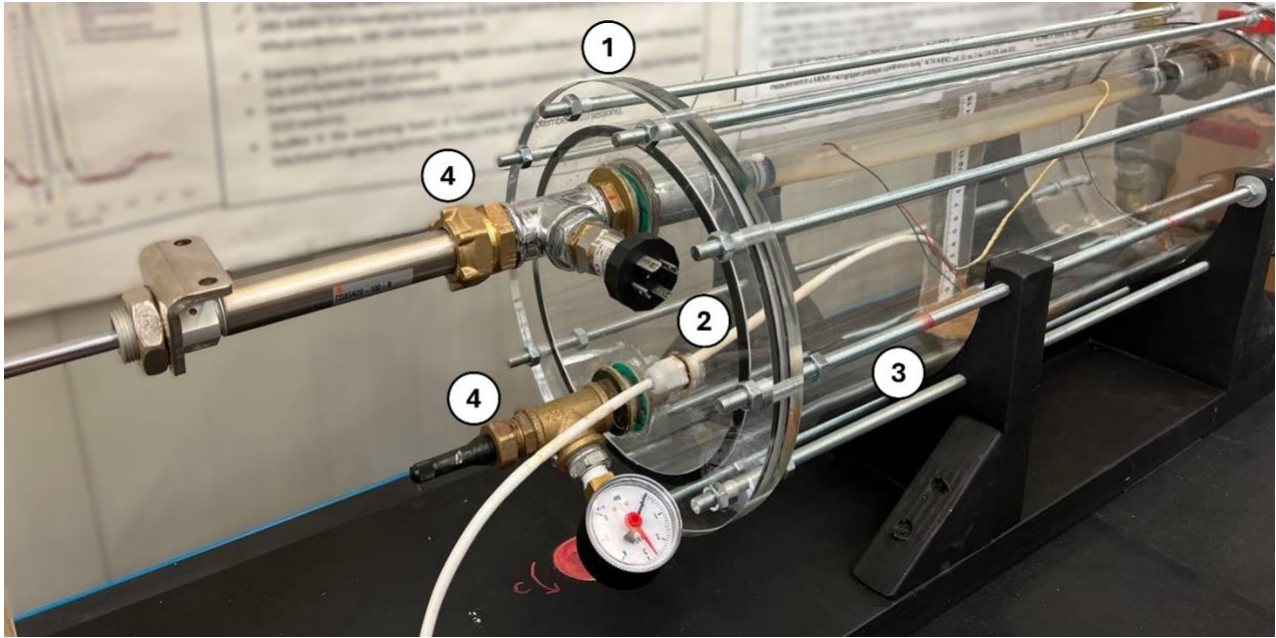


Figure 2.6. Arterial simulator. Detailed view of the external-environment components: circular cap (1), rubber gasket (2), threaded rods with nuts and locknuts (3), sleeves for communication between the internal and external environments (4).

Hydropneumatic accumulator

A hydropneumatic accumulator is installed in the circuit of the arterial surrogate. It consists of a chamber with an internal membrane that separates a liquid-filled compartment (water) from an air-filled one. It serves a dual purpose. First, the air volume provides a means to mimic the compliance of downstream vessels relative to the simulated artery. Second, this component is used to adjust the internal pressure within the arterial surrogate. The characteristics of the hydropneumatic accumulator are reported in Table 2.3.

Table 2.3: Characteristics of the hydropneumatic accumulator.

Characteristic	Value
Chamber material	Stainless steel
Total capacity	2 dm ³
Membrane material	Rubber
Maximum pressure	1 MPa

Piston and linear actuator

The piston (SMC - CD85N20-100-B) acts as the heart pump. By injecting a finite volume of working fluid into the arterial-surrogate circuit, it generates the pressure pulse. Its diameter was selected to match the dimensions of the arterial surrogate. To ensure the generation of repeatable pressure impulses, a linear actuator (Mecalectro F-91300 MASSY) was installed. By controlling the voltage applied to the solenoid, it is possible to regulate the

force exerted by the rod on the piston. The main characteristics of these components are listed in Table 2.4 and represented in Fig. 2.7.

Table 2.4: Main characteristics of the piston and linear actuator in the arterial simulator.

Characteristic	Value
Piston	
Diameter	20 mm
Maximum stroke	100 mm
Linear actuator	
Stroke	18 mm
Force	5-40 N
Supply range	6-250 Vcc

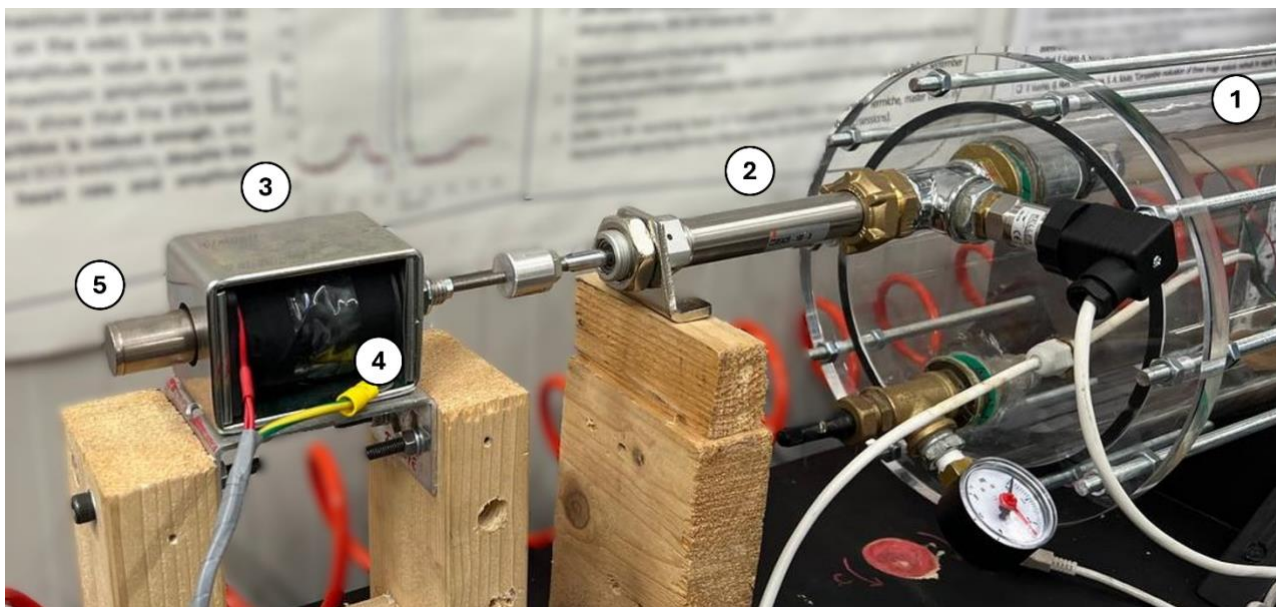


Figure 2.7. Arterial simulator with a detailed view of the elements generating the pressure impulse: arterial surrogate within the external chamber (1), piston (2), linear actuator (3), solenoid (4), rod (5).

Pressure transducers

Digital pressure transducers (Keller PA 23SY) were installed to measure the internal and external pressures acting on the walls of the surrogate. They are connected to the simulator chambers through hydraulic fittings. The sensors provide a voltage output and were interfaced either with an oscilloscope or with the data-acquisition board, depending on the specific requirement, to monitor the pressure values. The manufacturer supplied the corresponding calibration certificate. The main specifications are listed in Table 2.5.

Table 2.5. Main characteristics of the pressure transducers.

Characteristic	Value
Material	Stainless steel AISI 316L
Pressure interval	0-1 MPa
Accuracy	$\pm 2.5\% \cdot \text{scale range (@ } 20^{\circ}\text{C)}$
Power supply	15 V _{DC}
Output voltage	0-10 V _{DC}
Bandwidth	2 kHz
Response time	< 5 ms

2.3) Circuit configurations

All the components described above are interconnected to reproduce the propagation of the pressure wave along an arterial segment. During the laboratory experiments carried out in the context of this doctoral research, two main configurations were used [97], [197].

Open-loop circuit

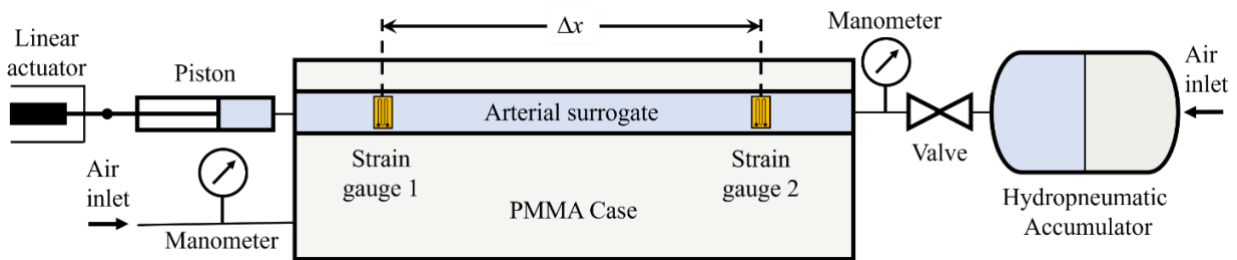


Figure 2.8. Schematic representation of the hydraulic layout of the arterial simulator in the “open-loop” configuration.

Fig. 2.8 shows a schematic representation of the open-loop configuration. In this setup, the arterial surrogate, placed inside the external chamber, is connected at one end to the piston and linear actuator, while its opposite end terminates at the hydropneumatic accumulator. This configuration is referred to as “open-loop” because the inlet and outlet of the surrogate are not connected through a return line. A valve is placed between the surrogate and the accumulator to separate the components during the testing phase. This prevents the reflected waves generated by the membrane from affecting the phenomenon of interest, as described in [194], [195], and it is useful for independently modelling the upstream “cardiac” impulse and the downstream load applied to the surrogate. In this case, the net fluid flow is macroscopically zero, allowing the propagation of the pressure wave to be isolated and studied independently.

Closed-loop circuit

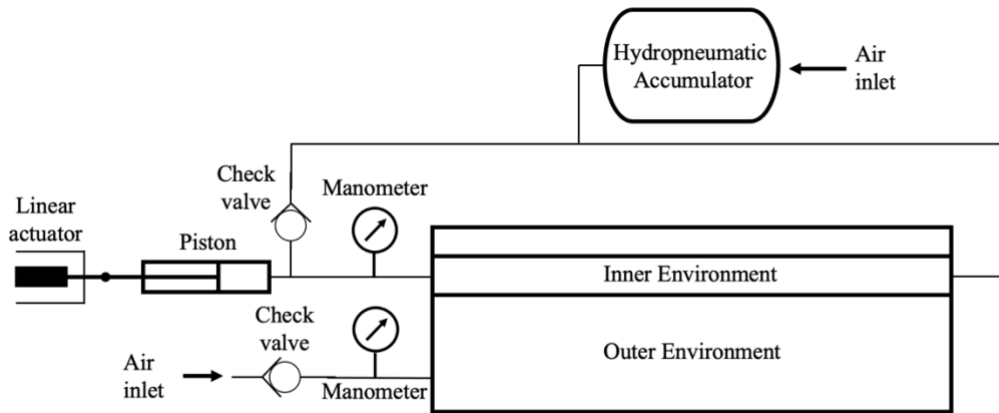


Figure 2.9. Schematic representation of the hydraulic layout of the arterial simulator in the “closed-loop” configuration.

Figure 2.9 provides a schematic representation of the closed-loop configuration. Unlike the previous setup, a different hose, made of polyvinyl chloride (PVC), is connected in a closed loop with the extremities of the arterial surrogate to let the working fluid flow through the surrogate. It is a flexible tube with viscoelastic behavior that allows it to dissipate the pressure wave and prevent it from re-entering the aortic surrogate; however, it is stiffer than a silicone rubber surrogate and thus can withstand the working pressures expected by the system without visibly deforming (compared with silicone rubber). The hydropneumatic accumulator is placed in parallel with the loop to mimic the compliance of the downstream arterial tree relative to the conduit under investigation. A check valve is placed between the end of the recirculation loop and the inlet of the surrogate. This ensures unidirectional fluid flow and guarantees that the pulse generated by the piston is fully conveyed into the surrogate. With this configuration, also well established in the literature [217], [126], the incoming pulse is influenced by the downstream conditions of the surrogate. It provides a more realistic simulation of the cardiovascular segment under investigation, as the fluid flow is no longer zero.

2.4) Requirements for PWV measurement

To perform PWV measurements within the arterial simulator, a set of requirements must be satisfied both in the selection of the most appropriate method and in the choice of the most suitable sensor, given the geometry and construction characteristics of the system.

Method requirements

The arterial surrogate has a relatively short length, which indicates that the measurement falls within the “local PWV” category (Section 1.2). In this configuration, the acquired pressure waveforms are similar, as the dissipative phenomena associated with the viscoelasticity of the conduits are not dominant. Noise within the acquired signals must also

be considered. In this context, operator-dependent influences should be minimized (e.g., filtering should be reduced as much as possible). These considerations lead to the choice toward *wave-based* or *model-based* methods, whose implementation and optimization are explored in Chapter 3.

Sensor requirements

The installation of the arterial surrogate inside the external case significantly restricts the types of sensors that can be used to detect the transit of the pressure wave within the conduit. Catheters, which allow direct pressure measurement, are difficult to install because they need to be inserted from outside the chamber, requiring additional hydraulic fittings. These would complicate the circuit geometry and increase the risk of generating unwanted reflected waves. Flow measurements are not feasible, as some simulator configurations (Section 2.3) operate under zero-flow conditions to isolate and study pressure-wave propagation alone. For these reasons, an alternative is to detect the transit of the pressure wave within the surrogate through measurements of circumferential strain on the conduit wall. In this context, optical measurements cannot be performed due to the difficulty of positioning the probes inside the pressurized external case; for the same reason, tonometric probes are also unsuitable. Consequently, strain sensors were directly applied to the external surface of the surrogate. An example is shown in Fig. 2.10.

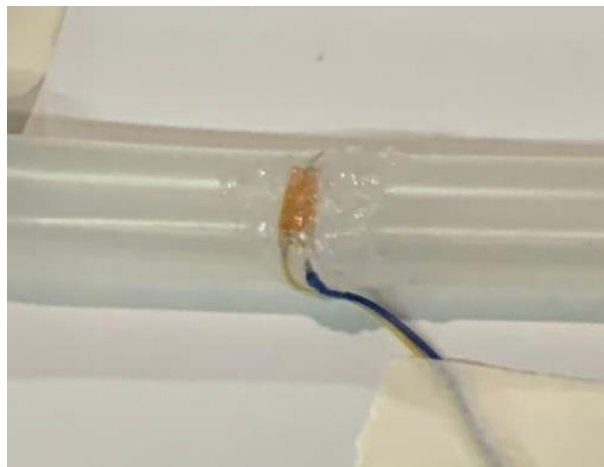


Figure 2.10. Example of a transducer mounted on the outer walls of the arterial surrogate.

Beyond the geometric constraints outlined above, the sensor must meet specific mechanical requirements. In particular, it must be able to detect the deformations experienced by the surrogate within the simulator. First, it must accommodate the static deformation resulting from the imposed ΔP value; second, it should detect minute variations in deformation associated with the transit of the pressure wave. These needs translate into two fundamental requirements.

The minimum detectable strain (ε_{min}) requirement arises from the necessity to capture subtle variations induced by the transit of the pressure pulse. This pulse creates an internal overpressure Δp up to 10 kPa within the arterial surrogate [218]. Therefore, ε_{min} has been theoretically derived considering the wall deformation induced by Δp under conditions where the surrogate exhibits its highest stiffness E_{max} (in the present discussion, $E_{max} = 8$ MPa is considered). To estimate the magnitude of these deformations, the analysis starts from Lamé's equations (2.2) and (2.3). Assuming that the surrogate wall thickness is negligible compared with its diameter, and adopting the small-deformation assumption, the Barlow/Mariotte relation is obtained [219]:

$$\sigma = \frac{p \cdot d}{2 \cdot h} \quad (2.8)$$

where σ is the circumferential stress resulting from the application of an internal pressure p to a vessel of diameter d and wall thickness h . Combining the principle of Hooke's law with (2.8):

$$\varepsilon_{min} = \frac{\sigma_{min}}{E_{max}} = \frac{\Delta p \cdot d_{min}}{2 \cdot h \cdot E_{max}} = 0.6 \% \quad (2.9)$$

considering that, for the intended application, the arterial surrogate has a resting outer diameter d_{min} of 20 mm and a wall thickness h of 2 mm. The value of 5% in (2.9) represents the minimum detectable measurement signal required for the sensor to accurately monitor the subtle diameter deformation changes associated with the pressure wave propagation.

The requirement for the maximum detectable strain (ε_{max}) stems from the need to capture the d variations resulting from the combined effect of the static pressure ΔP and the superimposed overpressure Δp . Assuming that the ε_{max} due to the application of the transmural pressure is set to $\varepsilon_{\Delta P} = 30 \%$, and considering that $\varepsilon_{min} \ll \varepsilon_{\Delta P}$, it follows that:

$$\varepsilon_{max} = \varepsilon_{\Delta P} + \varepsilon_{min} \approx \varepsilon_{\Delta P} \approx 30 \% \quad (2.10)$$

Therefore, the sensor design must ensure structural integrity and functionality up to the maximum deformation, thus capturing both the baseline static deformation and superimposed dynamic strains accurately. In the scientific literature, displacement measurement systems (e.g., resistive, capacitive and inductive systems) are commonly employed to detect and transduce displacements corresponding to strain ranges of this magnitude. However, as previously done in [220], [221], a strain-based measurement approach has been chosen and preliminarily investigated for a measurement range up to 30%, primarily due to the geometry and structure of the arterial simulator, which make it

difficult to apply displacement measurement systems. The solutions developed and optimized for this purpose are discussed in detail in Chapter 4.

3) Validation and suitability of measurement methods for PWV evaluation in the arterial simulator

The first goal of this thesis was to identify the optimal method for estimating PWV from the pressure waveforms acquired in the arterial simulator. The novelty lies in the adaptation and characterization of methods that are well established in the literature, with the specific aim of extending their use to a new application.

As an initial benchmark, the full-wave *cross-correlation* method (CC) was selected (section 3.1). As discussed in Section 1.2, when applied to entire waveforms recorded at closely spaced sites (“local PWV” measurements), cross-correlation provides accurate and reproducible results while minimizing operator dependence, since it does not require the explicit selection of points or regions of interest to quantify the temporal delay between the two waves. However, as is well known in literature (Section 1.2), with this approach it is not possible to totally neglect the contribution of reflected waves. To mitigate the impact of this phenomenon on the results and further improve PWV estimation, two additional methods were subsequently optimized, selected among those fulfilling the requirements discussed in Section 2.4:

- 1- A *wavelet-based method* (WL), which exploits time-frequency analysis to isolate the scales and time intervals that best capture forward wave propagation, with the aim of increasing accuracy and robustness while reducing sensitivity to noise and reflections (Section 3.2);
- 2- A *model-based method* (MB), which relies on a viscoelastic representation of the vessel wall to derive PWV as a physical parameter, enabling a more direct interpretation of stiffness and damping effects without considering the evaluation of PTT (Section 3.3).

With reference to the experimental setup described in Section 2, the following paragraphs provide a description of the simulation procedures, the measurement chains implemented, and the acquisition protocols adopted to test the aforementioned methods, whose results will be presented in Section 5.1.

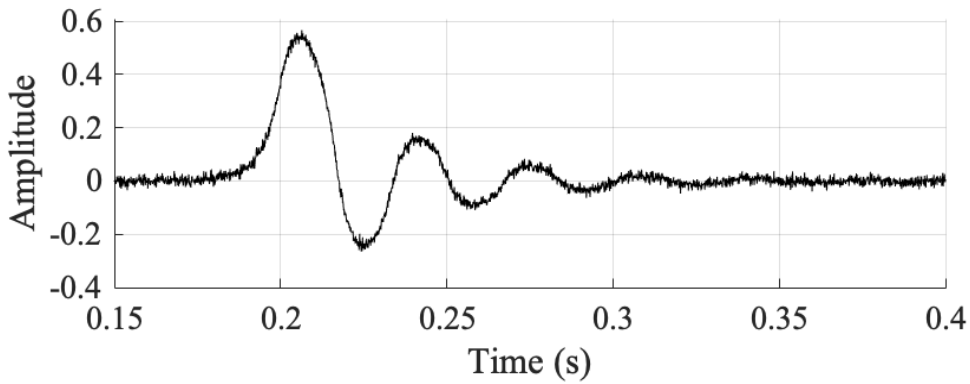
3.1) Application of the cross-correlation method

Below is a detailed outline of the tests carried out using the full cross-correlation method, aimed at estimating PWV within the arterial surrogate mounted in the simulator. In particular, the effectiveness of cross-correlation was first assessed against classical point-based methods using numerically simulated waveforms, reproducing only the forward waves generated by the simulator (section 3.1.1). Then, the suitability on experimental waveforms acquired on the simulator itself was assessed (section 3.1.2). Finally, the contribution of reflected waves was therefore quantified by means of simulations based on

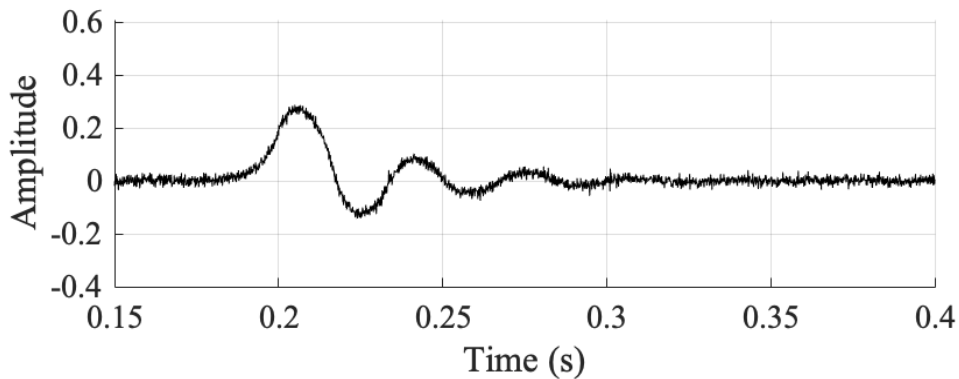
a one-dimensional mathematical model of wave propagation, which allowed the controlled generation of waveforms including reflections (section 3.1.3).

