

Evaluation of Nonlinear Wave Separation Method to Assess Reflection Transit Time: A Virtual Patient Study

Rahul Manoj, Raj Kiran V, Nabeel P M, *Member IEEE*, Mohanasankar Sivaprakasam and Jayaraj Joseph

Abstract— Conventional methods to calculate reflection transit time (RTT) is based on pulse counter analysis. An alternative to this approach is separating forward and backward components from a pulse waveform to calculate the RTT. State-of-the-art in wave separation requires simultaneously measured pressure and flow velocity waveforms. Practically, getting a simultaneous measurement from a single arterial site has its limitations, and this has made the translation of wave separation methods to clinical practice difficult. We propose a new method of wave separation analysis that requires only a single pulse waveform measurement using a multi-Gaussian decomposition approach. The novelty of the method is that it does not require any measured or modelled flow velocity waveform. In this method, the pulse waveform is decomposed into the sum of Gaussians and reconstructed based on model criteria. RTT is calculated as the time difference between normalized forward and backward waveform. The method's feasibility in using RTT as a potential surrogate is demonstrated on 105 diverse selections of virtual subjects. The results were statistically significant and had a strong correlation ($r > 0.79$, $p < 0.0001$) against clinically approved artery stiffness markers such as Peterson's elastic modulus (E_p), pulse wave velocity (PWV), specific stiffness index (β), and arterial compliance (AC). Out of all the elasticity markers, a better correlation was found against AC.

Clinical Relevance— This simulation study supplements the evidence for the dependence of pulse wave reflections on arterial stiffness. It provides a new method to study wave reflections using only a single pulse waveform.

I. INTRODUCTION

The arterial pulse waveform (pressure or diameter) is a superposition of a forward wave and a backward wave. The forward wave is the pulse wave during ventricular ejection, and the backward wave is the cumulative effect of all the reflections of the forward wave along the arterial tree. The major contributor to reflections is the tapering structure of the blood vessels, branching and stiffening of arteries [1]. It is the

Rahul Manoj and Raj Kiran V are with the Electrical Engineering Department, Indian Institute of Technology Madras, Chennai-600036, India (e-mail: rahulmanojkty@gmail.com).

Nabeel P M is with Healthcare Technology Innovation Centre (HTIC), Indian Institute of Technology Madras Research Park, Chennai-600113, India.

Jayaraj Joseph is with the faculty of Electrical Engineering Department. Mohanasankar Sivaprakasam is the Director of Healthcare Technology Innovation Centre and with the faculty of Electrical Engineering Department at Indian Institute of Technology Madras, Chennai-600036, India

compliance of the elastic arteries that helps in storing the pulsatile energy. As the ventricle closes abruptly, this energy is utilized for dampening the pulse waves at microcirculation. As the artery gets stiffer over time, the elastic arteries lose the capacity to store energy and therefore, pulse waves (both forward and backward) travel faster. In other words, reflections arrive early for a stiffer artery [2]. This can be estimated by measuring the time difference between forward and backward waves, called reflection transit time (RTT). The stiffness of the artery is estimated by clinically approved stiffness or elasticity markers like Elastic Modulus (E_p), Pulse Wave Velocity (PWV), specific stiffness index β and Arterial Compliance (AC). The expression for each marker is highlighted in TABLE I.

Quantification of reflection and RTT is conventionally performed by pulse contour analysis (PCA), which relies on fiducial/inflection points on the pulse morphology [3]. An alternative is using wave separation analysis (WSA), which decomposes the waves into forward and backward components [4]. Augmentation Index (AIx) is a clinically recognized tool in assessing reflection using PCA. However, the method is not reliable in accurately quantifying reflections as it depends on the arrival time and magnitude of reflections [5]. On the other hand, WSA involves decomposing the pulse waveform into its forward and backward components. The state-of-the-art technique in wave separation involves either a frequency domain [6] or time domain [7] approach for calculating characteristic impedance: both the methods requires simultaneously measured flow velocity and pressure waveform from the same artery site. Practical measurement challenges [8]–[10] and limitations imposed by the sensor form factors for achieving single site measurements makes these methods difficult in a clinical setting. A modified version of the frequency domain/impedance method, which uses an un-calibrated triangular flow waveform instead of the measured flow waveform, requires only a single pulse waveform to perform the wave separation analysis [11]. However, the method depends on the fiducial/inflection point of the pulse morphology to model the flow. In a different approach, the tube load model-based decomposition of pressure waves is obtained using a distal and proximal measurement of pressure wave alone. However, this technique ignores wave reflections due to arterial geometry