3.1.1) Test on simulated direct waves

This first test aims to compare some of the well-known methods for PTT estimation on waveforms similar to that provided from the mentioned arterial simulator [203]. The use of simulated signals has the advantage of isolating the phenomenon of pressure wave propagation, depending on the characteristics of the system [122], from other phenomena that overlap, such as turbulence effects of the flow [41]: in this way, it is possible to evaluate the performance of methods applied only to PTT estimation. For this purpose, some numerical simulations have been implemented in MATLAB environment: two waveforms, such as those in Fig. 3.1, have been generated, in order to reproduce the pressure pattern at two different sites on the arterial surrogate during pressure pulse transit; these waveforms, have noise components and amplitude attenuation depending on the path traveled within the vessel and its characteristics. Therefore, different delay values τ have been imposed between the two waveforms, which represent the PTT to be determined at the end of the simulation. Then, the waveforms are sampled and filtered to simulate the acquisition process. Finally, three methods for evaluating the PTT are applied.



(a)



(b)

Figure 3.1. Pressure waveforms over time: (a) in the first site and (b) the second one of the arterial surrogate.

Following is the description of all the test phases.

Waveform generation

Generally, in arterial simulators, arterial surrogate response can be modeled based on a second-order system behavior in which the mass of the system is constituted by the fluid inside the vessel, while the elastic and the damper elements are related to viscoelastic properties of the hose [222]. When a perturbation, e.g., a pressure pulse occurs, the pressure trend in two different sites of the vessel can be described by waveforms like the example shown in Fig. 3.1: curves are characterized by a maximum amplitude A_{max} , an oscillatory movement component, that depends on the system's fundamental frequency f_n , and a damping component due to pressure losses along the vessel and the viscoelastic properties [122].

In this work, to simulate the transit of a pulse wave through two different sites on the surrogate, a couple of waveforms ($y_{1,o}$ and $y_{2,o}$) have been independently generated in a MATLAB environment, considering that the maximum amplitude of the second one has been reduced by 50% compared to the first one to take into account the losses along the vessel. In this study, it is assumed that there is no significant change in the frequency content between the two waveforms: in fact, the two measurement sites are considered to be close to each other, e.g., tens of centimeters [203]. The main specifications of both generated waveforms are listed in Table 3.1.

Table 3.1. Characteristics of the simulated waveforms.

Characteristic	Value
Sample number	10^5
Duration	1 s
Fundamental frequency f_n	30 Hz
Maximum amplitude of $y_{1,o}$	$A_1 = 0.55$
Maximum amplitude of $y_{2,o}$	$A_2 = 50\%$ of A_1

In order to simulate a real data acquisition process, the following components of noise have been added to the generated signals:

- gaussian noise, whose amplitude has been obtained by setting a fixed Signal-to-Noise Ratio (SNR);
- a 50 Hz interference (n_P) from the power grid;
- a 5 Hz bending vibration (n_B) of the AS.

The resulting signals ($y_{1,r}$ and $y_{2,r}$) have been collected at a sampling rate of 10^4 S/s. Finally, the two waveforms have been filtered before being processed by the PTT measurement methods. In Fig. 3.2 the two signals are shown before and after the filtering process.

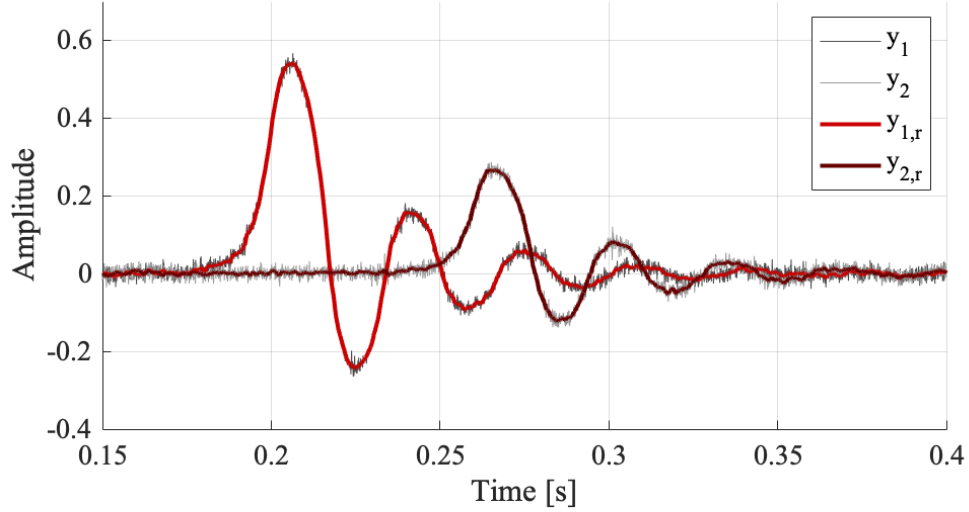


Figure 3.2. Waveforms with noise components ($y_{1,r}$ and $y_{2,r}$) and filtered waveforms (y_1 and y_2).

In particular, a low-pass filter has been applied based on a zero-phase filtering technique by processing data first forward and then backward. This allowed preserving the two waveforms in the time domain [223]. In Table 3.2 the characteristics of noise components and low-pass filter are reported.

Table 3.2. Characteristics of noise components and of low-pass filter.

Component		Characteristic	Value
Noise	Gaussian	SNR	15
	Power grid	Amplitude A_{np}	0.002
		Frequency f_{np}	50 Hz
	Bending vibrations	Amplitude A_{nb}	0.01
		Frequency f_{nb}	5 Hz
Low-pass filter		Cut-off frequency f_c	1 kHz

PTT estimation methods

The methods implemented to calculate the PTT between the two waveforms are Peak-to-Peak (PP), the Intersecting-Tangent (IT) and the Cross Correlation (CC) method. In the PP method, the PTT estimation is carried out by assessing the time distance between the main peaks of the waveforms, as shown in Fig. 3.3.

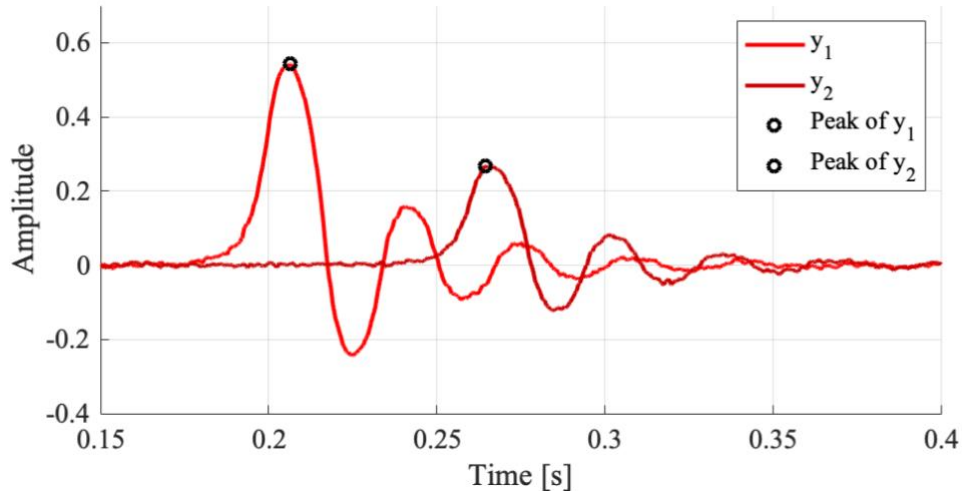


Figure 3.3. Example of individuation of waveforms in the peak-to-peak method.

In the IT method, the PTT is estimated by calculating the time distance between the waveforms' feet [77]. In particular, the maximum point of the first derivative over time of each signal has been first evaluated, then the tangent line has been drawn on each waveform at that point. The foot of the waveform has been identified by the intersection between the tangent line and the x -axis (Fig. 3.4). A 35% threshold of the maximum amplitude of the signal has been set to ensure that the forefront of the waveform is considered.

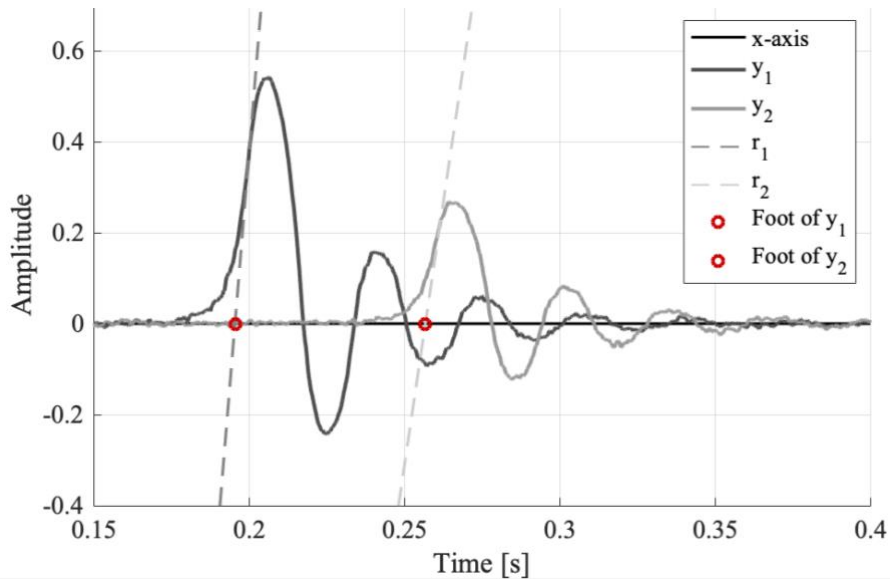


Figure 3.4. Individuation of waveforms foot with tangent-secant method.

In the CC method, the second waveform (y_2) is shifted along the x -axis step by step (as mentioned in section 1.3, one step is called lag where one lag corresponds to one sampling period), then, the integral of the product between y_1 and y_2 is calculated for each position: in this case (Fig. 3.5), the distance of the peak from zero multiplied by the sampling period is representative of the time distance between the two waveforms, that is the PTT.

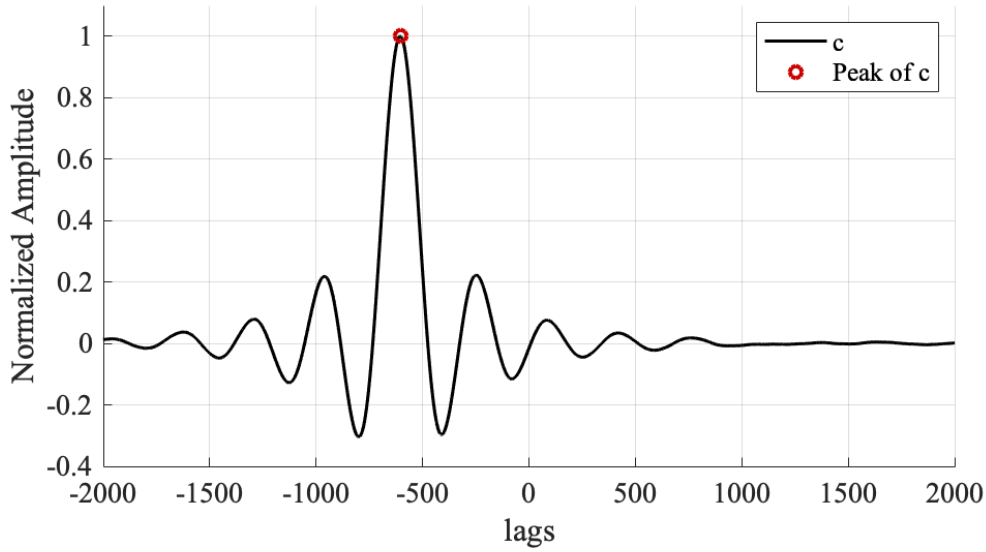


Figure 3.5. Example of peak individuation of cross-correlation function.

Uncertainty Analysis

To test the repeatability of the three methods applied to the AS, eleven Monte Carlo simulations (MCSs) have been carried out, one for each value of imposed delay τ , with 10^4 iterations each. Values of τ have been selected considering reasonable values of PTT measured locally in vessels, e.g., tens of centimeters, in which the PWV varies from physiological to pathological conditions, i.e., in the range 5-15 m·s⁻¹ [51], [65]. A distribution has been assigned to each value τ to consider the uncertainty given by the digital computational process. Noise contributions, added to waveforms, have been generated at each iteration. In addition, a distribution has been assigned to the cut frequency of the low-pass filter to evaluate the contribution of filtering. In Table 3.3, the specifications of all variables considered in the MCSs are listed.

Table 3.3. Distribution assigned to variables in MCSs.

Variable	Distribution	Variability
Imposed delay	Uniform	$\tau \pm 1\%$
Cut-off frequency	Uniform	$f_c \pm 1\%$
Amplitude of n_P	Uniform	$A_{nP} \pm 1\%$
Amplitude of n_B	Uniform	$A_{nB} \pm 1\%$

3.1.2) Test on waveforms acquired from the simulator

In this test, the same methods applied in section 3.1.1 have been applied to real waveforms acquired on the arterial simulator. The aim was to assess how the real physical phenomena occurring within the simulator affected the performance obtained respect then considering

only the simulated forward waves. For this purpose, a measurement campaign has been carried out on the arterial simulator by setting different transmural pressure values. The acquired waveforms, after being conditioned, have been processed with the three above-mentioned methods for PTT estimation.

Waveform acquisition and conditioning

To detect the transit of the pulse wave, two strain gauges (Micro-Measurement CEA-06-240UZ-120) have been glued with cyanoacrylate on the arterial surrogate at a known distance ($\Delta L = 25.0 \pm 0.1$ cm). Each strain gauge was connected in a quarter-bridge configuration to a channel of a strain gauge conditioner (Vishay 2120A) containing a Wheatstone bridge. The amplifier gain of both channels was set to the same value. The output signals from the conditioner have been connected, through BNC cables, to a DAQ board (NI USB-6251) for the acquisition of the strain gauge signals. An in-house NI LabView software has been implemented to process and store the signals. The main DAQ settings for data acquisition are listed in Table 3.4. The sample rate value has been chosen taking into account the distance between the strain gauges which requires a high temporal resolution to clearly distinguish PTT variations of 0.1 ms. The value of the signal length was chosen to ensure the acquisition of the entire transient phenomenon (pressure wave passage). The voltage range was selected taking into account the value set for the amplifier and the strain gauge strain magnitude, to take advantage of the full available resolution of the DAQ.

Table 3.4. Main settings of the DAQ board.

Characteristic	Nominal Value
Channel sample rate (kHz)	100
Signal length (s)	1.5
Number of channels	2
Voltage range (mV)	[-200; 700]

A measurement campaign has been carried out to validate the working principle of the arterial simulator (Table 3.5). Keeping the external pressure fixed, the internal pressure has been varied in steps to cause a change in transmural pressure: this procedure has been adopted to more closely mimic what happens in the human body where the pressure imposed from outside can reasonably be considered constant while the internal pressure of the vessels can vary according to the health condition of the individual. A total of ten acquisitions have been performed for each ΔP value. This procedure has been repeated for three different external pressures.

Table 3.5. Parameter settings for the measurement campaign. Pressure values are expressed as gauge pressure. All values are expressed as mean $\pm$ standard deviation (SD).

Parameter	Setting
Outer pressure (kPa)	$(50.0 \text{ to } 150.0) \pm 1.3$
Outer pressure steps (kPa)	50.0 ± 1.3
Transmural pressure (kPa)	$(0.0 \text{ to } 25.0) \pm 1.3$
Transmural pressure steps (kPa)	5.0 ± 1.3
System temperature ($^{\circ}\text{C}$)	22.0 ± 0.5

The maximum transmural pressure value ($\Delta P_{\max} = 25 \text{ kPa}$) reached was determined experimentally: laboratory tests showed that for values $\Delta P > 25 \text{ kPa}$ the bonding tightness between strain gauges and the arterial surrogate is no longer guaranteed probably due to the dilation differences between the materials of the two components. The minimum value of ΔP taken into consideration is $\Delta P_{\min} = 0 \text{ kPa}$ ($p_{in} = p_{out}$) to avoid the collapse of the vessel. The ΔP values were chosen by ensuring that a significant difference among them is provided also by taking into account the nominal uncertainty of the gauges ($\pm 1.3 \text{ kPa}$): the uncertainty of each ΔP is given by the sum in quadrature of the type B uncertainties declared for each gauge ($\pm 1.8 \text{ kPa}$) as type A contribution is considered negligible. Finally, six pressure values were selected taking into account the upper and lower limits determined above. The outer pressure maximum value has been imposed by paying attention to the maximum force that can be applied by the linear actuator. The piston used to generate the pressure pulse, being connected to the circuit externally to the external case, senses on one side the ambient pressure and on the other one the pressure inside the hydraulic circuit, which is given, as a first approximation, by the sum of the absolute values of the p_{in} and p_{out} applied on the walls of the surrogate [41]. The higher the absolute pressure inside the vessel, the more the piston resists displacement and consequently the more force the linear actuator must exert to move the piston and generate the impulse. Preliminary tests have shown that above 250 kPa (absolute pressure) the actuator cannot generate the right pressure pulse. Having defined the lower and upper limits of ΔP and p_{out} , the range of the internal pressure p_{in} can be determined from (2.1). Since PWV, and consequently PTT, also depends on the density of the inner fluid (2.7), the environment temperature has been monitored and kept constant through an air conditioning system during the measurement campaign. Temperature control is important, also, because it affects the mechanical characteristics of AS and the operation of electronic devices (e.g., measuring chain).

After the acquisition phase, a spectral analysis has been conducted, through the Fast Fourier Transform function in MATLAB, to assess the signal frequency content: through a zero-phase digital filtering technique [224], a Butterworth low-pass filter (1st order – cut-off frequency: 150 Hz) has been applied to remove high-frequency contributions related to

noise, and a Butterworth notch filter (1st order – stop-band frequencies: 49-51 Hz) has been applied to cut off the 50 Hz noise due to power grid interference.

PTT evaluation methods

For the PTT evaluation, the waveforms acquired from the simulator have been processed by MATLAB software, implementing three different methods known in literature (Section 1.3) and discussed below: the Peak-to-Peak method (PP), the Intersecting-Tangent method (IT) and the Cross-Correlation method (CC).

The PP method estimates the PTT by evaluating the difference between the two time instants ($\tau_{pp,1}$ and $\tau_{pp,2}$) at which the maximum peak of the two pressure waves occurs. Figure 3.6 shows an example of two acquired pressure signals in which the two peaks ($a_{1,max}$ and $a_{2,max}$) for the PTT estimation by the PP method have been identified.

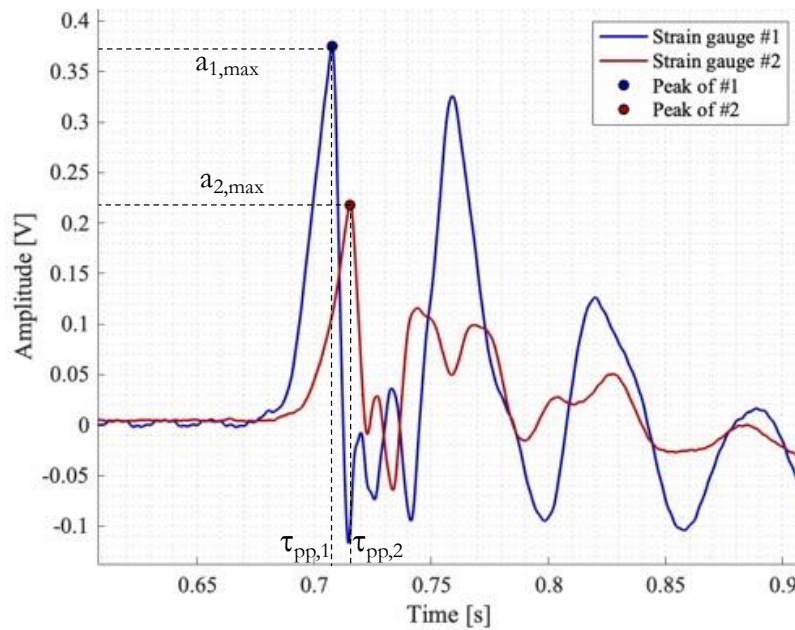


Figure 3.6. Example of peak individuation using the peak-to-peak method applied to simulator waveforms.

The IT method evaluates the PTT by calculating the time distance between the waveforms' feet. In particular, two straight lines are identified, representative (ideally, tangents) of the inclination of the positive slope of their respective pulse wave. To locate the lines, linear regression procedure is performed on a specific interval of the waveforms' upstroke identified by two values corresponding to a fraction of the maximum value of the waves. In particular, the interval has been chosen between 30% and 60% of the maximum, thus obtaining:

- $a_{start} = 0.30 \cdot a_{max}$
- $a_{end} = 0.60 \cdot a_{max}$

The foot of the waveforms has been identified in time by the intersection between the lines and the time axis. Similarly to the previous case, figure 3.7 shows the above pressure signals that have been processed by the IT method. The two tangent lines, passing through a_{start} and a_{end} , allow identifying the waveform feet ($\tau_{ts,1}$ and $\tau_{ts,2}$) for the PTT estimation.

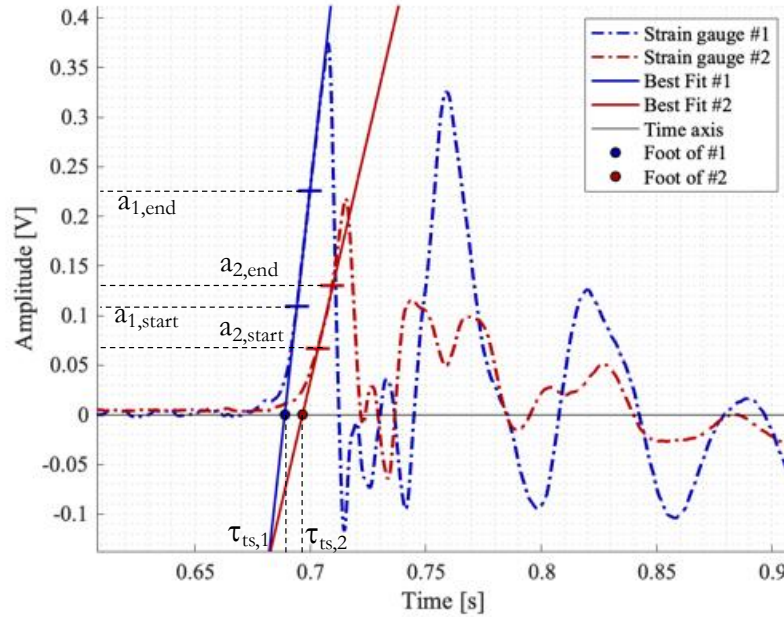


Figure 3.7. Example of foot individuation using the tangent-secant method applied to simulator waveforms.

Finally, applying the CC method to the waveforms, the second is shifted along the time axis step by step, then, the integral of the product between the two waveforms is calculated for each position. In the cross-correlation function, the number of lags (l_{cc}) that separate the peak from zero multiplied by the sampling period represents the time distance ($\Delta\tau_{cc}$) between the two waveforms, i.e., the PTT. Figure 3.8 shows the curve representing the cross-correlation between the two pressure signals, where the peak corresponding to their phase shift is identified, from which the PTT is estimated.

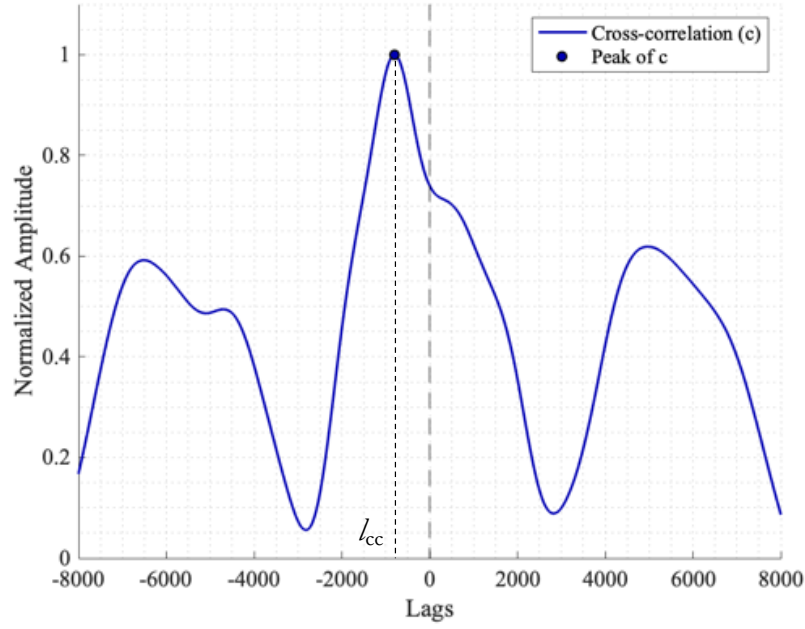


Figure 3.8. Example of peak individuation of cross-correlation function applied to simulator waveforms.

Uncertainty estimation

The uncertainty associated with the PTT values for each test condition has been estimated by summing in quadrature the contribution due to signal processing through the implemented methods (σ_{met}) and the one due to the repeatability of measurements under the same conditions (σ_{rep}):

$$\sigma_{PTT} = \sqrt{\sigma_{\text{met}}^2 + \sigma_{\text{rep}}^2} \quad (3.1)$$

Other sources of uncertainty (e.g., the resolution of the measurement system) were neglected in this analysis, as they resulted of an order of magnitude smaller than the contributions discussed above. For the estimation of the method uncertainty σ_{met} , a Monte Carlo Simulation (MCS) has been carried out for each acquisition, since it is well-known in the literature that this is a valid and robust tool for estimating uncertainties deriving from software-based measurement methods, following the approach adopted in [225], [226]. First of all, a distribution has been assigned to the cut-off frequency (f_c) of the low-pass filter applied in the pre-processing phase of the acquired data. Consequently, a distribution has been assigned to the quantities involved in the methods to calculate the PTT. For the PP method, a distribution has been assigned to $\tau_{\text{pp},1}$ and $\tau_{\text{pp},2}$ to consider the issues due to the identification of the time instant relative to the peak of the wave. For the IT method, a distribution has been assigned to the extremal values of the intervals (a_{start} and a_{end}) used to determine the tangent lines. As regards the CC method, similarly to the PP method, a distribution has been assigned to the lag that identifies the maximum correlation between

the two waves. Therefore, σ_{met} has been estimated as the standard deviation of the mean calculated considering the uncertainties related to the MCSs performed on the acquisitions under the same measurement conditions. In

$$\sigma_{PTT} = \sqrt{\sigma_{\text{met}}^2 + \sigma_{\text{rep}}^2} \quad (3.1)$$

3.6, the characteristics of the distributions assigned to the variables of interest for MCSs are listed. On the other hand, for the estimation of the repeatability contribution to uncertainty σ_{rep} , the dispersion of the PTT values from 10 pressure waves acquired and processed under the same test conditions has been computed.

Table 3.6. Distribution characteristics of MCSs variables.

Variable	Distribution	Variability
Cut-off frequency (Hz)	uniform	$f_c \pm 1$
PP time instants (ms)	uniform	$\tau_{\text{pp}} \pm 0.1$
TS interval limits (%)	uniform	$a_{\text{start}} \pm 1; a_{\text{end}} \pm 1$
CC lags	uniform	$l_{\text{cc}} \pm 1$

3.1.3) Influence of reflected waves on PWV estimation

As mentioned in section 1.2, the full cross-correlation (CC) as a method for PWV estimation faces a significant limitation due to the presence of reflected waves within the arterial vessels. Reflected waves are generated at various locations along the arterial tree where there are changes in impedance, as in the case of a variation in vessel stiffness [227]. The distortion they induce in the waveforms acquired at the two measurement sites can affect the accuracy of the cross-correlation analysis by shifting the location of the primary correlation peak, ultimately resulting in an inaccurate estimation of PWV [205], [228]. The influence of reflected waves on PWV measurements is widely acknowledged, and several studies attempted to mitigate their effects by analyzing specific segments of the pulse waveforms [140], [205], but these approaches often lack standardization and are susceptible to operator influence. In this context, the effect of reflected waves on the PWV assessment by applying full cross-correlation is an aspect that seems to be poorly investigated.

This test focuses on providing a contribution quantifying the effect of reflected waves on PWV outcomes from CC applied to the whole waveform. In particular, the goal is to estimate the quality of PWV measurements through CC processing and analysis applied to the arterial simulator, that is characterized by a simplified geometry and a higher stiffness compared with large arteries, where reflection sites are located very close to the measurement points. To this aim, simulated pressure waves were generated propagating at

different known velocities within the arterial surrogate, with the aid of 1D mathematical models based on the geometry and characteristics of the previously mentioned arterial simulator.

Implemented characteristics of the Arterial Simulator

The features implemented in the mathematical model to generate the pressure waves reflect those of the arterial simulator. They includes a silicone rubber conduit, serving as an arterial surrogate, anchored at both ends with two copper sleeves. Fig. 3.9 schematically represents the described system.

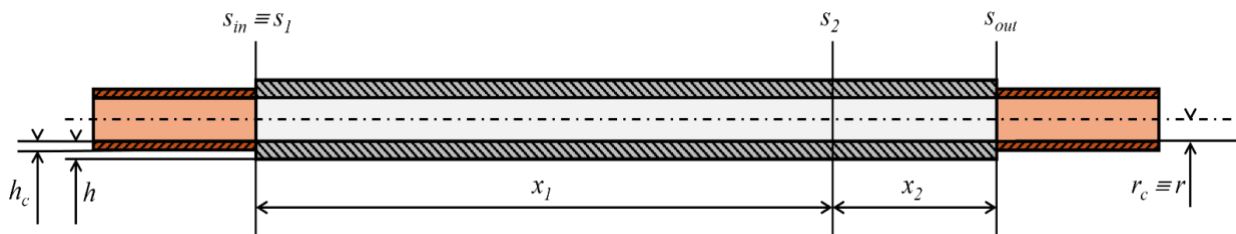


Fig. 3.9. Schematic view of the main components of the arterial simulator implemented in the mathematical model.

The length $l = x_1 + x_2$ denotes the distance between the ends of the conduit, s_{in} and s_{out} . The quantities r and r_c represent the inner radius of the silicone rubber conduit and that of the copper sleeves, respectively. Similarly, h and h_c denote the wall thickness of the silicone rubber conduit and the copper sleeves. The measurement sites are located at a distance x_1 from each other. The first measurement site s_1 lies on the initial cross-section of the silicone rubber vessel ($s_1 \equiv s_{in}$). The second measurement site s_2 is located at a distance x_2 from the final cross-section of the silicone rubber conduit. The elastic modulus of the copper sleeves E_c is assumed to be constant, whereas the elastic modulus E of the silicone rubber conduit is considered variable to simulate different stiffness levels. The quantities v and v_c are the Poisson's ratios of the silicone rubber and copper, respectively. The nominal values of the abovementioned parameters are reported in Table 3.6.

Table 3.6. Parameter's values used for the mathematical model implementation.

Parameter	Value
Length l	50 cm
Surrogate radius r	16 mm
Sleeves radius r_c	16 mm
Surrogate thickness h	2 mm
Sleeves thickness h_c	1 mm
Sites distance x_1	40 cm
End distance x_2	10 cm

Parameter	Value
Surrogate Young's modulus E	1, 2, 3, 4, 5, 6 MPa
Sleeve Young's modulus E_c	120 Gpa
Surrogate Poisson ratio ν	0.48
Sleeves Poisson ratio ν_c	0.33

Mathematical Relations for Pulse Waveforms generation

A surrogate composed of an isotropic material, for which nonlinearities can be neglected, is considered. Furthermore, the conduit is considered thin-walled, and the perturbation is infinitesimal. Under these assumptions, the wave propagation speed within the surrogate can be estimated using the Moens-Korteweg equation [141]:

$$PWV_0 = \sqrt{\frac{E \cdot h}{2 \cdot \rho \cdot r \cdot (1 - \nu^2)}} \quad (3.2)$$

where ρ denotes the density of the fluid inside the vessel.

After a perturbation p_{in} at the inlet, the pressure wave propagates along the conduit with speed PWV_0 . Due to the viscoelastic nature of the conduit and the shear stresses between the fluid and the conduit wall, the waveform experiences both attenuation and distortion along its path [195]. The wave propagation is governed by the following frequency-domain expression:

$$p(x) = p_0 \cdot e^{-\gamma x} \quad (3.3)$$

where $p_0 = p_{in}$ in the case of forward waves and $p(x)$ represents the pressure wave at a distance x from the beginning of the tube. The coefficient γ is the complex propagation constant describing wave damping and phase shifting [186]:

$$\gamma = \alpha + j\beta \quad (3.4)$$

Here, the real part α regulates the attenuation of the wave, while the imaginary part $j\beta$ accounts for the phase shift. Assuming that the viscoelastic material of the conduit is modeled using the Standard Linear Solid model, α can be expressed as [195]:

$$\alpha = \frac{\omega}{c_0} \cdot \frac{1}{\sqrt{1 - f_v}} \quad (3.5)$$

where ω is the angular frequency, and f_v is the ratio between the imaginary and real parts (E_j and E_r , respectively) of the complex elastic modulus:

$$f_v = \frac{E_j}{E_r} \quad (3.6)$$

For silicone rubber, f_v is assumed around 0.2 [229]. On the other hand, b can be expressed as [186]:

$$\beta = \frac{\omega}{c_0} \quad (3.7)$$

Once the pressure wave reaches the distal end of the vessel s_{out} , it encounters a discontinuity caused by the presence of the copper sleeve. This results in a partial reflection of the pressure wave, as follows [230]:

$$R = \frac{p_b}{p_f} = \frac{Z_0^{-1} - Z_1^{-1}}{Z_0^{-1} + Z_1^{-1}} \quad (3.8)$$

where Z_i is the impedance of the medium through which the wave propagates and can be expressed as:

$$Z_i = \frac{\rho_i \cdot c_i}{A_i} \quad (3.9)$$

with ρ_i denoting the fluid density, c_i the wave velocity, and A_i the cross-sectional area for the medium i , where $i = 0, 1$ refers to the surrogate and the sleeve. The propagation of reflected waves can also be modeled by applying (3.3).

Waveforms Generation

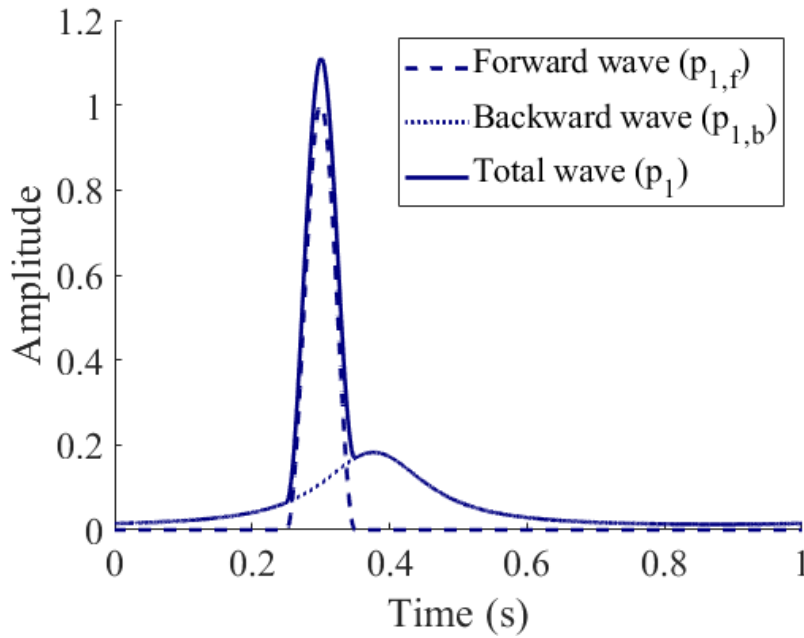
An in-house MATLAB script was implemented to generate the two waveforms simulating the pressure waves acquired at the two measurement sites, p_1 and p_2 , respectively. Both signals have a total duration of 1 s, with a sampling frequency of 10 kHz, ensuring a temporal resolution of 0.1 ms. These waveforms are considered as the sum of the contributions from the forward and reflected waves at each measurement site. The forward wave at s_1 ($p_{1,f}$) coincides with the input perturbation p_{in} . It corresponds to a raised cosine pulse, a function that is practical to implement and commonly used to simulate pulse waveform inputs [230]. This perturbation has a duration of 100 ms, with its peak occurring at 0.3 s. The forward pressure wave at s_2 ($p_{2,f}$) is computed by applying (3.3), setting $x = x_1$. The pressure wave at the reflection point s_{out} is evaluated in a similar way, with $x = x_1 + x_2$. At this point, the magnitude of the reflected wave p_b relative to the incident one should be

computed through (3.8). However, since the reflection coefficient R is, in this case, close to unity ($R = 0.98 \div 0.99$), in this preliminary analysis, the partial back-propagation was assumed negligible, considering the wave entirely reflected. The backward wave at s_2 ($p_{2,b}$) is obtained by (3.3), setting $p_0 = p_b$ and $x = x_2$. Similarly, the backward wave at s_1 is derived through (3.3), with $x = x_1$. Then, all contributions are combined as follows:

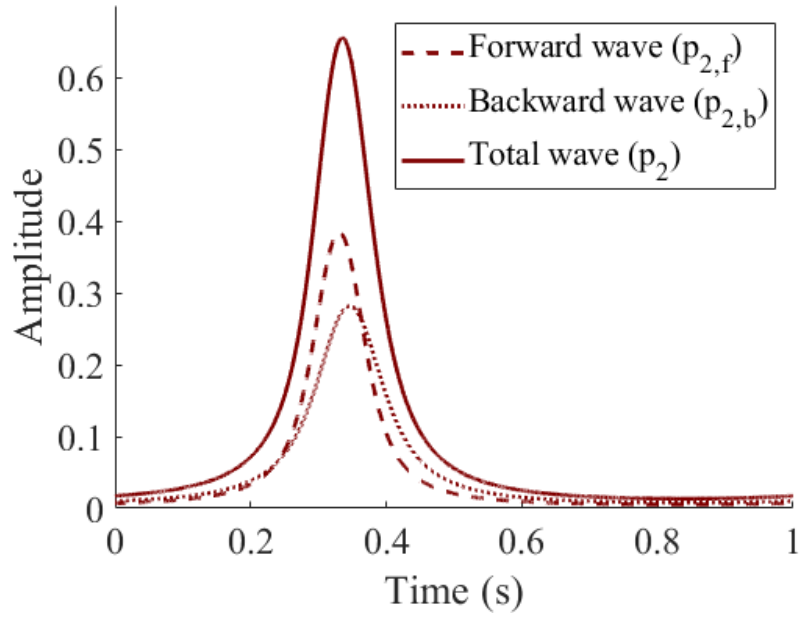
$$p_1 = p_{1,f} + p_{1,b} \quad (3.10)$$

$$p_2 = p_{2,f} + p_{2,b} \quad (3.11)$$

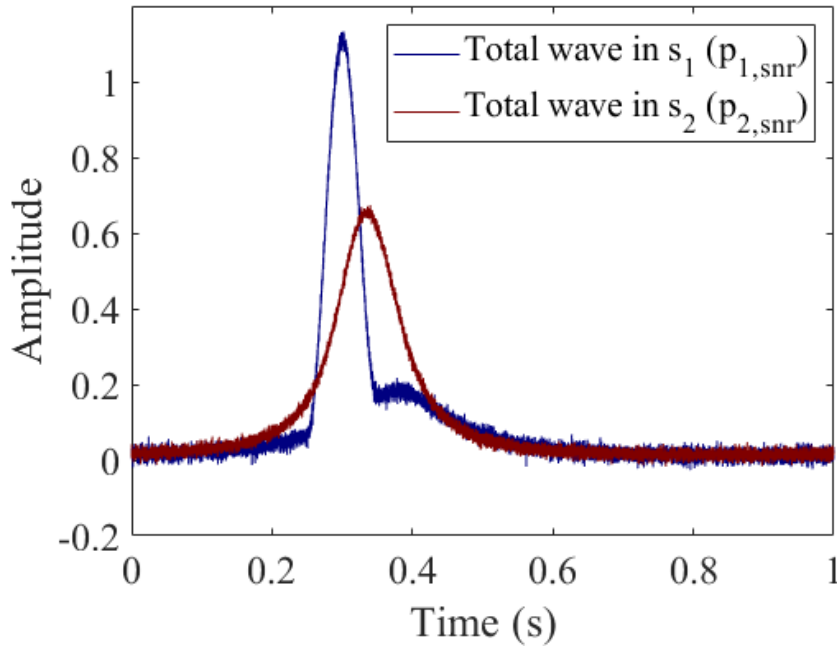
The resulting waveforms p_1 and p_2 along with their forward and reflected components, are illustrated in Fig. 3.10a and 3.10b, respectively. Finally, white Gaussian noise is added to the resulting signals ($p_{1,snr}$ and $p_{2,snr}$) with a variable signal-to-noise ratio SNR (Fig. 3.10c). SNR values equal to 5, 10, 15 and 25 dB were chosen in this study based on evaluations performed on measurement signals collected in a laboratory environment during previous experimental studies [163].



(a)



(b)



(c)

Figure 3.10. Examples of the generated waves: (a) total wave and its forward and reflected components at measurement site s_1 ; (b) total wave and its forward and reflected components at measurement site s_2 ; (c) total waves at the two measurement sites with SNR = 25 dB.

Application of the cross-correlation Method

As previously mentioned, CC is employed in this work to evaluate the time delay between p_1 and p_2 , to assess how the contribution of reflected waves impacts the PWV estimation, as compared to the theoretical value PWV_0 . To preliminarily assess noise robustness, the

signals were analyzed without any prior filtering. Once the PTT was estimated through cross-correlation, the resulting PWV was calculated using the following formula:

$$PWV = \frac{x_1}{PTT} \quad (3.12)$$

Uncertainty Analysis

To estimate the uncertainty associated with the PWV values obtained through the application of cross-correlation, Monte Carlo simulations were carried out, as in [231], [232]. Specifically, one simulation (10^4 cycles) was performed for each combination of E and SNR values, resulting in a total of 21 simulations. As a first step, the variability of PWV_0 was evaluated. To this end, a uniform distribution was assigned to each variable in (3.2). The factor v was considered constant, as a first approximation, since its contribution is reasonably smaller than that of the other terms. The variability of E was selected conservatively, given the lack of clear references in both the literature and standards. The uncertainties in r and h were derived from laboratory measurements conducted on an arterial surrogate similar to the one simulated in this study. The uncertainty associated to r was estimated by considering the variation in water density between 18 °C and 22 °C. Subsequently, to assess the variability of the PWV values computed via cross-correlation, uncertainty contributions were assigned to x_1 and x_2 in (3.3) and (3.12). These contributions were estimated by considering the uncertainty in sensor placement on the arterial surrogate during laboratory experiments. All values assigned to the variables are reported in Table 3.7.

Table 3.7. Monte Carlo Simulations Variables

Variable	Distribution	Bounds
Surrogate Young's modulus E	Uniform	$\pm 10\%$
Surrogate radius r	Uniform	± 0.1 mm
Surrogate thickness h	Uniform	± 0.1 mm
Fluid density ρ	Uniform	± 20 kg·m ⁻³
Distance x_1	Uniform	± 0.5 mm
Distance x_2	Uniform	± 0.5 mm

3.2) Application of a wavelet-based method

Given the well-known limitation of the cross-correlation approach in its inability to isolate the contribution of reflected waves, alternative approaches for PWV estimation within the simulator were explored. One of the selected candidate solutions was a wavelet-

based method (WL). Similarly to the strategy adopted in [72], this WL method analyze the wavelet complex cross-spectrum of the pressure waveforms. Although it requires higher computational complexity than the CC method (Section 1.2), it enables isolation of the phenomenon of interest (in this case, the upstroke) by allowing the selection of a specific Region of Interest (ROI) as a function of both time and frequency.