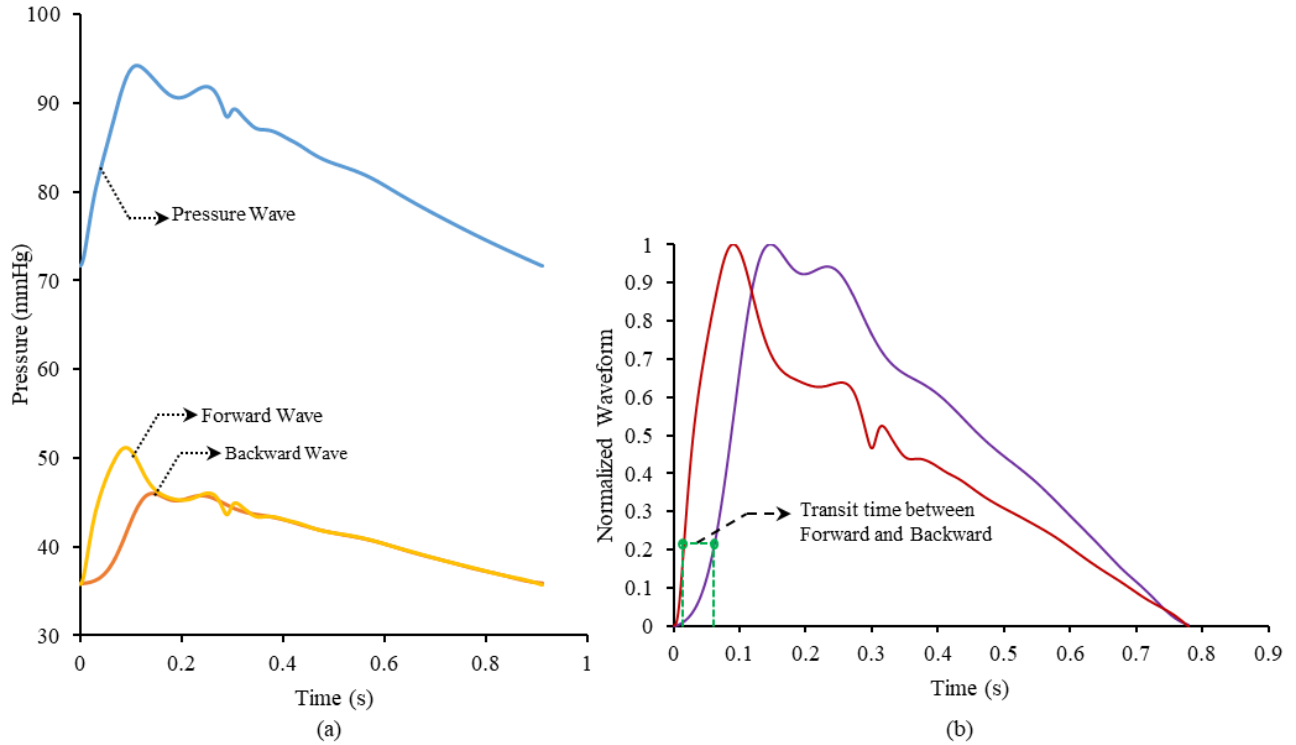


Fig.1. (a). Wave separation using multi-Gaussian approach, (b) Calculation of reflection transit time after normalising the forward and backward waves

(tapering and branching) and arterial stiffens [12] and assumed reflections are due to peripheral resistance alone.

Accounting for the above challenges, we have developed a new modelling approach that relies only on a single pulse waveform and does not require any modelled or measured flow velocity waveform. The model uses multi-Gaussian decomposition to separate forward and backward waves from the parent pulse waveform and estimate the time difference between the normalized signals. This time difference (RTT) has been compared against clinically approved elasticity markers such as E_p , PWV, β , and AC to observe the correlation and statistical significance to act as a potential stiffness surrogate.