This method, described below, was first applied to simulated waveforms on which different time delays and noise levels were imposed, also accounting for undersampling (Section 3.2.1). This was done to validate the effectiveness of the method. Subsequently, the approach was applied to *in vitro* signals acquired on the arterial simulator, at three different transmural pressure settings (Section 3.2.2). This was performed to assess the impact of the variability introduced by the real-world phenomenon.

Method implementation

To assess the PTT between two time series $x(t)$ and $y(t)$, the wavelet transforms of the signals ($W^x(t,s)$ and $W^y(t,s)$) are performed, in order to extend their domain into a two-dimensional space, where t and s represent time and scale, respectively. Morlet wavelet is used as a “mother wavelet”. Then, the complex cross-spectrum is estimated as:

$$W^{xy}(t,s) = W^x(t,s)W^{y*}(t,s) \quad (3.13)$$

where $*$ denotes the complex conjugate.

The time-scale map is converted to a time-pseudo-frequency map. This provides a complex cross-spectrum ($W_{t,f}^{xy}$) containing modules ($|W_{t,f}^{xy}|$) and phases ($\phi(W_{t,f}^{xy})$) information as a function of time and frequency. As will be described in the following, specifically for the waveform type under investigation, a subsection of the derived time-pseudo-frequency map is selected to study the part of the phenomenon of greatest interest (the upstroke). Finally, the PTT can be calculated as follows [72]:

$$PTT = \left| \sum_{t=t_1}^{t_2} \sum_{f=f_1}^{f_2} \widehat{W_{t,f}^{xy}} \cdot \frac{\phi(W_{t,f}^{xy})}{2\pi f} \right| \quad (3.14)$$

where t_1 and t_2 are the extremes of the time interval bounding the phenomenon and f_1 and f_2 specify the frequency range of interest, with

$$\widehat{W_{t,f}^{xy}} = \frac{W_{t,f}^{xy}}{\sum |W_{t,f}^{xy}|} \quad (3.15)$$

where the denominator is the cumulative sum of the terms considered.

The intervals $[t_1, t_2]$ and $[f_1, f_2]$ delineate the subset of points used to refine the selected ROI. In this study, the time interval $[t_1, t_2]$ taken into account corresponds to part of the first wave upstroke, i.e., $t_1 = 10\%$ and $t_2 = 98\%$ of t_{peak} which is the time instant of the wave peak (Fig. 3.11a and Fig. 3.11c). Conversely, the frequency range $[f_1, f_2]$ of interest has been evaluated by performing the Fourier transform of the signals. The frequencies f_1 and f_2 fall in the range of 3-18 Hz for the simulated waves (Fig. 3.11b), and 3-40 Hz for those experimentally acquired through the AS (Fig. 3.11d). The area bounded by the intervals above identifies the subsection of complex cross-spectrum where the PTT estimation is carried out.

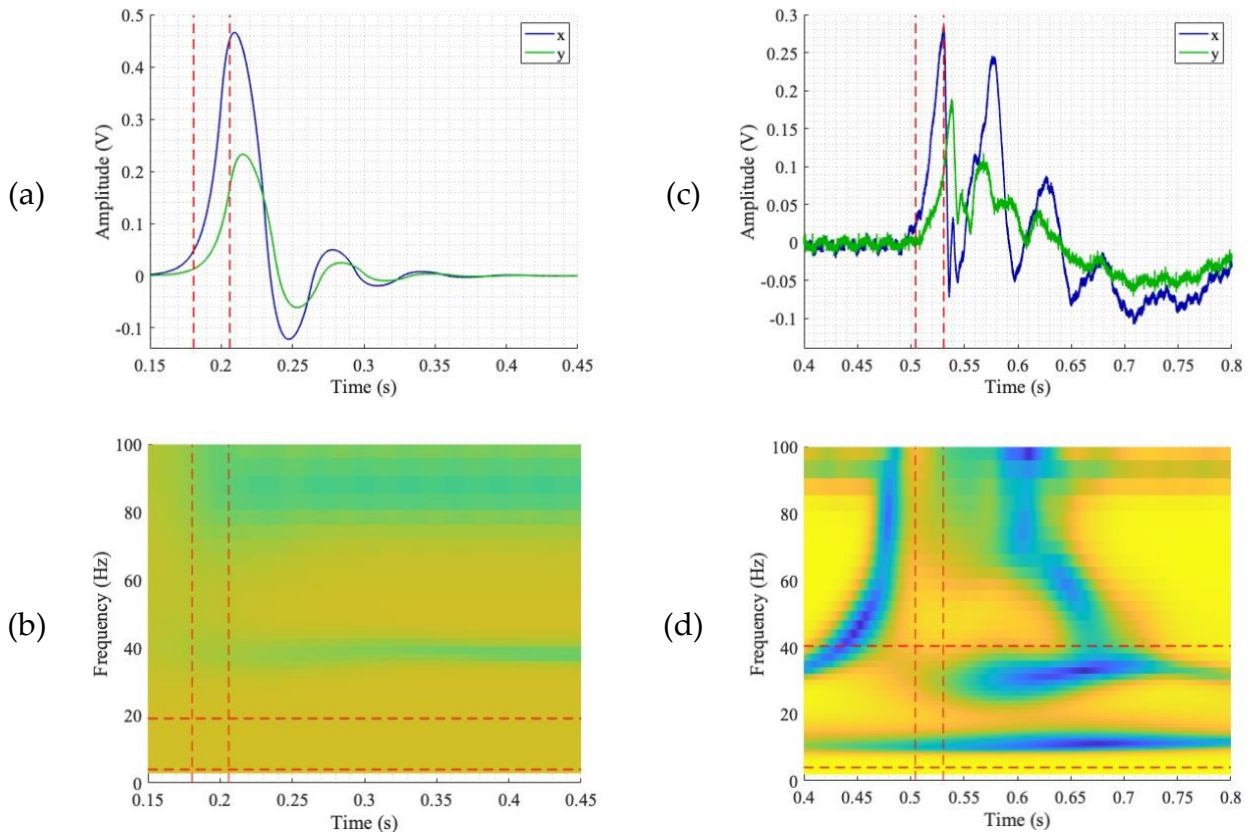


Figure 3.11. Application of the wavelet-based method. (a) example of two simulated signals with an imposed delay of 5.9 ms. Dashed lines indicate the time interval of the phenomenon of interest; (b) complex cross-spectrum of the two waveforms, where the area identified by the intersection of the dashed red lines represents the subsection considered for PTT estimation; (c) example of two signals acquired at an external and internal pressure of 50 and 65 kPa, respectively. Dashed lines indicate the time interval of the phenomenon of interest; (d) complex cross-spectrum of the two signals, where the area identified by the intersection of the dashed red lines represents the subsection considered for PTT estimation.

The experimental protocol adopted to apply the WL method to both simulated waveforms and real waveforms acquired from the simulator is described in greater detail in the following chapter, respectively Section 3.2.1 and section 3.2.2.

Uncertainty Estimation

To estimate the uncertainty contribution introduced by the implemented processing method, Monte Carlo Simulations have been carried out, one for each test condition. A uniform distribution has been assigned to the frequency interval ($f_1, f_2 \pm 1$ Hz) and time interval ($t_1, t_2 \pm 1\%$ of t_{peak}). To determine the number of cycles for the simulations, the convergence of both the mean and standard deviation values has been checked.

3.2.1) Test on simulated waveforms

Before applying the WL method to real signals acquired experimentally, it has been validated on waveforms simulating the behavior of real ones, under different conditions [163]. Specifically, different time delays between waves have been imposed, and white gaussian noise has been added at different values of Signal to Noise Ratio (SNR). In addition, the effect of lower time resolution has been investigated through undersampling.

Waveforms Generation

In agreement with the assumptions made in [96], the simulated waveforms represent the response of a second-order system to a pulse input. Their characteristics have been chosen from the analysis of real waveforms with the aim of reproducing, as close as possible, the specific behavior of the system when it is isolated from other disturbances, e.g., multiple reflections due to system components. This approach, though a simplification, allows to focus on the phenomenon of interest, i.e., pressure wave propagation within the vessel. For this purpose, with an initial sampling frequency (f_s) of 10^5 Hz, two square waves (x' and y') with the same frequency (f_g) and the same damping over time have been generated. In this context, the fundamental frequency of the simulated waves (f_g) is similar to that measured in the experimental setup (the arterial simulator). Two different amplitudes ($A_{x'}$ and $A_{y'}$) have been set to simulate the energy dissipation of the pressure wave as it travels through the aortic surrogate. A low-pass filter with a specific cut-off frequency (f_c) has been applied to shape the signals and smooth the edges that characterize square waves (i.e., wave shaping). Finally, the second waveform has been time-shifted by a known delay. In Table 3.8, the main characteristics of the generated waveforms are resumed. An example of the obtained signals (x and y) is shown in Fig. 3.11a.

Table 3.8. Main Characteristics of the Generated Waveforms and Test Conditions

Variable	Symbol	Value
Square waves' frequency (Hz)	f_g	16
Square waves' amplitudes	$A_{x'}, A_{y'}$	1.0, 0.5
Low-pass cut-off frequency (Hz)	f_c	16
Delay (ms)	t	5.1, 5.5, 5.9

Variable	Symbol	Value
Signal to Noise Ratio (dB)	SNR	No noise, 25, 15, 5
Sampling frequency (Hz)	f_s	10^5 , 10^4 , $5 \cdot 10^3$

Test Conditions

The validation of the method has been carried out for different test conditions. Three delays (τ) have been set to simulate different shifting in time of the second systolic upstroke. White gaussian noise has been added to the signals at three SNR levels to test the method even at different noise levels similar to operating conditions. In addition, for one value of SNR, the method has been tested in the case of lower time resolution. All test conditions are listed in Table 3.8.

3.2.2) Test on Simulator Waveforms

The same method described above, after being applied to the simulated waveforms, was then applied to the real ones [163]. In the following, the measurement campaign protocol used to acquire them.

Experimental setup and acquisition protocol

To detect the passage of the pressure wave, two strain gauges are glued at a known distance on the surrogate and connected to a control unit for signal conditioning. Both pressure and strain signals are acquired by LabView software through a DAQ board. The main DAQ settings for data acquisition are listed in Table 3.9.

Table 3.9. Main DAQ Settings for Data Acquisition through the Arterial Simulator

Variable	Value
Sampling frequency (kHz)	100
Signal length (s)	1.5
Number of channels	2
Voltage range (mV)	-200, 700

The sampling frequency has been chosen to achieve a temporal resolution of 0.01 ms. The voltage range has been adjusted based on the amplified output from the strain gauge control unit. An example of the signals acquired is shown in Fig. 3.11c. Three ΔP values have been tested by setting the external pressure to 50 kPa and adjusting the internal pressure to 50, 65 and 75 kPa. For each test condition, five measurements have been carried out to consider the repeatability contribution of the experimental system.

3.3) Application of a model-based method

In addition to the wavelet-based method discussed earlier, a model-based approach was also evaluated. As described in Section 1.2, model-based methods estimate PWV by treating it as an intrinsic parameter of the mathematical model used to describe the fluid-dynamic phenomena occurring within the arterial simulator. The method implemented in this study is relatively complex due to the number of governing equations, but it was considered promising for three reasons:

- It can reduce the influence of reflected waves through the selection of an appropriate frequency spectrum;
- It estimates PWV without relying on PTT measurements;
- It provides direct information on the elastic modulus of the arterial surrogate.

Moreover, it is one of the few model-based methods that can be applied by measuring a single physical quantity, in this case, the strain of the surrogate. This method, based on the mathematical model presented in [194], relies on analyzing the viscoelastic behavior of the vessel walls and its influence on pressure-wave propagation. The proposed approach, described below, was tested on waveforms acquired from the arterial simulator under different transmural pressure settings. To evaluate the obtained outcomes, the PWV values estimated by the model will be compared with those derived from the estimation using the full cross-correlation method.

Proposed method description

The proposed method (Viscoelastic Behavior Analysis-based method - VBA) aims to derive Young's modulus (E) of the vessel material by analysing the damping it induces on the pressure wave as it travels through the conduit. Then, it estimates the PWV using the Moens-Korteweg formula [54]:

$$PWV = \sqrt{\frac{hE}{2\rho r}} \quad (3.16)$$

where h and r are the thickness and the inner radius of the vessel, respectively, while ρ is the density of the inner fluid. For (3.16) and subsequent relations, the following assumptions are made: nonlinearities in the fluid and the tube are neglected, dynamic phenomena are quasi-one-dimensional, the vessel is uniform and made of an isotropic material, the fluid is incompressible and Newtonian, gravitational effects are omitted.

The viscoelastic behaviour of the vessel walls can be modeled as a spring-damping system [233]. When a viscoelastic element undergoes deformation, a portion of the strain

energy is stored elastically, while the remaining is dissipated as heat or internal friction. The constitutive relationship between the internal pressure p and the resulting conduit cross-sectional area A can be expressed [194], [233] in general form as:

$$p = G \cdot A \quad (3.17)$$

where G corresponds to the reciprocal of the compliance per unit length of the vessel (distensibility) [234], [235] and consists of a real part, expressing the elastic component, and an imaginary part, representing the viscous one. The quantities in (3.17) can be rewritten as functions of the angular frequency ω . The circumferential strain ε , directly related to the deformation of A [194], [214], can also be expressed as follows:

$$\varepsilon = \text{Re}\{|\varepsilon(\omega)| \cdot e^{j(\omega t - kx)}\} \quad (3.18)$$

where t is time, x is the distance along the vessel axis and k is the wave number [194]. Due to the loss of a portion of the energy, the deformation of the arterial surrogate causes damping and distortion of the pressure waveform during its transit [194]. Wall shear stress also contributes to the decay of the pressure transient as the wavefront propagates upstream [236]; therefore, it is important to account for its contribution. The wall shear stress τ [194] can be expressed as:

$$\frac{2\tau}{\rho r} = -F \cdot U \quad (3.19)$$

where U is the velocity of the inner fluid. The friction function F can take different forms depending on the adopted model. In the specific case of laminar flow [194], it can be expressed as:

$$F = \frac{8\eta}{\rho r^2} \quad (3.20)$$

where η is the dynamic viscosity of the fluid. To quantify the propagation of the damping, it is possible to compare the deformation of the surrogate during the transit of the pressure wave at two different measurement points separated by a distance Δx (ε_1 and ε_2 , respectively). To achieve this, a transfer function H can be defined [194], based on the notation introduced in (3.18):

$$H = \frac{\varepsilon_2(\omega, \Delta x)}{\varepsilon_1(\omega, 0)} = e^{-jk\Delta x} \quad (3.21)$$

Taking into account the viscoelastic contribution represented by G in (3.17) and the effect of shear stress described by F in (3.19), it is possible to express the following dispersion relation [194]:

$$k^2 = \frac{\rho}{A_0 G} \omega(\omega - jF) \quad (3.22)$$

where A_0 is the internal cross-sectional area of the vessel when no stress is applied. The relation between G and E can be expressed with (3.23) as reported in [237]:

$$E = \frac{2\pi(1 - \nu^2)r^3}{h} |G| \quad (3.23)$$

where ν is the Poisson's ratio. Therefore, based on the mathematical relations above, the method involves acquiring deformation waveforms through an experimental campaign and then determining k by (3.21). Next, G is obtained from (3.22), followed by the calculation of E using (3.23). Finally, PWV is calculated through (3.16).

Measurement Chain

Two strain gauges (Luchsinger - CEA-06-240UZ-120) were glued on the external surface of the vessel at a distance Δx of 21.0 ± 0.1 cm to detect the circumferential strain due to the pressure wave transit. They were connected to a strain gauge control unit (Vishay 2120A) for signal conditioning. A DAQ (National Instruments - NI USB-6501) connected to a PC was used for acquisitions. An in-house LabVIEW VI was developed to manage and save data. The post-processing operations were performed by an in-house MatLab script. For the pressure monitoring, two manometers (Keller – PA-23SY) were installed and connected to the same DAQ. The pressure values were displayed on the PC monitor using the LabVIEW VI above.

Measurement Campaign

The measurement campaign took place in an air-conditioned laboratory at room temperature ($T_{amb} = 23 \pm 1$ °C). During the tests, the pressure p_{out} was set at 50.0 ± 2.5 kPa and kept fixed. As for the pressure p_{in} , it was varied from 50.0 ± 2.5 kPa to 75.0 ± 2.5 kPa in increments of 5 kPa. For each ΔP step, 10 measurements were carried out. Each measurement consisted of acquiring signals from the strain gauges during piston movement to record the transient dynamics of the phenomenon of interest. Each acquisition was performed over 1.5 s with a sampling rate f_s of 100 kHz. The latter was chosen to ensure a temporal resolution of 0.1 ms. The signals were filtered in the post-processing phase through a Butterworth low-pass filter with a cutoff frequency f_c of 200 Hz. The filter's cutoff

frequency was set one decade higher than the estimated characteristic frequency of the phenomenon under investigation.

Uncertainty Estimation

The measurement uncertainty related to the imposed transmural pressure values was not considered, as the aim of this study is to compare the results of the two methods. Therefore, since the results of both methods came from the same acquisitions, ΔP values were considered as reference values. Uncertainties were expressed as standard deviations (SDs) of the relative mean values.

Concerning the PWV values from the VBA method, the uncertainty was estimated by considering the contributions of the method and the measurement repeatability. First, a Monte Carlo Simulation (MCS) was carried out to assess the method variability. MCS is a well-established method for assessing measurement uncertainty by propagating probability distributions [232], [238]. In particular, 10^5 cycles were set, assigning a uniform distribution to each variable listed in Table 3.10 and considering their variability within (3.16) and from (3.18) to (3.23). Uniform distribution was assigned to the variables because, in terms of standard deviation, it is a more cautious approach for the uncertainty estimation. The MCS was repeated for each measurement to account for measurement variability. The uncertainties associated with the values of Young's modulus (E), also derived from the application of this method, were estimated using the same procedure.

Regarding PWV values from the cross-correlation method (reference), the uncertainty was estimated by propagating the contribution of the quantities in (1.3). The uncertainty of the distance Δx , also expressed as l in (1.3), between the two strain gauges was estimated 0.1 cm. The variability of the PTT depends on contributions from both measurement repeatability and the method. The latter was evaluated as in [96], but it turned out to be negligible compared to the former contribution, as it affects the overall uncertainty by at least one order of magnitude less.

Table 3.10. Monte Carlo Simulation Variables

Variable	Mean value and bounds
ρ (kg·m ⁻³)	1000 ± 20
η (Pa·s)	98·10 ⁻⁵ ± 4·10 ⁻⁵
r (mm)	8.0 ± 0.1
h (mm)	2.0 ± 0.1
Δx (cm)	21.0 ± 0.1
f_c (Hz)	200 ± 1

4) Development of innovative sensors

The second goal of this thesis was to identify the optimal sensor for detecting the transit of the pressure wave within the arterial surrogate. The key contribution is the design and implementation of custom-developed and innovative sensors for a novel application in the international context, with particular emphasis on their metrological characterization, an aspect that is often treated only marginally in this research area.

As an initial reference, conventional foil strain gauges were employed. These sensors offer several advantages: they exhibit a linear response within a defined strain range, provide high sensitivity, feature well-characterized and reproducible behaviour and are widely available with standardized specifications and calibration procedures. However, during the laboratory experiments it was observed that, for this specific application, they introduce an insertion error in the measurement of the circumferential strain of the conduit. A comparison between the technical specifications of the surrogate material and those of the strain gauges shows that the difference in their elastic moduli spans at least two orders of magnitude. As a consequence, the strain gauges locally restrict the deformation field of the arterial surrogate, limiting the possibility of modulating its elastic modulus. Furthermore, given the strain levels involved in this application, these sensors risk operating outside their linear range.

To overcome the limitations associated with this solution, alternative sensing technologies satisfying the requirements listed in Section 2.4 were explored. In particular, the development of two stretchable sensor configurations was investigated, each based on a different technology:

1. *Conductive ink-based sensors*: these sensors are directly deposited onto the conduit using Aerosol Jet Printing. Among their various advantages, they provide high sensitivity and eliminate the mechanical interference associated with adhesive layers in the deformation of the conduit-sensor system (Section 4.1).
2. *Bragg fiber-based sensors*: these devices incorporate a fiber Bragg grating embedded within an elastomeric ring. This configuration ensures excellent adhesion between the conduit and the sensor without the use of adhesives and further ensures a wide strain range due to the compliance of the sensor matrix (Section 4.2).

The following sections describe the different configurations in detail, including the design, fabrication, and testing procedures adopted to evaluate the performance of these sensing solutions. The corresponding results will be presented in Section 5.2.

4.1) Development of a sensor based on conductive ink

The first proposed transducer is a particular stretchable strain sensor composed of a carbon-based conductive powder and a polymer matrix. It was directly deposited on the arterial surrogate using Aerosol Jet Printing (AJP) technology. AJP is an emerging technology gaining attention in the field of printed electronics [239]. It offers several advantages [239], [240], [241]: non-contact deposition allows printing on various materials and non-planar surfaces. The high printing resolution (less than 10 μm) enables the deposition of sensors with complex geometries confined to very small spaces. Direct deposition on the substrate makes the technology cost-effective, as no production waste is generated [239], and no intermediate substances are required. In addition, the high production speed allows for large-scale process scalability. These advantages also attract significant interest in AJP technology in the biomedical field [239], [242], [243]. These considerations motivated the use of this technology for developing a sensor capable of detecting the passage of the pressure wave within the arterial surrogate. Accordingly, the main goal of the following test is to evaluate the suitability of the sensor for this application, including the performance parameters described in Section 2.4.

Production process

In particular, the transducer investigated in this study consist of a stretchable carbon conductive paste (DuPont Intexar PE671) that exhibits a piezoresistive behavior as strain varies. Although the manufacturer does not provide specific information on the elastic modulus of the material, it recommends application to thermally stable substrates for wearable electronics applications. The paste was deposited directly on the external surface of the arterial surrogates using the AJP technique (Fig. 4.1).

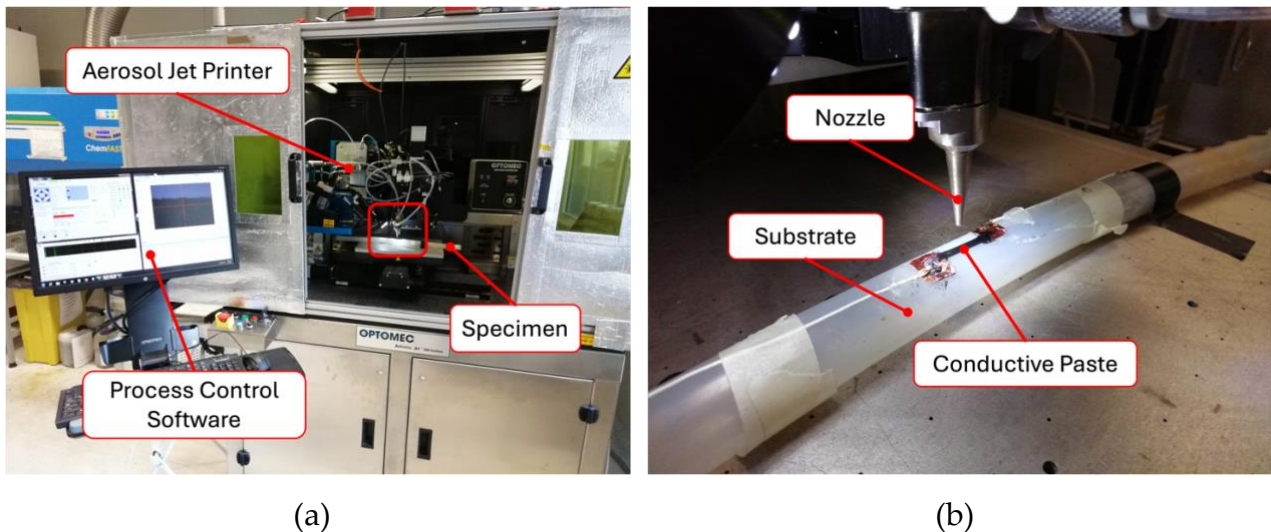


Figure 4.1. Overview of the Aerosol Jet Printing process: (a) The equipment used for sensor printing, the red box indicates the printing area; (b) an example of a tube undergoing the printing process.

The printing process involved alternating deposition of multiple conductive paste layers with curing in an oven (130 °C for 15 minutes), repeated three times. The pneumatic configuration with the wide deposition head and a deposition speed of 1 mm/s was used for printing. The flow rate set was 2000 SCCM (@1.23 psi), 2000 SCCM (@24.6 psi) and 1000 SCCM (@0.72 psi) for the three deposition phases of conductive paste, respectively. In Fig. 1a, the equipment used for sensor printing is shown, and in Fig. 1b an example of a specimen during the printing process can be observed.

As mentioned above, for application in the arterial simulator, the circumferential strain was of primary interest. However, for ease of implementation, the sensor was placed with its strain-sensitive direction parallel to the conduit's axis. To carry out the characterization tests, six specimens were fabricated, and two sensors were deposited on each specimen. Their main geometrical and electrical characteristics are reported in Table 4.1. The heterogeneity of these characteristics reflects the variability of the production process. The latter was affected by, among other factors, the different thickness of the sensors due to the different number of layers for each and the different number of curing steps performed on each silicone rubber substrate.

Table 4.1. Main geometrical and resistive characteristics of each sensor.

Specimen	Sensor	Dimensions (L × H)	Nominal Resistance (kΩ)
1	a	17.5 mm × 1.3 mm	7.03
	b	17.9 mm × 1.4 mm	3.59
2	a	18.7 mm × 1.1 mm	7.50
	b	18.8 mm × 1.2 mm	3.23
3	a	15.9 mm × 1.3 mm	1.39
	b	16.2 mm × 1.3 mm	1.02

A schematic representation of a specimen is shown in Fig. 4.2a, where two sensors were deposited symmetrically with respect to the central section of the tube at a distance $S = 12$ mm. Quantities L and H represent the portion of the sensor printed directly on the rubber and the width of the strain-sensitive element, respectively. The thickness of the sensor is not represented. The sensor ends were connected to copper sheets glued to the tube, onto which the electrical wires used for resistance measurement were soldered. An example of a completed specimen is shown in Fig. 4.2b.

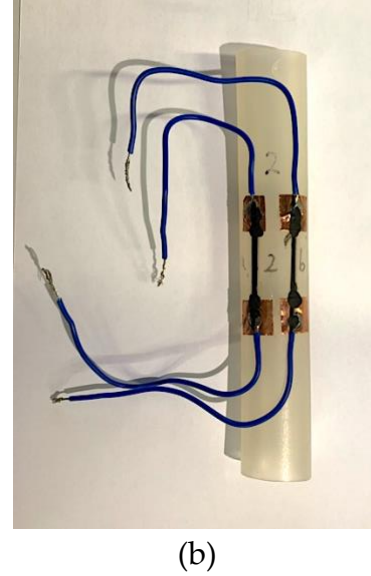
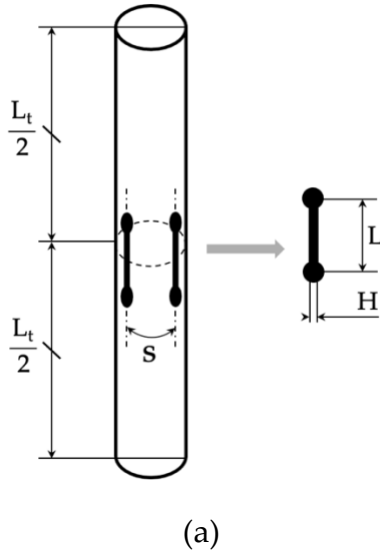
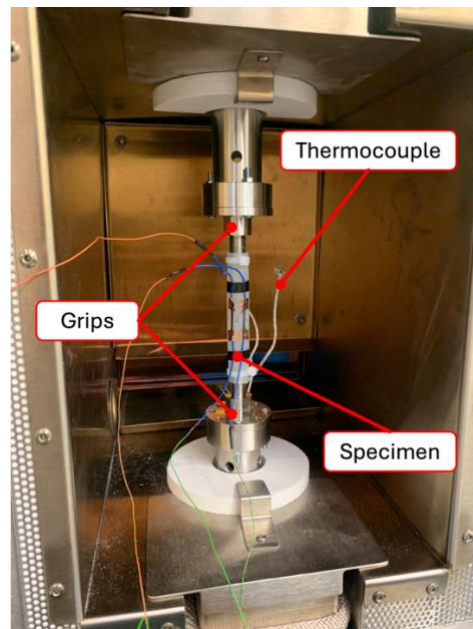
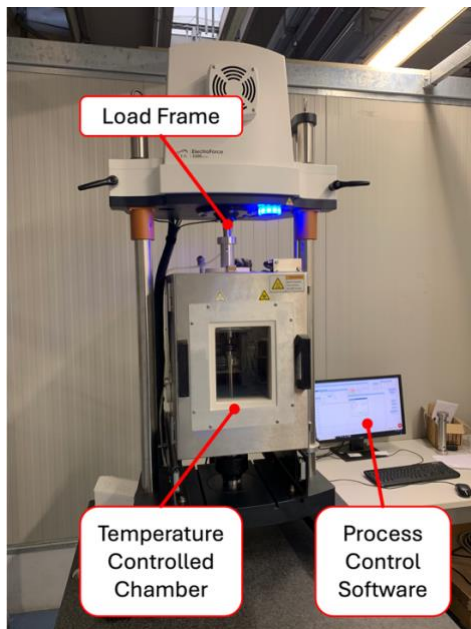


Figure 4.2. Example of a specimen after the production process: (a) configuration of the two sensors on the silicon rubber substrate; (b) specimen before the measurement campaign.

Mechanical characterization

For mechanical characterization, each specimen was positioned, using suitable grips, within a load frame (ElectroForce 3300 series) capable of performing both static and dynamic tensile tests (Fig. 4.3). The system is equipped with a temperature-controlled chamber with a tolerance of $\pm 0.5\text{ }^{\circ}\text{C}$ (Fig. 4.3a). The temperature is monitored by a type K thermocouple. The initial distance between the grips L_0 , which determines the length of the specimens in the absence of deformation, was set at $100.0 \pm 0.3\text{ mm}$. No pretensioning was applied to the specimens before testing. Once L_0 was set, the displacement between the grips ΔL was monitored by a High Aspect-ratio Dielectric Sensor (HADS) installed directly on the machine. Fig. 4.3b shows a detailed view of a specimen mounted within the load frame.



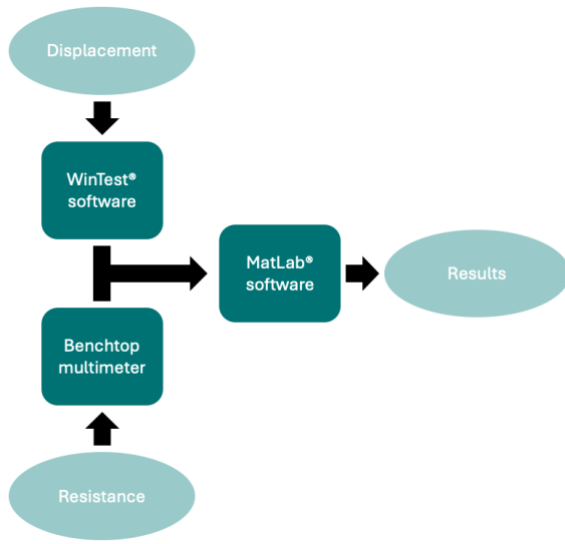
(a)

(b)

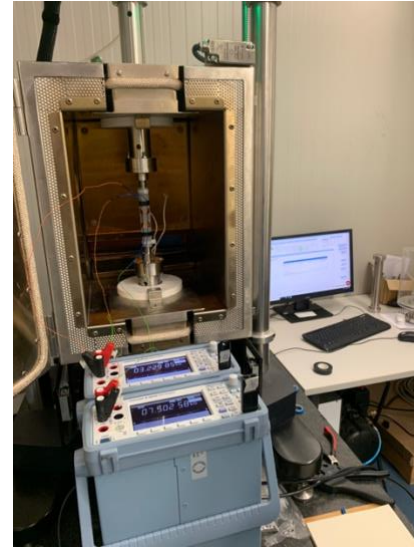
Figure 4.3. The load frame used for tensile tests on specimens: (a) The machine with the temperature-controlled chamber; (b) A detail of a specimen positioned with proper grips. The thermocouple used for temperature monitoring is also visible.

Measurement Chain

The overall scheme of the measurement chain configuration is shown in Fig. 4.4a. The displacement values ΔL , imposed on the specimens by the load frame, were recorded directly by the proprietary software of the machine (WinTest®). In addition, two-wire resistance measurements were carried out by a benchtop multimeter (Yokogawa DM7560) to collect resistance values simultaneously from both AJP-based sensors. The signals were acquired on USB memory in two separate files (.csv) and then imported into MatLab® for post-processing operations. Fig. 4.4b provides an overview of the measurement chain used for data acquisition.



(a)



(b)

Figure 4.4. The measurement chain used for signal acquisition: (a) block diagram of the main steps of the acquisition process; (b) an overview of the measurement chain ready to carry out the acquisition campaign.

Measurement Campaign

This section describes some details of the mechanical tests carried out on the specimens in order to characterize their performance and thus evaluate their suitability with the application in [214]. As mentioned above, the specimens were subjected to tensile tests by imposing known strain values. Since both the behavior of the sensors and their tensile limit before failure were not known, the maximum deformation value applied during the tests was $\varepsilon_{test,max} = 0.7\%$, that was reasonably defined as conservative.

The displacement and resistance signals were acquired using the equipment described in Subsection 3.4, both at a sampling frequency of 20 Hz. Each test lasted $5 \cdot 10^3$ s, during which 10^5 samples were collected (approximately 83 minutes). A waiting time of 120 min was

observed before starting the tests to allow the measurement chain warmup. The acquisitions of displacements and resistances started simultaneously, synchronized via a trigger event. Since the intended application of the sensors does not involve a significant change in system temperature, the dependence of resistance as a function of temperature was not evaluated in this study. For this reason, all tests were conducted under repeatable conditions, maintaining a constant temperature of 24.0 ± 0.5 °C. Further details specific to each test performed are provided below.

- *Static Test:* The static test involved subjecting the specimen to strain steps $\Delta\varepsilon = 0.1\%$, from the undeformed state, i.e., $\varepsilon_0 = 0$, to $\varepsilon_{test,max}$. Each imposed deformation interval was applied by the load frame in 100 ms and maintained constant for 600 s. Despite the application of constant strain, the resistance value R was expected to change over time because of the viscoelastic behavior due to the polymeric nature of the specimens [245], [246]. Therefore, R was estimated as the mean $\pm$ standard deviation (SD) of the last 20 values acquired at the end of 600 s, just before the next strain step $\Delta\varepsilon$ was applied. Conversely, the initial resistance R_0 was assumed as the mean $\pm$ SD of the last 20 values acquired at the beginning of the test, just before the first strain step was imposed. With the aim to estimate the uncertainty contribution due to the hysteresis phenomenon, a load-unload cycle was performed.
- *Dynamic Test:* The dynamic test involved subjecting the specimen to varying deformation values by imposing a sine function through the load frame. Specifically, two tests were performed for each specimen, in which the sine wave frequency was set to 0.01 and 0.1 Hz. The deformation range remained as specified in the static test above, starting from ε_0 and to $\varepsilon_{test,max}$. Considering that each period of the sine wave corresponded to one load-unload cycle, 45 and 450 load-unload cycles were performed for the first and second tests, respectively. The resistance value was expected to settle as a function of strain as the cycles increased. Consequently, the resistances R_0 and R for the dynamic test were estimated and expressed in terms of mean value $\pm$ SD from load-unload cycles once the settling period had passed. Thus, it was possible to assess the contribution of uncertainty due to the repeatability of the measurements.
- *Maximum Elongation Test:* The maximum elongation test involved subjecting the specimen to varying deformation values with a ramp pattern, up to the point of sensor breaking, i.e., when it no longer provided electrical continuity. For this test only, the load frame was set to impose linearly increasing strain values from ε_0 to 10.0% with a rate of 1 mm/min. The maximum strain set for this test is not related to the requirements of the application, as in Equation (8), but was set to evaluate the maximum elongation that the sensors could reach. The maximum elongation test was applied to one specimen, and thus to two AJP-based sensors.

- *Fatigue Strength Test:* The fatigue strength test is applied subjecting the specimen to a cyclic deformation range for 10^4 cycles. Specifically, the sensors underwent deformations between ε_0 and $\varepsilon_{test,max}$. The test, performed on a single specimen, was conducted at a frequency of 1 Hz.

Measurement Uncertainty Analysis

Below, the procedure adopted for estimating the measurement uncertainty of the quantities used in the sensor characterization process is described in detail, expressed as standard deviation. First, the uncertainty of directly measurable quantities, i.e., displacement ΔL and resistance R , was estimated. Then, by properly combining all the contributions, the uncertainty of the strain ε and relative resistance variation $\Delta R / R_0$ was estimated.

- *Displacement and Strain Uncertainties:* As mentioned above, L_0 was set at a distance of 100.0 ± 0.3 mm using a standard reference gauge block provided by the manufacturer of the load frame. The uncertainty associated with the imposed displacements ΔL between the grips of the load frame was estimated from the calibration certificate of the testing machine, i.e., $\sigma_{\Delta L} = 0.025$ mm. By combining the relative uncertainty contributions of L_0 and ΔL , a maximum uncertainty for ε of 0.03% was obtained. Since the minimum strain value applied to the specimen was 0.1%, its contribution to the estimation of uncertainties for derived quantities, e.g., the gauge factor, can reasonably be considered negligible.
- *Resistance and Relative Resistance Variation Uncertainty:* The uncertainty associated with the resistances R_0 and R , acquired with the bench multimeter, was estimated by combining the repeatability contribution, and the uncertainty contribution provided by the instrument, which also depends on the range set (i.e., 1-10 k Ω according to the sensor under test). The uncertainty of the resistance variation relative to the initial value $\sigma_{\Delta R/R_0}$ was estimated by summing in quadrature the contributions from the readings of the initial and final resistance values.
- *Sensor Transfer Function and Prediction Bounds:* As described above, the sensor transfer function was derived by weighted least squares fit applied to variations in relative resistance measurements as a function of imposed strain. The weights were assessed as the inverse of the variance of the relative resistance variation values, combining the contributions in Subsection 6.2 with the repeatability contribution estimated from the load-unload cycles. Prediction bounds were estimated by considering the uncertainties of the coefficients obtained from the linear regression model. Specifically, they were assumed as the maximum interval between the two extremal lines of the pencil of lines derived from the regression coefficients and their uncertainties.

4.2) Development of a sensor based on Fiber Bragg Grating

The second proposed sensing solution consists of a Fiber Bragg Grating (FBG) embedded into a ring-shaped flexible matrix designed to conform circumferentially to the surrogate surface. FBGs are fiber optic sensors that provide high sensitivity to mechanical deformation, with inherent immunity to electromagnetic interference (EMI) and excellent metrological properties [247]. Their small size and light weight allow for seamless integration onto curved and compliant surfaces, minimizing disturbance to the system's mechanical behavior. Recent advances have further enhanced the applicability of this technology through the integration of FBGs into flexible matrices, enabling conformable sensing solutions [248]. This configuration not only enhances the grating adherence and mechanical compliance with soft and deformable substrates like vascular phantoms but also facilitates a more robust and stable attachment to an external surface. These advantages make FBG-based flexible sensors ideally suited for capturing real-time diameter variations in compliant arterial models, opening new opportunities for high-fidelity, non-invasive monitoring of cardiovascular dynamics in experimental setups.

Therefore, following the approach adopted for the previous sensor, the purpose of the next test is to determine whether this sensor meets the requirements of the application, including the performance criteria presented in Section 2.4.

FBG Background and Working Principle

FBGs are optical fiber sensors that operate like a notch band filter. When illuminated by a broadband light source, they reflect a specific wavelength, known as the Bragg wavelength (λ_B), which satisfies the Bragg condition:

$$\lambda_B = 2n_{eff}\Lambda \quad (4.1)$$

with n_{eff} is the effective refractive index of the fiber core and L the grating length. FBGs are intrinsically sensitive to ε and temperature (T) since a change in these parameters causes a shift of λ_B ($\Delta\lambda_B$). If the T contribution can be considered negligible, FBGs work as strain sensors with $\Delta\lambda_B$ directly proportional to the applied ε . However, when FBGs are embedded in flexible substrates (like the ring-shaped one fabricated in the present study), this direct proportionality may be altered due to mechanical interactions between the fiber and the host material. Factors such as matrix stiffness and geometry can influence the effective strain experienced by the grating. For this reason, the development of this solution requires a dedicated ad-hoc characterization.

Design and Fabrication

The ring-shaped flexible matrix is designed to wrap circumferentially around the external surface of the surrogate of an arterial simulator. This geometry was chosen to ensure that the sensor was capable of capturing variations in vessel diameter ϕ resulting from pulsatile pressure changes. By embedding the optical fiber within a flexible ring-shaped matrix, the FBG remains conformal and mechanically coupled to the vessel wall without considerably altering its compliance. This configuration should allow monitoring the dynamic ϕ changes, which can be used to estimate pulse wave propagation and derive PWV in the simulated vascular system. The proposed sensor was fabricated by following four main steps (Fig. 4.5):

1. *Mold design and 3D printing:* A 3D computer model of the mold was created using CAD software (OnShape). The mold was designed with a negative cavity with a diameter of 19 mm and a height of 3 mm, allowing precise shaping of the casting material. Then, the mold was printed using a 3D printer (Ultimaker S5) in polylactic acid (PLA).
2. *Silicone preparation:* A two-part liquid silicone rubber (Dragon Skin™ 20, Smooth-On, Macungie, PA, USA) was prepared by mixing components A and B in a 1:1 weight ratio. The mixture was then degassed under vacuum to eliminate air bubbles and ensure uniform consistency.
3. *Casting process:* The FBG was positioned in the mold under slight pre-tension to maintain alignment during curing. The prepared silicone mixture was then poured into the mold, encapsulating the fiber.
4. *Curing:* After 4 hours, the complete curing of the silicone matrix was achieved, and the flexible sensor with the desired ring shape was removed from the mold.

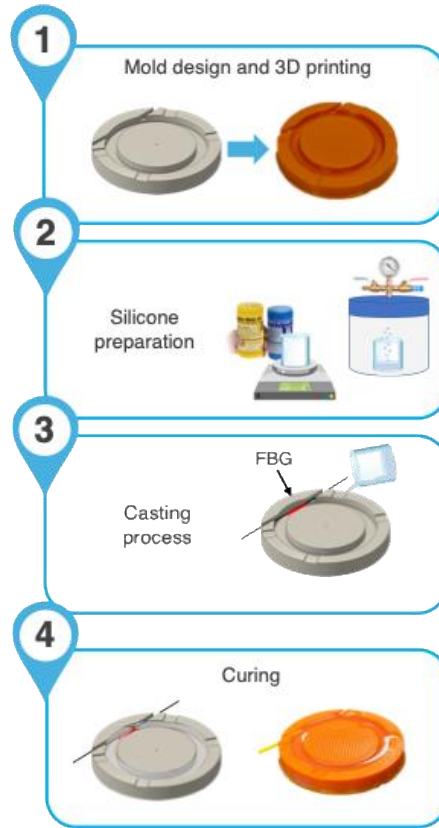


Figure 4.5. The main step of the fabrication procedure from the design and 3D printing of the mold (step 1) to the silicon curing (step 4).

Experimental Setup and Protocol

The preliminary evaluation of the sensor’s suitability for the intended application was carried out under controlled laboratory conditions, maintaining a constant temperature throughout the test. The testing protocol involved imposing predetermined surrogate ϕ values, defined by a custom-made reference gauge system 3D printed in PLA. The reference gauge system consisted of a set of seven concentric cylindrical inserts (4 mm height), with nominal ϕ from 20 mm to 26 mm in 1 mm increments. For more details, see Fig. 4.6.