II. METHODS

A. Multi-Gaussian Wave Separation Model and Calculation of RTT

The non-linear wave separation model is a sum of N Gaussian curves having amplitude (A_i , $i = 1$ to N), mean positions (M_i , $i = 1$ to N) and standard deviation positions from the respective mean (C_i , $i = 1$ to N). The input to the multi-Gaussian approach model is the pressure cycle without any DC offset, which is a pulse pressure (PP) cycle, $H(t)$, as expressed in (1). The DC offset is the diastolic blood pressure (DBP) value. The non-linear multi-Gaussian model (See (2)) is fit for the pulse pressure cycle.

$$H(t) = P(t) - \text{DBP} \quad (1)$$

$$G(t) = \sum_{i=1}^N A_i e^{-\frac{1}{2} \times \frac{(t-M_i)^2}{C_i^2}} \quad (2)$$

Where, $G(t)$ is the curve fit model as a result of non-linear optimization, with A_i , M_i and C_i being the optimizing parameters. The non-linear optimization is implemented in LabVIEW (National Instruments, USA) using Levenberg-Marquardt (LM) algorithm. The LM method is very robust in finding non-linear least squares problems. For a given input $H(t)$, the optimizing problem is to find the parameters A_i , M_i , C_i of $G(t)$, such that the sum of least squares of the deviations $P(A_i, M_i, C_i)$ is minimized for a given set of k empirical pairs of independent and dependent variables, as shown in (3).

$$\hat{P} \in \operatorname{argmin}_P P(A_i, M_i, C_i) \equiv \operatorname{argmin}_P \sum_{i=1}^k H(t_i) - G(t_i)^2 \quad (3)$$

The N Gaussian curves are then sorted in ascending order, based on mean location value (M_i). The curve with least value

TABLE I STIFFNESS MARKERS

Stiffness Marker	Expression
Elastic Modulus (Peterson) (kPa)	$E_p = \frac{\Delta P}{\Delta D/D}$
Specific Stiffness, β	$\beta = \frac{\ln(\frac{P_s}{P_d})}{\Delta D/D}$
PWV (From Bramwell-Hill Equation) (m/s)	$\text{PWV} = \sqrt{\frac{D_D}{2\rho} \times \frac{\Delta P}{\Delta D}}$
Arterial Compliance (AC) (mm ² /kPa)	$\frac{\pi \times (D_S^2 - D_D^2)}{4\Delta P}$