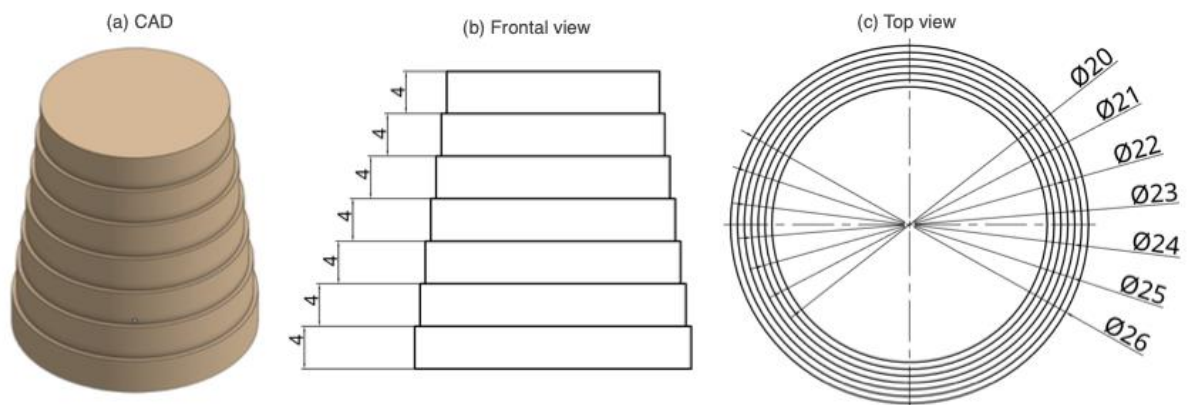


Figure 4.6. The reference gauge system design (a) with its dimensions on (b) the frontal and (c) top planes expressed in mm.

A first static calibration of the ring-shaped sensor was carried out as follows. The transducer was moved from the smallest to the biggest reference gauge (Fig. 4.7a) and was retained for approximately 3 min before moving to the following one. Changes in the FBG output within the matrix were recorded using an FBG interrogator (si155 HYPERION platform, LUNA Inc.) at a sampling frequency of 100 Hz and a laptop (Fig. 4.7b).

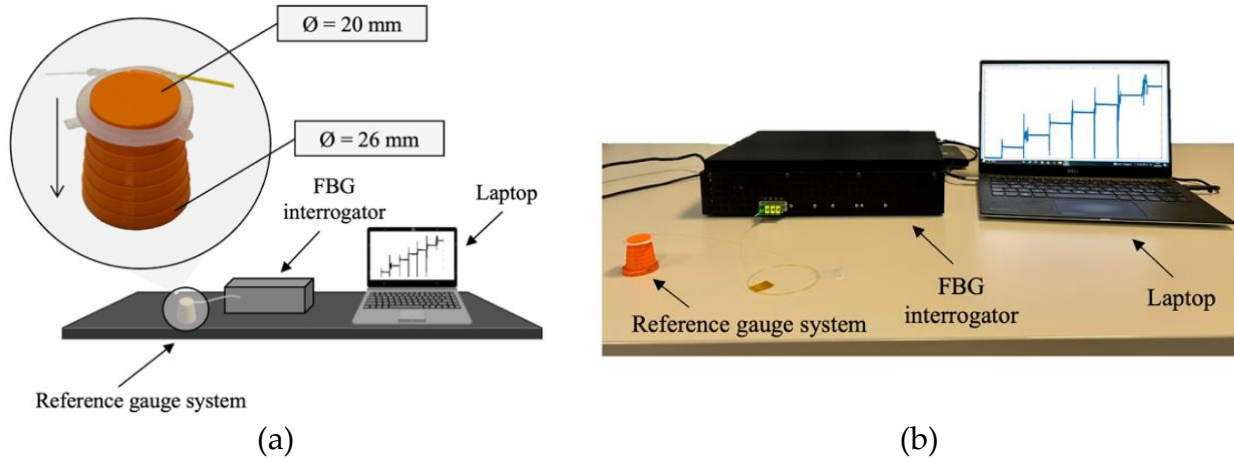


Fig. 4.7. The experimental setup: (a) a zoom on the reference gauge system with the sensor positioned in the first reference gauge, the FBG interrogator and the laptop used to collect data; (b) a photo of the actual experimental setup.

Data Analysis

Data were processed in MATLAB environment. The $\Delta\lambda_B$ values of the FBG enclosed in the ring-shaped flexible matrix recorded for each diameter ϕ were averaged to obtain the corresponding mean $\Delta\lambda_B$ value. The ϕ values were expressed in terms of ε (%), by assuming ϕ_{min} as the initial diameter. Preliminarily, the standard deviation was estimated for each reference gauge as the dispersion of the data during each 3-minute test to account for stability and any drift. Finally, the calibration curve $\Delta\lambda_B$ as a function of ε was obtained by applying the least squares method to retrieve the straight line that best approximates the experimental data.

5) Results and discussions

To identify the most suitable solutions for PWV measurement within the arterial simulator, the following sections present and discuss the results obtained from the experimental tests described in detail in the previous chapters. Specifically, Section 5.1 outlines and discusses the outcomes of applying the methods for PTT and PWV estimation described in Chapter 3. Section 5.2, otherwise, reports and analyzes the performance of the sensing systems designed to detect the transit of the pressure wave within the arterial surrogate through measurements of its circumferential strain.

5.1) Methods performances

Three methods were identified as suitable candidates for PWV estimation within an arterial surrogate, according to the criteria defined in Section 2.4: full cross-correlation (CC), a wavelet-domain analysis method (WL) and a model-based approach that relies on a mathematical representation of the surrogate's viscoelastic behavior (VBA). These methods were applied both to simulated waveforms and to real signals acquired from the arterial simulator, in order to assess their performance in terms of accuracy and precision, including under noisy and undersampled conditions.

In the following, after presenting and discussing the results obtained for each method, they are compared. The purpose of this comparison is to identify the most promising method, which will be the subject of further optimization in future work.

5.1.1) Full cross-correlation results

As already mentioned in section 3.1, the CC method was first tested on simulated waves reproducing only the forward component of the pressure waves generated by the simulator. It was then applied to real waveforms acquired directly from the experimental setup described in Section 2. Finally, it was applied to simulated waves that also included the contribution of reflected components, with the aim of quantifying their influence.

Simulated direct waves

In the first test, the CC method is applied to simulated waves containing only the forward-propagating component (Section 3.1.1). This method is compared with the results obtained from two well-known point-based approaches: the intersecting-tangent (IT) and the peak-to-peak (PP) methods. The results are reported in Table 5.1. For each method, the estimated delay (ED) and the discrepancy (bias) are provided as a function of the imposed delay (ID) used to generate the simulated waveforms.

Table 5.1. Results of the three methods with respect to imposed delay values. Outcomes are expressed as mean $\pm$ Standard Deviation (SD).

ID τ (ms)	Peak-to-Peak		Intersecting-Tangent		Cross-Correlation	
	ED (ms)	Bias (ms)	ED (ms)	bias (ms)	ED (ms)	bias (ms)
10.4 $\pm$ 0.1	10.6 $\pm$ 0.9	0.2 $\pm$ 0.9	11.1 $\pm$ 0.7	0.7 $\pm$ 0.7	10.4 $\pm$ 0.1	0.0 $\pm$ 0.1
15.7 $\pm$ 0.1	15.8 $\pm$ 0.9	0.1 $\pm$ 0.9	16.5 $\pm$ 0.7	0.8 $\pm$ 0.7	15.7 $\pm$ 0.1	0.0 $\pm$ 0.1
20.1 $\pm$ 0.1	20.0 $\pm$ 0.9	0.1 $\pm$ 0.9	20.8 $\pm$ 0.7	0.7 $\pm$ 0.7	20.1 $\pm$ 0.1	0.0 $\pm$ 0.1
25.3 $\pm$ 0.1	25.3 $\pm$ 0.9	0.0 $\pm$ 0.9	25.9 $\pm$ 0.7	0.6 $\pm$ 0.7	25.3 $\pm$ 0.1	0.0 $\pm$ 0.1
30.9 $\pm$ 0.1	31.1 $\pm$ 0.9	0.2 $\pm$ 0.9	31.6 $\pm$ 0.7	0.7 $\pm$ 0.7	30.9 $\pm$ 0.1	0.0 $\pm$ 0.1
35.3 $\pm$ 0.1	35.4 $\pm$ 0.9	0.1 $\pm$ 0.9	36.0 $\pm$ 0.7	0.7 $\pm$ 0.7	35.3 $\pm$ 0.1	0.0 $\pm$ 0.1
40.1 $\pm$ 0.1	40.0 $\pm$ 0.9	0.1 $\pm$ 0.9	40.8 $\pm$ 0.7	0.7 $\pm$ 0.7	40.1 $\pm$ 0.1	0.0 $\pm$ 0.1
45.6 $\pm$ 0.1	45.6 $\pm$ 0.9	0.0 $\pm$ 0.9	46.2 $\pm$ 0.7	0.6 $\pm$ 0.7	45.6 $\pm$ 0.1	0.0 $\pm$ 0.1
50.2 $\pm$ 0.1	50.3 $\pm$ 0.9	0.1 $\pm$ 0.9	50.9 $\pm$ 0.7	0.7 $\pm$ 0.7	50.2 $\pm$ 0.1	0.0 $\pm$ 0.1
55.9 $\pm$ 0.1	56.0 $\pm$ 0.9	0.1 $\pm$ 0.9	56.7 $\pm$ 0.7	0.8 $\pm$ 0.7	55.9 $\pm$ 0.1	0.0 $\pm$ 0.1
60.5 $\pm$ 0.1	60.4 $\pm$ 0.9	0.1 $\pm$ 0.9	61.2 $\pm$ 0.7	0.7 $\pm$ 0.7	60.5 $\pm$ 0.1	0.0 $\pm$ 0.1

Considering the discrepancy between attended and measured values, the IT method shows a higher gap, with a maximum discrepancy of 0.8 ms, whereas PP and CC methods are comparable with maximum discrepancies of 0.1 ms and 0.0 ms, respectively. The restrained discrepancies are likely due to the fact that the generated waveforms do not include all the frequency contents characterizing actual waveforms acquired from the arterial simulator. As regards the standard deviation (SD) values, PP and TS methods are 0.9 ms and 0.7 ms, respectively, and they keep constant for increasing time delays. On the other hand, SD values for the CC method are smaller than the others (i.e., ± 0.1 ms) since the temporal resolution, determined by the sampling frequency setting, in this case, represents the main uncertainty contribution. This test suggests that the CC method outperforms traditional point-based approaches (i.e., IT and PP) when applied to waveforms similar to those generated by the arterial simulator.

Real waves from simulator

In the second test, the CC method is applied to the waveforms acquired from the simulator (Section 3.1.2) for different values of transmural pressure ΔP , and thus for different PWV values. As before, it is compared with the IT and PP methods. Table 5.2 reports the results obtained for increasing ΔP values under three different external-pressure p_{out} conditions.

Table 5.2. PTT values provided by the PP, IT, and CC methods applied to the waveforms acquired from the arterial simulator for different ΔP and p_{out} conditions. The results are expressed in milliseconds, in terms of mean $\pm$ SD.

ΔP (kPa)	$p_{out} = 50 \text{ kPa}$			$p_{out} = 100 \text{ kPa}$			$p_{out} = 150 \text{ kPa}$		
	PP	IT	CC	PP	IT	CC	PP	IT	CC
0	7.4 ± 0.1	7.5 ± 0.5	7.6 ± 0.2	7.4 ± 0.1	8.0 ± 0.6	7.9 ± 0.1	7.5 ± 0.1	7.0 ± 0.6	8.0 ± 0.1
5	7.3 ± 0.1	7.2 ± 0.5	7.5 ± 0.1	7.6 ± 0.1	7.4 ± 0.4	8.0 ± 0.1	7.6 ± 0.1	7.2 ± 0.8	8.0 ± 0.1
10	7.4 ± 0.1	7.3 ± 0.4	7.6 ± 0.1	7.6 ± 0.1	8.1 ± 0.6	8.1 ± 0.1	7.7 ± 0.1	7.1 ± 1.4	8.1 ± 0.1
15	7.5 ± 0.1	7.8 ± 0.4	7.8 ± 0.1	7.7 ± 0.1	7.7 ± 0.8	8.2 ± 0.1	7.8 ± 0.1	7.4 ± 1.6	8.2 ± 0.1
20	7.6 ± 0.1	8.4 ± 0.8	7.9 ± 0.1	7.8 ± 0.1	8.3 ± 0.8	8.3 ± 0.1	7.8 ± 0.1	7.5 ± 1.7	8.3 ± 0.1
25	7.7 ± 0.1	8.4 ± 0.7	8.1 ± 0.1	7.8 ± 0.1	8.3 ± 0.8	8.4 ± 0.1	7.8 ± 0.1	6.9 ± 1.5	8.3 ± 0.1

The outcomes for the IT method are found to be compatible with the ones for the other two methods but they are characterized by the highest standard deviation values. The corresponding uncertainty is up to 10%, 11% and 23% of the mean value, respectively for the measurements carried out with p_{out} of 50 kPa, 100 kPa and 150 kPa. The advantage of the IT method is that it is less affected by multiple reflections [77] since it focuses on the first part of the upstroke of the waveforms. However, the high uncertainty of results is likely due to the sensitivity of the method to tangent line slope. Indeed, a small gradient variation reflects in a non-negligible time-shifting of the foot of the waveforms. Since the waveform upstroke is also determined by other frequencies in addition to the characteristic one of the phenomena, the variability of the collected waves could cause a dispersion of the results higher than the other methods.

As regards the PP and CC methods show less dispersion, although most of the results seem not compatible among them. The advantage of the PP method is its ease of implementation and low computational cost. However, the limitation of the technique is that the waveform is highly dependent on the choice of the measurement site [121] because (a) the waveform may change its shape given dissipations due to viscoelastic effects and (b) reflections, which are generated close to vessel bifurcations or occlusions, return back and overlap with the direct wave. Therefore, the peak of the resulting wave may differ in time position and amplitude from that of the single direct wave. Thus, even if the method provides a narrow uncertainty, almost constant and below 1.4%, the resulting average values may deviate from the true values, since the shape of the second waveform is different from the first one. Distortion in the shape of pressure waves is a problem that also affects the CC method [79]. To avoid the influence of wave distortions due to reflections, CC is used in the literature by considering only the ramp-up, but from laboratory tests, we found that the results are highly dependent on the foot of the wave considered. Therefore, in this study as in [120], also given the small distance between the two measurement sites, it is assumed, in agreement with [121], that the contribution of this effect is negligible compared to the same contribution for the PP method, and then the whole wave is considered for PTT calculation with this method. Further investigation needs to be conducted about the choice

of the wave portion taken into consideration. The uncertainty values (standard uncertainty) of PTTs deriving from CC method application, are almost constant and below 1.3%.

To evaluate the compatibility between the three methods results has been used the formula suggested by [249]:

$$|\mu_x - \mu_y| \leq \sigma_x + \sigma_y \quad (5.1)$$

where x and y represent two of the three methods, μ and σ represent the mean value and the standard deviation of results in a specific test condition reported in table 5.2, respectively. Compatibility is verified if inequality in (5.1) is met. Table 5.3 shows, for all test conditions in table 5.2, the result of applying inequality (5.1) between the three methods. Specifically, a green box indicates that the inequality is met. On the contrary, a red box indicates that there is no compatibility between the results considered.

Table 5.3. Compatibility between the three methods. According to (5.1), green and red boxes indicate respectively the presence or the absence of compatibility between two results.

ΔP	$p_{out} = 50 \text{ kPa}$			$p_{out} = 100 \text{ kPa}$			$p_{out} = 150 \text{ kPa}$		
	PP-TS	TS-CC	CC-PP	PP-TS	TS-CC	CC-PP	PP-TS	TS-CC	CC-PP
0	Green	Green	Green	Green	Green	Red	Green	Red	Red
5	Green	Green	Green	Green	Green	Red	Green	Red	Red
10	Green	Green	Green	Green	Green	Red	Green	Red	Red
15	Green	Green	Green	Green	Green	Red	Green	Red	Red
20	Red	Green	Red	Green	Green	Red	Green	Red	Red
25	Red	Green	Red	Green	Green	Red	Red	Red	Red

In most cases, according to (5.1), the compatibility of the results is ensured for PP and TS methods but is not respected between CC and both other methods: in particular, as the external pressure increases, the mean values of CC move away from those of TS and PP. In general, the increasing trend in PTT mean values, for all the three methods, confirms an effective variation in PWV due to transmural pressure changes.

Building on the previous statements, it is worth noting that also the scientific literature confirms CC as a robust method for PTT assessment, as already highlighted in section 1.3. This is further supported by its reproducibility even in the presence of noise in the acquired signals and in cases of reduced temporal resolutions. Therefore, in the present study it has been considered the best of the three methods to evaluate the change in PWV within the aortic surrogate caused by the change in transmural pressure.

Effects of reflected waves

This test was carried out to assess the extent to which reflected waves affect the values returned by the cross-correlation method. To this end, the method was applied to simulated

waveforms, and the resulting PWV estimates were compared with the phase-shift values taken as reference PWV_0 (section 3.1.3). Table 5.4 shows the test outcomes as a function of the elastic modulus and SNR values imposed to generate the waveforms. Additionally, the Maximum Error (ME) is reported. ME is the absolute percentage error calculated between the highest mean PWV outcome and the mean value of PWV_0 , for a given Young's modulus.

Table 5.4. Values of PWV_0 and PWV as a Function of Young's Modulus and SNR expressed as mean $\pm$ standard deviation

Young's modulus E (MPa)	PWV_0 ($m \cdot s^{-1}$)	PWV ($m \cdot s^{-1}$)				ME (%)
		SNR = 25 dB	SNR = 15 dB	SNR = 10 dB	SNR = 5 dB	
1.0 ± 0.1	12.7 ± 0.4	12.3 ± 0.5	12.3 ± 0.5	12.3 ± 0.6	12.3 ± 0.8	3.1
2.0 ± 0.2	18.0 ± 0.6	18.4 ± 0.8	18.4 ± 0.9	18.4 ± 1.1	18.5 ± 1.5	2.7
3.0 ± 0.3	22.0 ± 0.7	23.8 ± 1.1	23.8 ± 1.2	23.9 ± 1.6	24.0 ± 2.4	9.0
4.0 ± 0.4	25.5 ± 0.8	28.9 ± 1.4	29.0 ± 1.7	29.0 ± 2.2	29 ± 3	13.7
5.0 ± 0.5	28.5 ± 0.9	33.9 ± 1.7	33.9 ± 2.1	34.1 ± 2.9	34 ± 5	21.0
6.0 ± 0.6	31.2 ± 1.0	38.8 ± 2.0	38.9 ± 2.6	39 ± 4	40 ± 6	28.2

It is worth noting that, as E increases, the cross-correlation tends to overestimate PWV values compared to the theoretical PWV_0 . In this regard, ME remains below 10% for $E \leq 3$ MPa, and reaches a maximum of approximately 28% for $E = 6$ MPa. This suggests that as the time shift between the reflected and forward waves decreases, cross-correlation is less effective. Moreover, at a fixed Young's modulus, PWV values increase slightly with higher noise levels, although the overestimation remains below 2%. These findings reasonably suggest that variations in the imposed SNR level have a negligible effect on the difference between PWV mean values, confirming what found in the literature about the robustness of the cross-correlation method even under noisy conditions [250]. However, for a given Young's modulus, the increase in noise leads to greater uncertainty in PWV results.

The percentage uncertainty with respect to the mean value of PWV_0 never exceeds 3.4%. As for the uncertainty of PWV, on the other hand, for a given SNR level, it arises with increasing Young's modulus. This behavior may be due to the variability associated with the distances x_1 and x_2 , which becomes increasingly significant for the reliability of the PWV measurement as the wave velocity increases [65].

5.1.2) wavelet-based method results

Similarly to the CC method, the WL approach was first tested on simulated waveforms to verify its applicability, and subsequently on real waveforms acquired from the simulator to evaluate the method's sensitivity in detecting PWV variations induced by changes in ΔP (Section 3.2).

Simulated direct waves

Table 5.5 shows the PTT values obtained from the application of the implemented method to the simulated waves, for different imposed delays and SNR levels. Moreover, the percentage errors with respect to the imposed delays have been included. The measurement uncertainty expressed as standard deviation (SD) has been computed as the sum in quadrature of the standard uncertainty associated with the method and the contribution of temporal resolution for each test condition.

Table 5.5. PTT Outcomes (Mean $\pm$ SD) and Percentage Errors from Simulated Waveforms for Different SNR Values

Imposed Delays (ms)	PTT (ms)				Percentage Error (%)			
	No noise	25 dB	15 dB	5 dB	No noise	25 dB	15 dB	5 dB
5.1	5.24 $\pm$ 0.04	5.23 $\pm$ 0.04	5.16 $\pm$ 0.08	5.10 $\pm$ 0.03	2.7	2.5	1.2	< 0.1
5.5	5.65 $\pm$ 0.04	5.64 $\pm$ 0.04	5.58 $\pm$ 0.06	5.51 $\pm$ 0.05	2.7	2.5	1.4	0.1
5.9	6.05 $\pm$ 0.05	6.04 $\pm$ 0.08	6.11 $\pm$ 0.07	5.82 $\pm$ 0.08	2.5	2.4	3.6	1.4

It can be seen that the percentage errors, in general, are low and remain below 4 % for the three imposed delays, regardless of the SNR level. For the above test conditions, the method seems to overestimate the mean PTT values in most cases. This behavior is likely due to the frequency content in the interval $[f_1, f_2]$. In this regard, the selection criterion of the frequency range $[f_1, f_2]$ deserves to be investigated in more detail in the next future. Moreover the relative measurement uncertainties related to the mean values do not exceed 1.6%, suggesting that the method is quite robust for different SNR values.

Table 5.6 shows the results obtained from processing the simulated and undersampled waveforms at SNR = 15 dB. For simplicity, the outcomes at the initial sampling frequency (10^5 Hz) are again included.