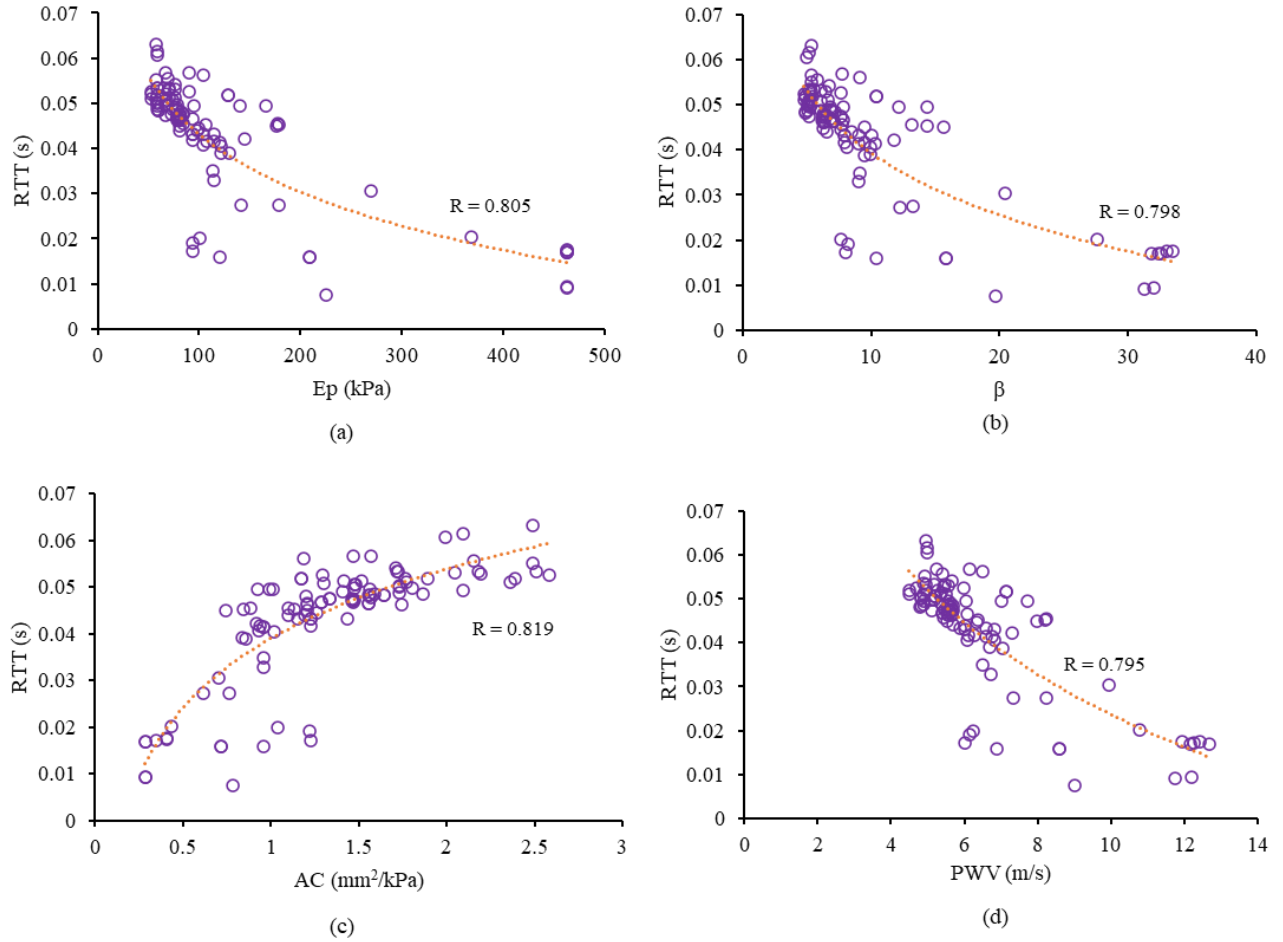


Fig.3. (a) Correlation plot of RTT against Peterson elastic modulus (E_p), (b) Correlation plot of RTT against specific stiffness index (β), (c) correlation plot of RTT against arterial compliance (AC), (d) correlation plot of RTT against pulse wave velocity (PWV).

of M_i is labelled as 1, and the one with the highest value of M_i is the N^{th} curve. Criteria for selecting N depends on limiting maximum error ($|H(t) - G(t)|$), code execution time (Loop Time) and the sum of least square error ($\sum |H(t) - G(t)|^2$). Here, we have considered $N = 8$, $\{|P_P(t) - P_M(K, t)| < 3\%$, Loop Time (Sampling Rate = 1 kHz) $< 1s\}$. The Gaussian curves are now superimposed as per the logic given below in (4) and (5) to separate forward and backward waves.

$$P_B(t) = \frac{1}{2} \times \left(DC_{\text{OFF}} + \sum_{i=m}^N A_i e^{-\frac{1}{2} \times \frac{(t-M_i)^2}{C_i^2}} \right) \quad (4)$$

$$m = 1; \text{ if } SO_{\text{LOC}} \text{ of } P(t) < SBP_{\text{LOC}} \text{ of } P(t)$$

$$m = 2; \text{ if } SO_{\text{LOC}} \text{ of } P(t) > SBP_{\text{LOC}} \text{ of } P(t)$$

Where, SO_{LOC} is the shoulder point of $P(t)$ [13], and SBP_{LOC} is the time location of SBP of $P(t)$. $P_F(t)$ and $P_B(t)$ are forward and backward waves, respectively. DC_{OFF} is the DC offset that was initially removed before applying the multi-Gaussian model. DC Offset is equal to the DBP value of $P(t)$. Finally, the forward wave can be obtained as in (5).

$$P_F(t) = P(t) - P_B(t) \quad (5)$$

Reflection Transit Time (RTT) is measured as the time difference between similar fiducial points on the normalized forward and backward wave as in (6).

$$RTT = t_{\text{forward}} - t_{\text{backward}} \quad (6)$$

B. Virtual Subject Database

Spectral/hp-element framework Nektar++ [14] is used to simulate the virtual subjects database, based on 1D modelling of the arterial tree. The multi-Gaussian modelling approach was verified on this virtual subject's database. The database [15] contains pulse waves representative of a healthy subject (25 – 75 years) whose haemodynamic parameters (age-related trends) are varied to create virtual subjects for in silico evaluation of haemodynamics and pulse wave indices. 30-35 subjects were selected for each Type A, Type B and Type C wave morphology [13] each, with an overall SBP range from 85.81 mmHg to 163.79 mmHg and DBP from 49.79 mmHg to 96.42 mmHg for the age 25 to 75 years. A total of 105 virtual subjects satisfying the above conditions provides a pilot study group to demonstrate the feasibility of the proposed method and, to estimate RTT across a range of BP and pulse morphology conditions.

III. RESULTS AND DISCUSSIONS

A. Subject Demography

Pressure waveform from carotid artery pressure from 105 virtual subjects from age 25 years to 75 years with 95 normotensives (SBP: 90 – 140 mmHg, SBP: 60 – 100 mmHg) and 10 hypertensives (SBP > 140 mmHg and DBP > 100

mmHg) virtual subjects are collected. The mean SBP was 117.47 ± 13.04 mmHg, and the mean DBP was 71.31 ± 6.83 mmHg. The subjects were selected such that a sufficient number of Type A, Type B and Type C waveform morphologies [13] are verified with the modelling approach and respective RTT is measured and compared against clinically validated elasticity indices.