Table 5.6. PTT Outcomes (Mean $\pm$ SD) from Simulated Waveforms for Different Sampling Frequencies

Imposed Delay (ms)	PTT (ms)		
	$f_s = 10^5$ Hz	$f_s = 10^4$ Hz	$f_s = 5 \cdot 10^3$ Hz
5.1	5.16 $\pm$ 0.08	5.1 $\pm$ 0.1	5.1 $\pm$ 0.2
5.5	5.58 $\pm$ 0.06	5.2 $\pm$ 0.1	5.6 $\pm$ 0.2
5.9	6.11 $\pm$ 0.07	5.8 $\pm$ 0.1	5.9 $\pm$ 0.2

The first results of the application of the method are promising and seem to confirm that it is effective in estimating the PTT between waveforms with short delays. In particular for $f_s = 10^4$ Hz, the average percentage error among all imposed delays is around 2.4 %, while for $f_s = 5 \cdot 10^3$ Hz, it is no more than 0.6 %, better than $f_s = 10^5$ Hz which is about 2.6 %. Moreover, for undersampled waves, the main uncertainty contribution is given by the temporal resolution, while in the case of the initial sampling rate, the method uncertainty seems to be predominant. This behavior, in agreement with the literature, seems to confirm

that the method used for the PTT estimation is robust at low temporal resolution even with waves similar to those produced by the proposed arterial simulator.

Real waves from simulator

Table 5.7 shows the PTT values obtained by processing the waves acquired from the arterial simulator. The trend of the results is consistent with that expected. In fact, considering the operating principle of the simulator described in Section 2, the deformation state of the surrogate walls induced by the applied transmural pressure causes a decrease in the elastic modulus of the silicone rubber, which results in an increase in the expected PTT.

Table 5.7. PTT Outcomes (Mean $\pm$ SD) from Acquired Waveforms as a Function of ΔP

Transmural Pressure (kPa)	PTT (ms)
0	5.4 $\pm$ 0.2
15	5.6 $\pm$ 0.2
25	5.9 $\pm$ 0.2

The results show that the implemented method is sensitive in detecting expected changes. From the uncertainty analysis, it can be noticed that the contribution related to resolution is negligible given the high sampling rate.

5.1.3) Model-based method results

The method based on the analysis of the viscoelastic behavior of the arterial surrogate (VBA) was applied directly to the real waveforms acquired from the arterial simulator (Section 3.3). Its outcomes were compared with those obtained using the cross-correlation (CC) method, which in this case was taken as the reference. In Fig. 5.1, the PWV values measured with the two methods are shown as a function of the applied ΔP . The velocity trend appears to decrease as the transmural pressure increases.

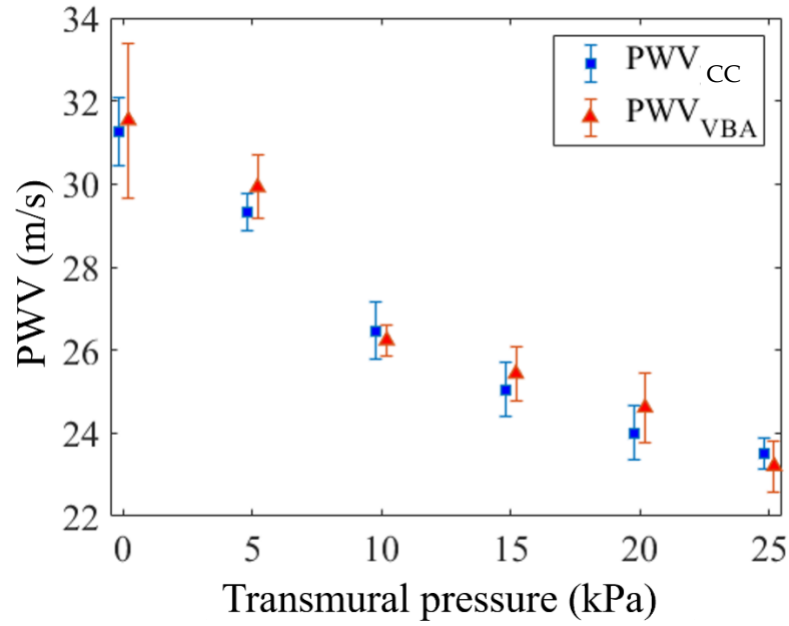


Figure 5.1. PWV outcomes as a function of the transmural pressure applied to the arterial surrogate, calculated using the VBA and CC methods. The values are shown as the mean $\pm$ SD.

This behavior is consistent with the literature, as elastomers generally exhibit a lower elastic modulus with increasing applied stress within a certain range, as mentioned in Section 2. The mean PWV values evaluated using the VBA method range from $31.5 \text{ m}\cdot\text{s}^{-1}$ to $23.2 \text{ m}\cdot\text{s}^{-1}$ for a ΔP from 0 kPa to 25 kPa. The uncertainties range from a minimum of 1.4% to a maximum of 5.9% relative to their respective mean values. The laboratory tests indicate that the higher contribution to uncertainty is attributable to the repeatability of the measurements. The elevated uncertainty at 0 kPa is suspected to arise from instability during pressure wave propagation, as the vessel is subjected to alternating compression and tension states induced by oscillating positive and negative pressures. Regarding the PTT method, the mean PWV values range from $31.3 \text{ m}\cdot\text{s}^{-1}$ to $23.5 \text{ m}\cdot\text{s}^{-1}$, with ΔP varying from 0 kPa to 25 kPa. The corresponding relative uncertainties range from a minimum of 1.6% to a maximum of 2.7%.

Table 5.8 presents all the results and the associated uncertainties obtained from the application of both methods for each imposed ΔP value, i.e., Young's modulus outcomes, PWV values calculated using the VBA method (PWV_{VBA}), as well as the ones obtained with the CC method (PWV_{CC}). Additionally, APE is also reported. Compared to the PTT method, the VBA method shows an Absolute Percentage Error (APE) varying between 0.9% and 2.5%.

Table 5.8. Results from the two Methods as a function of ΔP

ΔP (kPa)	E (MPa)	PWV_{VBA} ($\text{m}\cdot\text{s}^{-1}$)	PWV_{CC} ($\text{m}\cdot\text{s}^{-1}$)	APE (%)
0	8.0 ± 0.6	31.5 ± 1.9	31.3 ± 0.8	0.8

ΔP (kPa)	E (MPa)	PWV _{VBA} (m·s ⁻¹)	PWV _{CC} (m·s ⁻¹)	APE (%)
5	7.2 ± 0.6	29.9 ± 0.8	29.3 ± 0.5	2.0
10	5.5 ± 0.4	26.2 ± 0.4	26.5 ± 0.7	0.9
15	5.2 ± 0.4	25.4 ± 0.6	25.0 ± 0.7	1.5
20	4.9 ± 0.4	24.6 ± 0.8	24.0 ± 0.6	2.5
25	4.3 ± 0.4	23.2 ± 0.6	23.5 ± 0.4	1.2

To assess the compatibility between the two datasets [249], the following inequality was verified for each pair of PWV values corresponding to the i -th ΔP value ($i = 1, \dots, 6$):

$$|PWV_{VBA,i} - PWV_{PTT,i}| > \sigma_{VBA,i} + \sigma_{PTT,i} \quad (5.2)$$

Eq. 5.2 is consistently satisfied, suggesting that the two methods are in agreement. Based on these outcomes, the VBA method appears to represent an alternative approach compared to traditional methods based on PTT estimation. It overcomes some typical difficulties, e.g., the choice of a characteristic point or a wavefront portion to evaluate the pulse transit delay. Moreover, it provides a direct assessment of the vessel stiffness. However, the method appears to be sensitive to the frequency spectrum considered for the calculation of Young's modulus. Indeed, it is crucial to isolate and examine only the characteristic frequencies of the phenomenon under investigation.

5.1.4) Comparison of the methods' outcomes

Table 5.9 summarizes the main results obtained with the proposed methods as a function of the tests they were subjected to, and also reports the corresponding reference methods or reference values used for comparison.

As discussed in Section 1.2, in clinical practice, i.e., when applied to waveforms acquired from human subjects, the IT method is typically adopted as the reference approach [expert consensus]. However, for the application addressed in this study, it was shown in Section 5.1.1 that the performance of this method was surpassed by the CC method, which, particularly in the test with simulated forward waves, provided results that were both more accurate and more precise with respect to the reference values. Therefore, as also noted in Section 2.4, it is reasonable to exclude point-based methods from the comparison when identifying the most performant approach for PWV estimation within the arterial simulator.

When comparing the CC and WL methods on simulated forward waveforms, the former proved to be more accurate, yielding a bias below 1 % relative to the mean reference value, and more precise, with a standard deviation below 1% relative to the same reference. In tests performed on real waveforms acquired from the simulator, the WL method exhibited higher uncertainty (3.7 % versus 1.3 % for the CC method), likely because identifying the most

appropriate ROI is challenging. Indeed, laboratory testing confirmed that the method's accuracy and precision depend on the selected time and frequency intervals. Despite these limitations, the WL method demonstrated good performance also under noisy and undersampled conditions (Section 5.1.2).

The VBA method proved to be more demanding from an implementation standpoint, as it relies on several assumptions regarding the phenomena occurring within the simulator. Moreover, laboratory tests confirmed that the method is highly sensitive to the selected ROI, even more so than the WL method. When compared against the values provided by the CC method on real waveforms acquired from the simulator, the VBA method exhibited a maximum bias of 2.5% and a relative uncertainty of 5.9%. Considering the limitations discussed above, it can be regarded as an alternative to the other two methods, given its distinctive capability to provide information directly related to the surrogate stiffness.

Table 5.9. Comparison of the results obtained with the proposed methods as a function of the test type.

Method	Reference	In silico		In vitro	
		bias	SD	bias	SD
CC	Theoretical value	< 1 %*	< 1 %*	-	1.3 %
WL	Theoretical value	4 %	1.6 %	-	3.7 %
VBA	CC	-	-	2.5 %	5.9 %

* The results do not include the contribution of reflected waves, which was investigated in a dedicated study (Section 5.1.1).

The results indicate that, in terms of accuracy and precision, the cross-correlation method is the most performant. It is important to note, however, that these results do not account for the contribution of reflected waves. The test conducted to quantify the effect of reflections on the CC outcomes showed that the mean values are affected by a bias of up to 3% for PWV values up to 18 m/s. This finding is encouraging, as under physiological conditions PWV typically ranges from 5 m/s to 15 m/s.

Accordingly, the method ultimately selected as the most promising for the present application is CC, which will therefore be the subject of further investigation. In particular, it is necessary to examine in greater depth the influence of reflections on the real waveforms acquired from the simulator and to standardize a procedure to compensate for the bias affecting CC by means of a correction coefficient.

5.2) Sensors' performances

Two different transducers were developed with the aim of identifying the most performant solution capable of detecting the passage of the pressure wave within the arterial surrogate. During the design phase, specific solutions were adopted to ensure

compliance with the simulator's geometrical requirements, as defined in Section 2.4. The first proposed solution consists of a carbon-based conductive ink deposited directly onto the surrogate using AJP technology. The second solution is a silicone ring with an integrated FBG sensor. Both solutions were evaluated through strain tests to assess their performance in terms of maximum and minimum detectable deformation (ε_{max} and ε_{min}) required by the application (section 2.4).

The following sections describe in detail the results obtained from the experimental tests (Sections 5.2.1 and 5.2.2). Then, the outcomes of the two solutions are compared and discussed in order to identify the most promising approach (section 5.2.3).

5.2.1) Conductive Ink results

The results of the conductive-ink-based sensors are reported below as a function of the tensile tests they were subjected to, according to the procedures described in Section 4.1.

Static Test

In Fig. 5.2, an example of the sensor response to the application of static strain steps can be observed, both in the loading and unloading phases (Fig. 5.2a and Fig. 5.2b, respectively). It can be noted that during the application of the steps $\Delta\varepsilon$, there is always an increase in resistance. Then, when the input strain remains constant, the resistance decreases following an exponential law. This behavior is known in literature as 'overshoot' [222] and its magnitude is directly proportional to the strain value and strain rate for the same material [251]. This phenomenon highlights the viscoelastic nature of the specimens [245], [246].

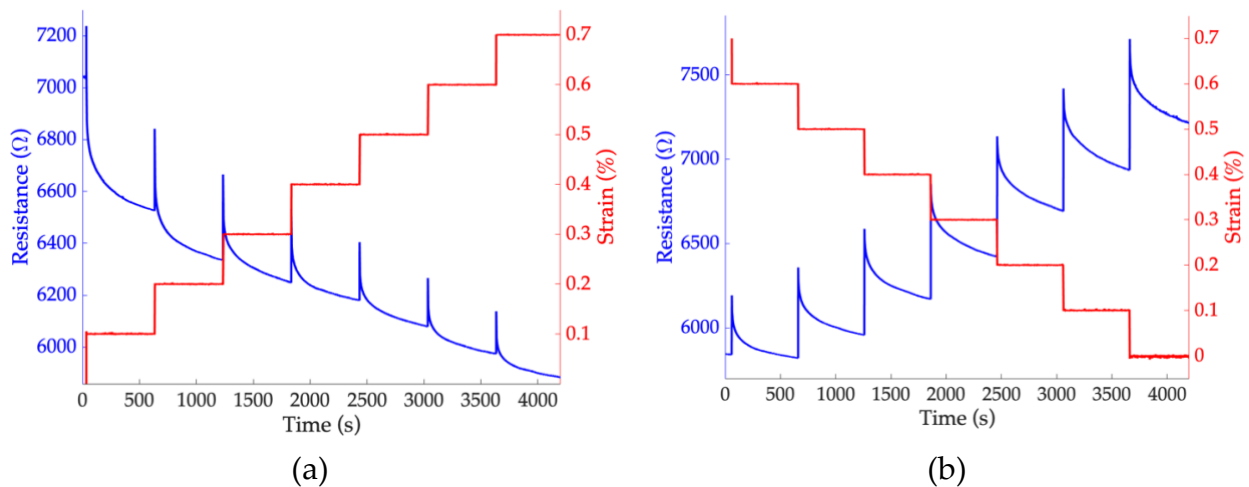


Figure 5.2. Trends of resistance over time acquired from sensor 1a during the static test: response during (a) the loading phase and (b) unloading phase.

Overall, considering the response of the sensor throughout the static test, it can be observed that the resistance value decreases with increasing strain (Fig. 5.2a), and vice versa (Fig. 5.2b). This behavior, known in the literature [252], could be due to the strain of the

polymer matrix, which in this case corresponds to an elongation of the sensor, allowing better contact between the conductive particles within a certain strain range [253]. Based on these considerations, it is assumed that this effect was amplified by the overlapping layer structure of which the sensors are composed (As described in Section 4.1), promoting particle contact between the different layers. This issue deserves further investigation in the future by comparing sensors with varying number of layers.

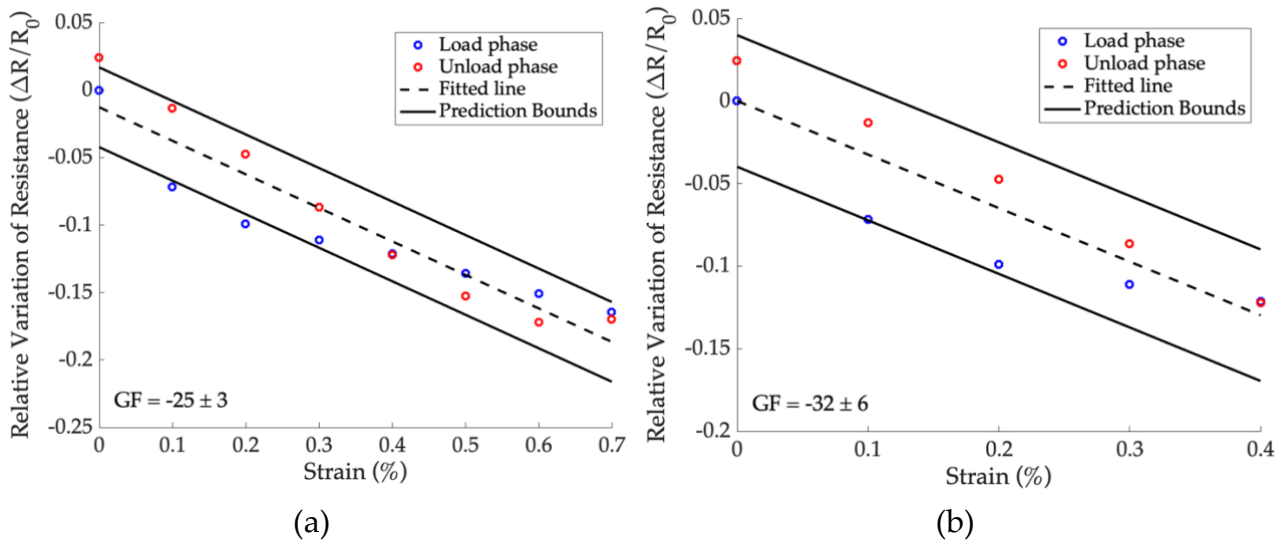


Figure 5.3. Relative resistance variation during loading and unloading phases as a function of the strain in the static test for sensor 1a. The line resulting from weighted least squares linear regression with its prediction bounds are also shown: (a) entire strain range and (b) strain range up to 0.4%.

Fig. 5.3 shows the resistance results obtained for sensor 1a for both the loading and unloading phases as a function of the imposed strain. The straight line from the linear regression and corresponding prediction bounds are also shown. In Fig. 5.3a, the trend for the entire imposed strain range can be observed, while a focus on strain values up to 0.4% is provided in Fig. 5.3b. Gauge Factor (GF) outcomes (expressed as mean $\pm$ SD), R^2 coefficients, prediction bounds and the minimum detectable strain $\varepsilon_{min,ink}$ obtained for each sensor are listed in Table 5.10 for both strain ranges in Fig. 5.3.

Table 5.10. Gauge factor, prediction bounds and minimum detectable strain for each sensor estimated for two strain intervals.

Sensor	Strain interval (%)	GF	R^2	Prediction Bounds (Ω/Ω)	$\varepsilon_{min,ink}$ (%)
1a	[0.0 – 0.7]	-25 ± 3	0.88	± 0.031	0.3
	[0.0 – 0.4]	-32 ± 6	0.86	± 0.040	0.3
1b	[0.0 – 0.7]	-19 ± 3	0.79	± 0.031	0.3
	[0.0 – 0.4]	-25 ± 4	0.81	± 0.037	0.3
2a	[0.0 – 0.7]	-10 ± 5	0.30	± 0.036	0.8

2b	[0.0 – 0.4]	-26 ± 10	0.55	± 0.035	0.3
	[0.0 – 0.7]	-9 ± 5	0.23	± 0.033	0.7
	[0.0 – 0.4]	-27 ± 11	0.53	± 0.034	0.3
3a	[0.0 – 0.7]	-7 ± 3	0.39	± 0.029	0.9
	[0.0 – 0.4]	-18 ± 3	0.83	± 0.021	0.3
3b	[0.0 – 0.7]	-10 ± 2	0.57	± 0.027	0.6
	[0.0 – 0.4]	-20 ± 3	0.87	± 0.020	0.3

Globally, sensors on the same surrogate exhibit similar behavior, while the wide prediction bounds confirm a hysteresis phenomenon. It can be noticed that higher R^2 values are obtained for the strain range up to 0.4% and the response seems more linear. In this range, the minimum detectable strain of the sensors is 0.3%, while this is not always valid considering the strain interval up to 0.7%.

Dynamic Test

Fig. 5.4 shows the behavior of a sensor subjected to cyclic strain loading in the range 0.0% to 0.7% at frequencies of 0.01 Hz (Fig. 5.4a) and 0.1 Hz (Fig. 5.4b). It can be observed that the sensor required at least ten preconditioning cycles before reaching a stable behavior.

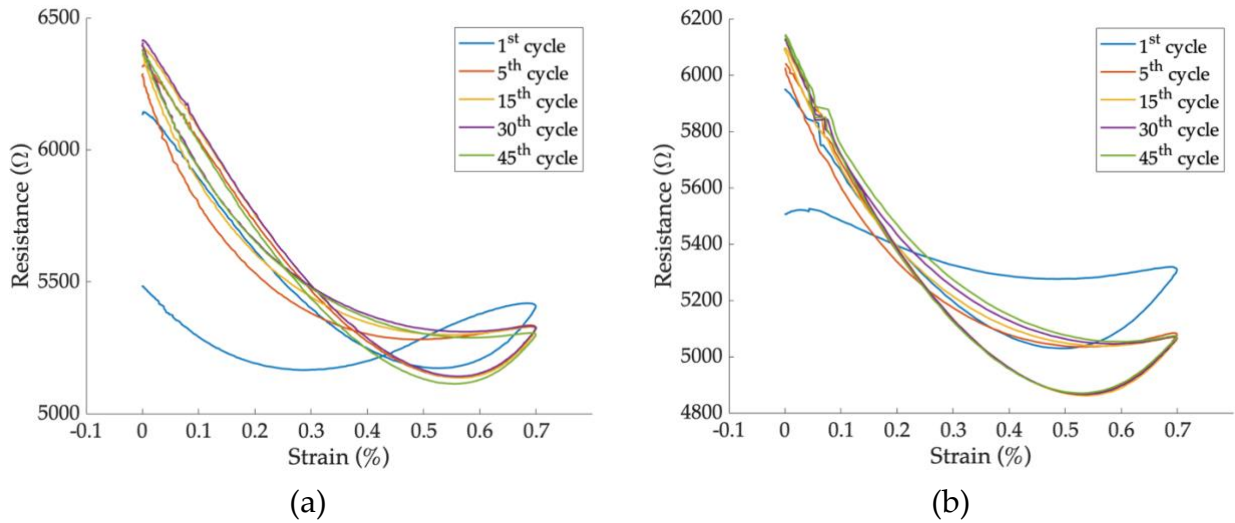


Figure 5.4. Response of sensor 2b at sinusoidal strain values: dynamic test at (a) 0.01 Hz and (b) 0.1 Hz.

The change in resistance within the strain range of 0.0 to 0.7% does not appear linear. This hypothesis was confirmed by the fact that fitting the trend with a second-order polynomial (Fig. 5.5a) yields an R^2 coefficient > 0.99 . Therefore, in this case, the weighted linear least squares regression was carried out only for strains up to 0.4% (Fig. 5.5b).

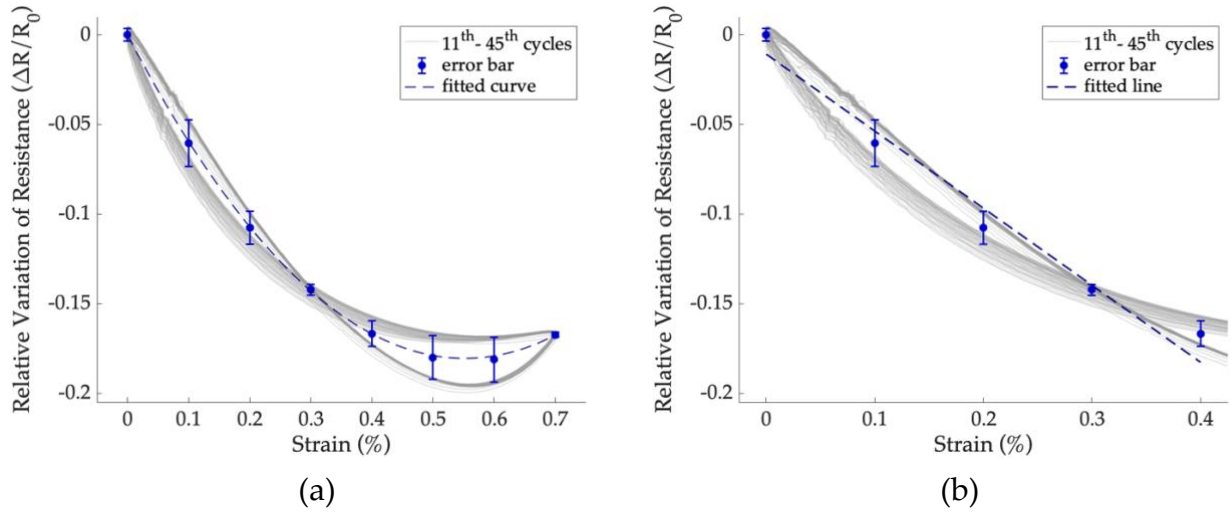


Figure 5.5. Interpolation of the response of sensor 2b as a function of the strain applied during the dynamic test at 0.01 Hz. The error bars represent the standard deviations estimated from the measurements performed during the loading-unloading phases for each strain value: (a) second-order polynomial fitting over the entire strain range and (b) linear fitting within the strain range up to 0.4%.

In Table 5.11, the GF values calculated during the dynamic tests are shown for a strain interval of 0.0 to 0.4% at frequencies of 0.01 and 0.1 Hz, respectively. Moreover, the corresponding R^2 values for each fitting, the prediction bounds, and the minimum detectable strain are provided.

Table 5.11. Gauge factor, prediction bounds and minimum detectable strain for each sensor estimated for the two frequencies of the dynamic test.

Sensor	Test Frequency (Hz)	GF	R^2	Prediction Bounds (Ω/Ω)	$\varepsilon_{min,ink}$ (%)
1a	0.01	-27 ± 2	0.88	± 0.024	0.2
	0.1	-44 ± 2	0.93	± 0.026	0.2
1b	0.01	-25 ± 2	0.88	± 0.023	0.2
	0.1	-38 ± 2	0.92	± 0.024	0.2
2a	0.01	-43 ± 1	0.98	± 0.012	0.1
	0.1	-50 ± 1	0.97	± 0.016	0.1
2b	0.01	-41 ± 1	0.98	± 0.012	0.1
	0.1	-51 ± 1	0.98	± 0.013	0.1
3a	0.01	- ⁽¹⁾	-	-	-
	0.1	-35 ± 1	0.97	± 0.013	0.1
3b	0.01	-17 ± 1	0.81	± 0.015	0.2
	0.1	-37 ± 1	0.96	± 0.016	0.1

⁽¹⁾ Results are not available due to sudden sensor failure.

In the applied strain range, a general increase in sensor sensitivity was found between the dynamic test at 0.1 Hz and the static test. This is shown by an increase in absolute GF values ranging from 37% to 95%. The phenomenon could be justified by the fact that by increasing the strain rate (i.e., increasing the test frequency at the same strain interval), the specimen responds more rigidly [254]. A decrease in prediction bounds between dynamic and static tests ranging from 20% to 65% was found, suggesting a reduction of the hysteresis phenomenon. The minimum detectable strain of the sensors under dynamic test was between 0.1 and 0.2%, in agreement with the specifications required by the application.

Maximum Elongation Test

Fig. 5.6 show the resistance trends as a function of the changes in strain during the maximum elongation test carried out on specimen 2. It can be observed that sensors 2a and 2b reached a maximum strain of 8.0% and 5.3%, respectively. These results are consistent with those reported in the current literature for sensors produced through AJP technology [240]. Unfortunately, these values do not currently meet the requirements of the application. It is hypothesized that the maximum strain attainable by the sensor is limited by (a) the composition of the conductive material, whereby the carbon-particle loading reduces its ultimate elongation with respect to the matrix in which it is dispersed [255], and (b) the imperfect compatibility between the surrogate and the conductive ink, observed during the experimental tests.

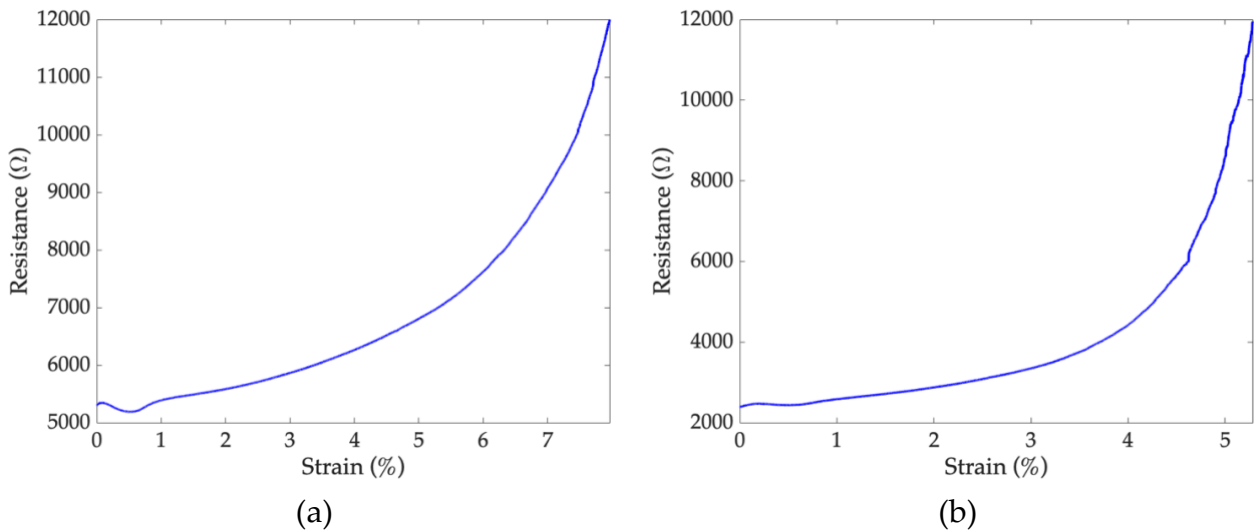


Figure 5.6. (a) Sensor 2a and (b) sensor 2b behavior during the maximum elongation test performed at 1 mm/min.

In Fig. 5.6, the sensor's peculiar behavior in the 0.0 - 1.0% strain range can be observed. Indeed, at first, the resistance increased, then decreased for a limited interval, and then increased again. This behavior, described in [253], [256], depends, among other factors, on the percentage of carbon particles within the conductive paste. It would be interesting to

impose a pretensioning on the sensors before their testing to obtain a more stable behavior of the sensors for a wider strain range.

Fatigue Strength Test

Specimen 1 was subjected to the fatigue resistance test: failure occurred at the 223rd and 237th cycle for sensors 1a and 1b, respectively. Fig. 5.7 shows the response of sensor 1a as a function of the applied strain when it is still intact (Fig. 5.7a) and after crack formation (Fig. 5.7b). A change in sensor behavior can be observed near the failure (Fig. 5.7b) compared to the beginning of the test (Fig. 5.7a). Crack propagation is highlighted by a general increase in the average resistance values. Moreover, a response shift is found: while a minimum strain corresponds to a maximum resistance (Fig. 5.7a), a minimum resistance is observed near the minimum strain. Based on these considerations, the dependence of sensor resistance on frequency requires further investigation, since, in the context of dynamic tests, the application of the same strain at a frequency of 0.1 Hz did not cause any failure even after 450 cycles.

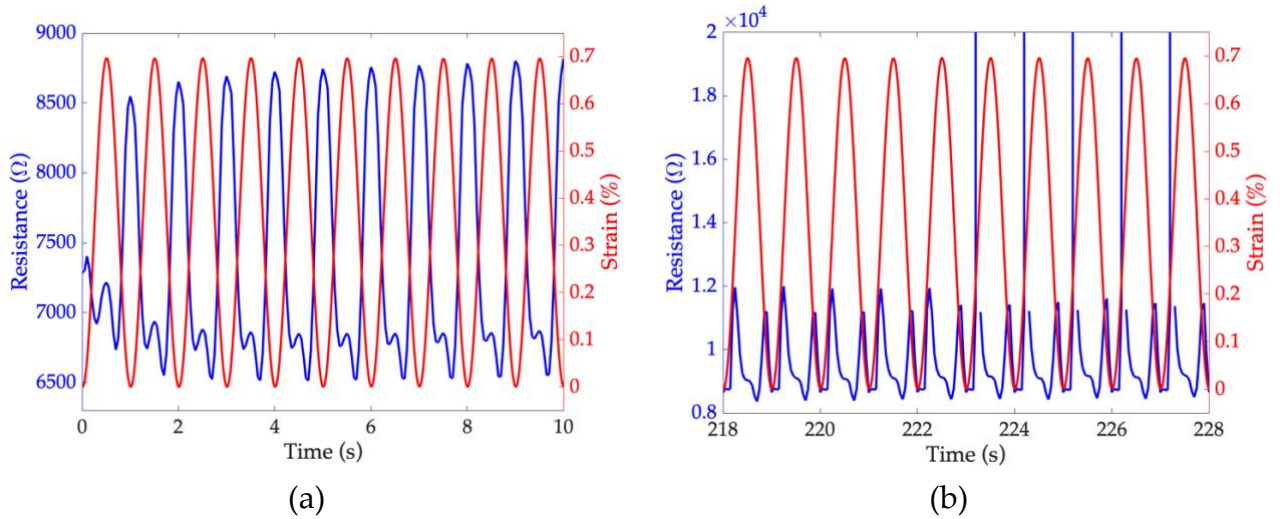


Figure 5.7. Resistance variations of sensor 1a with respect to strain values, related to fatigue strength test: (a) behavior of sensor still intact, at the beginning of the test; (b) behavior of sensor after crack formation and at the time of rupture.

5.2.2) FBG-based sensor result

The solution consisting of a silicone ring integrating an FBG sensor was preliminarily tested through a static test, according to the procedures described in Section 4.2.

Fig. 5.8 shows the variation of $\Delta\lambda_B$ as a function of ε . The trend is increasing for increasing strain levels. The average values of $\Delta\lambda_B$ range from 0.06 to 0.42 nm for strain levels of 0% and 30%, respectively. Regarding the standard deviations, a maximum relative uncertainty of less than 0.5% is found. The calibration curve ($R^2 = 0.994$) is also shown in Fig. 5.8, along with the corresponding 68% confidence bounds. Hence, a sensitivity of 0.0119 nm/% is retrieved as the calibration curve slope over the measurement interval from 0% to 30%, with

a relative standard uncertainty of 3.5%. The sensitivity value and the width of the confidence bounds suggest that the sensor is capable of discriminating strain levels down to 2.6%, thus not satisfying the imposed ε_{min} requirement. In the future, this value should be verified through repeated deformation tests, including under dynamic conditions, to assess the magnitude to which viscoelastic effects, and thus hysteresis, affect the confidence bounds. Furthermore, preliminary experimental results show that the sensor can detect strain levels up to 30% maintaining linear behaviour throughout the measurement range. This suggests compliance with the specified ε_{max} criterion. However, this result should be confirmed through repeated deformation tests to verify the presence of any slippage between the optical fiber and the silicone ring that could impair measurement repeatability.

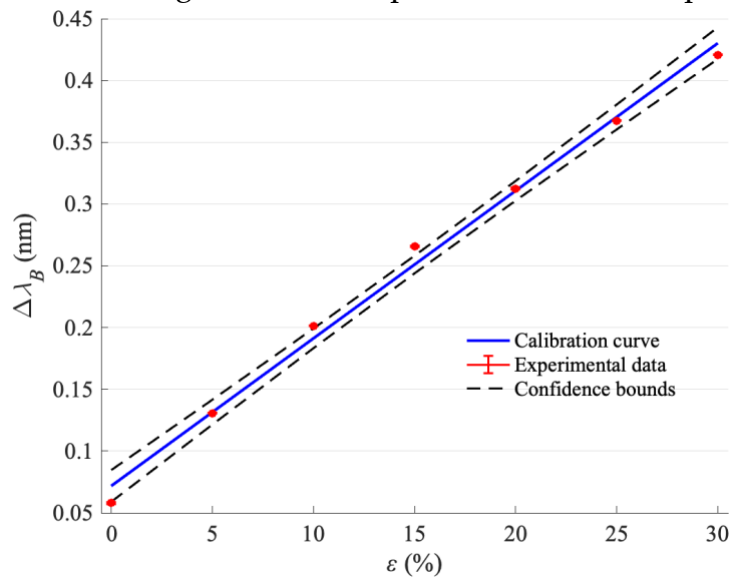


Figure 5.8. The calibration curve (solid blue line), the experimental data expressed as mean $\pm$ standard deviation (red dots with bars), and the 68% confidence bounds (black dashed lines).

5.2.3) Comparison of the sensors' outcomes

Table 5.12 summarizes the best results achieved by each proposed solution under the corresponding static and dynamic tests.

Table 5.12. Best sensor results obtained from the tests they were subjected to.

Sensor	Requirements		Static tests		Dynamic tests		
	ε_{max}	ε_{min}	ε_{max}	ε_{min}	ε_{max}	ε_{min}	Fatigue failure
Conductive Ink	30 %	0.6 %	8 %	0.3 %	1.4 %	0.1 %	450 cycles
FBG-based sensor	30 %	0.6 %	30 %*	2.6 %	-	-	-

* a preliminary result that warrants further investigation

The conductive ink appears to meet the application requirements only partially. It demonstrated the ability to detect small strain levels: indeed, its high sensitivity and the magnitude of hysteresis enabled ε_{min} to be distinguished down to 0.3% in static tests and 0.1% in dynamic tests. However, these sensors were not able to reach the maximum strain required by the application. This behavior is likely due to imperfect adhesion between the sensor and the substrate. In addition, it is suspected that the carbon fraction used as the conductive agent, while increasing electrical conductivity, adversely affects the mechanical properties and thus reduces elongation during tensile tests, as mentioned in Section 5.2.1.

Also The FBG-integrated silicone ring appears to partially meet the application requirements. It demonstrated the ability to reach the maximum detectable strain required by the application, although the current evidence is based on preliminary testing. The magnitude of any slippage between the silicone matrix and the FBG should be evaluated as the deformation approaches the application-imposed maximum. This can be investigated through tests involving repeated loading–unloading cycles. If the adhesion between the sensor and the substrate is compromised at strains around 30%, the relative displacement between the two components could impair the repeatability of the sensor output, rendering the solution unsuitable. By contrast, the solution did not appear to meet the minimum detectable-strain requirement. It is necessary to assess the extent to which viscoelastic effects introduced by the silicone ring affect the width of the confidence bounds and, consequently, the resulting ε_{min} , which is 2.6% based on the present tests. To increase the sensor's minimum detectable strain, the FBG could be integrated into a stiffer silicone ring, so that the deformation is transmitted more uniformly along the entire ring circumference and, consequently, to the FBG sensor. At that point, however, it would be necessary to quantify the insertion error introduced by using a stiffer sensor on the arterial surrogate.

In conclusion, the solution identified as the most suitable for use within the arterial simulator is the conductive-ink-based sensor. Indeed, although it did not fully meet the application requirements in the tests performed, it remains promising for several reasons. First, the literature indicates that conductive inks, in specific cases, could achieve larger strains than those attained in the present study [257]. Further work is therefore needed to investigate compatibility with new combinations of surrogate and sensing materials [258], as well as more complex geometries that can mitigate the onset of uncontrolled cracking at comparable strain levels [259]. Second, alternative deposition technologies for conductive inks can be explored, including the equally promising Direct Ink Writing, which enables the evaluation of different material formulations [260], [261].

6) Conclusions

6.1) Research project overview and novelty

This PhD work focused on the development and validation of technical solutions for measuring Pulse Wave Velocity (PWV) within a novel variable-stiffness arterial simulator. The underlying motivation was to contribute to the development of an instrument that could, in the future, serve as a reference system for verifying the functionality and performance of the devices currently used in clinical practice to assess arterial stiffness. Indeed, arterial stiffness is widely recognized as an independent risk factor for the early diagnosis of cardiovascular diseases in clinical settings. To this end, it is essential to ensure that PWV can be measured within the proposed simulator with high accuracy and precision.

Within this framework, this research achieved two main objectives:

1. **Identification of a suitable PWV measurement method in the arterial simulator.** Three methods, already established in the literature, were selected and tested for the first time on the waveforms generated by the arterial simulator, while accounting for real phenomena characteristic of the experimental apparatus, such as the influence of reflected waves, signal noise, and undersampling. The methods were then assessed and compared in terms of accuracy and precision. The results indicated that the most promising approach is the full cross-correlation method. Among its additional advantages, it does not require the selection of a Region of Interest (ROI) for transit-time estimation.
2. **Development of a sensor to detect the transit of the pressure wave within the arterial surrogate.** Two strain-measurement technologies, representative of the state of the art in international biomedical research, particularly in the field of wearable sensors, were selected. Based on these technologies, two innovative sensors were developed to comply with the geometric constraints imposed by the application. The two solutions were tested and compared to verify whether the achievable strain range met the application requirements. The results showed that the conductive ink-based sensor is the most promising solution. Among its additional advantages, it exhibits high resolution, simplicity of measurement chain and a reduced insertion error.

Overall, this research represents a step forward in the study and refinement of instrumentation relevant to the diagnosis of cardiovascular diseases (Section 6.2) and provides several directions for further investigation into the technical aspects characterizing the instruments adopted to verify the functioning of both currently adopted solutions and those still under development (Section 6.3).

6.2) Technical and scientific impact

The contribution of this research to the international landscape is twofold.

1. On the one hand, the investigation aimed at identifying a method for PWV measurement enabled the testing of approaches already established in the literature, further corroborating and validating their robustness under specific conditions (e.g., noise and undersampling), even when applied to different datasets. Indeed, the waveforms generated by the proposed simulator are distinctive and differ substantially from those acquired in humans or produced by other in vitro systems. This is due to the device's unique structural configuration and its innovative operating principle. Moreover, the study highlighted the strengths and identified the limitations of methods that currently represent major lines of investigation in the scientific literature, when applied to an application that is both novel and internationally relevant, and that therefore warrants further study and development. While arterial simulators lack some of the complex damping reflections and distortions inherently present in vivo, the ability to operate in a highly controlled and reproducible environment provides a critical metrological advantage. This allows for a rigorous comparison of different measurement techniques against a known ground truth, a benefit that greatly outweighs the limitations of a simplified hemodynamic model.
2. On the other hand, the development of innovative transducers for detecting the passage of the pressure wave within an arterial surrogate enabled state of the art strain measurement techniques, currently at the forefront of biomedical and wearable-sensing research, to be evaluated in a completely new application. This made it possible to provide evidence on the potential and limitations of these sensors, both in terms of compatibility with materials and geometrical constraints, and with respect to the mechanical requirements specific to the present application. In addition, the proposed solutions were characterized from a metrological standpoint, an aspect that is often overlooked in studies of this kind.

6.3) Future developments

The promising results obtained provide a solid starting point and offer numerous directions for further refinement and optimization of the solutions investigated in this study.

PWV method: correction and standardization

The proposed direction is to focus on optimizing the full cross-correlation method, as it is less affected by the uncertainty associated with ROI selection for PTT estimation. A priority for future work is the standardization of a protocol to compute a correction coefficient to be applied to the PWV estimates returned by full cross-correlation. The goal is to minimize the

influence of reflected waves on the accuracy of the results. Alternatively, a refined mathematical model could be employed to identify and remove reflections within the actual waveforms generated by the simulator, ensuring that cross-correlation is applied exclusively to the forward-wave component. This optimization could be achieved through sensor fusion techniques that leverage the complementarity of model-based methods. Once the method has been optimized on the arterial simulator, which could serve as a test bench, it may be possible to apply it to more challenging scenarios, such as in vivo applications. Standardizing a method to isolate the signal of interest from the contribution of reflected waves could be useful for estimating blood vessel stiffness by integrating the method into the systems currently used in clinical practice. Moreover, the arterial simulator can be used to develop and validate an in vitro reference infrastructure for robust, reproducible and traceable measurement of Pulse Wave Velocity (PWV). In fact, existing non-invasive measurement devices often provide numerical PWV values without a rigorous separation among measurand definition, acquisition chain, signal quality, uncertainty, traceability and reproducibility. This limits comparability across systems, laboratories and datasets: the arterial simulator here developed can contribute to fill this gap by providing an in vitro framework for calibration, quality control, reproducibility and traceable validation of PWV measurement.

Exploring new sensor fabrication solutions

Given that the conductive-ink-based sensor proved to be the most promising solution, and in view of the rapid expansion of conductive-ink technologies in biomedical applications, particularly in wearable devices, their use should be further investigated in depth. Therefore, future work should include studying the compatibility of different combinations of surrogate materials and conductive inks, through optimized material formulations and layer architectures. The objective is to improve adhesion between the substrate and the sensing element in order to maximize performance. In addition, new deposition strategies should be evaluated. In particular, Direct Ink Writing (DIW) is known to enable the deposition of layers with controllable geometry and thickness while providing high printing resolution.

FBG sensor: dynamic characterization and metrological maturity

Given that the FBG-based sensor has not yet been tested in depth, the next step is to move from preliminary feasibility to metrological maturity. To achieve this, tensile tests with repeated loading–unloading cycles on multiple specimens should first be conducted to verify the preliminary results obtained so far. In addition, the dynamic behavior should be investigated to quantify the effects associated with the viscoelasticity of the constituent materials, including hysteresis, frequency response, and phase lag. It will also be necessary

to assess the influence of external factors, such as temperature, and to investigate long-term stability.

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