B. Regression Analysis

Regression plots between RTT and clinically relevant elasticity markers (Ep, PWV, AC and β) are shown in Fig.3(a) – (d). A statistically significant and strong correlation ($r > 0.79$, $p < 0.0001$) was obtained between RTT and elasticity markers. There exists an inverse logarithmic trend between RTT and Ep, PWV, and β respectively and a logarithmic trend with AC. The trend is in accordance with the literature [15] and physiologically rational. Out of all the elasticity markers, AC was found to have the highest correlation with RTT ($r = 0.819$), followed by Ep ($r = 0.805$) PWV ($r = 0.798$) and β ($r = 0.795$). The plot of AC is more spread, whereas, for Ep and β , it is more focused on certain regions. The fiducial point to measure RTT was taken as the first derivative maxima point on both the forward and backward waves. First derivative maxima were found to have more correlation with the stiffness markers than other fiducial points (data not shown).

Wave reflections is a cumulative effect of arterial geometry and elasticity. RTT calculated from the reflection wave is having a significant correlation with elasticity markers. Arteries get stiffer as one moves up in their vascular age. This reduces the distensibility of the large arteries like the aorta and carotid in storing the pulsatile energy, which is essential in maintaining constant flow at the micro-circulation level. This inability to store pulsative energy is revealed as an increase in the values of SBP and PP. Having stiffer arteries means pulse waves travel at a high velocity, and the same applies to reflection waves, which appears early. This is manifested as a decrease in RTT for high elasticity markers.

C. Limitations and Future Works

The study has explored a diverse set of virtual subjects to prove the feasibility of separating the waves and estimating RTT as a potential stiffness surrogate. Further exploration is required in using in vivo data to validate the methodology. The underlying principle being wave decomposition; approaches using variants of the Gaussian functions are under development that can further improve the accuracy and computational cost aiding clinical settings where multi-model measurements are practically challenging.

IV. CONCLUSION

In this work, we have successfully demonstrated a proof of measurement principle using a multi-Gaussian modelling approach to decompose a pulse waveform into its forward and backward components without the requirement of any measured or modelled flow velocity waveforms. Using separated waves, we were able to estimate a potential stiffness surrogate. RTT was measured and validated against clinically approved stiffness markers like Ep, PWV, β and AC. A statistically significant and strong correlation was obtained for RTT against all four stiffness markers. This shows the potential of RTT to be used as a surrogate for stiffness

evaluation and proves the novelty in the method in using only a single pulse waveform to arrive at RTT.

REFERENCES

- [1] B. E. Westerhof and N. Westerhof, "Magnitude and return time of the reflected wave: The effects of large artery stiffness and aortic geometry," *J. Hypertens.*, vol. 30, no. 5, pp. 932–939, 2012.
- [2] O. Lichtenstein, M. E. Safar, E. Mathieu, P. Poitevin, and B. I. Levy, "Static and Dynamic Mechanical Properties of the Carotid Artery From Normotensive and Hypertensive Rats," pp. 346–351, 1998.
- [3] T. S. Phan *et al.*, "Aging is Associated With an Earlier Arrival of Reflected Waves Without a Distal Shift in Reflection Sites," *J. Am. Heart Assoc.*, vol. 5, no. 9, 2016.
- [4] R. W. Chang *et al.*, "Determining arterial wave transit time from a single aortic pressure pulse in rats: Vascular impulse response analysis," *Sci. Rep.*, vol. 7, no. January, pp. 1–9, 2017.
- [5] P. Segers *et al.*, "Limitations and pitfalls of non-invasive measurement of arterial pressure wave reflections and pulse wave velocity," *Artery Res.*, vol. 3, no. 2, pp. 79–88, 2009.
- [6] N. Westerhof, P. Sipkema, G. C. V. Den Bos, and G. Elzinga, "Forward and backward waves in the arterial system," *Cardiovasc. Res.*, vol. 6, no. 6, pp. 648–656, 1972.
- [7] K. H. Parker, "An introduction to wave intensity analysis," *Med. Biol. Eng. Comput.*, vol. 47, no. 2, pp. 175–188, 2009.
- [8] A. P. G. Hoeks, J. M. Willigers, and R. S. Reneman, "Effects of assessment and processing techniques on the shape of arterial pressure-distension loops," *J. Vasc. Res.*, vol. 37, no. 6, pp. 494–500, 2000.
- [9] R. Manoj, R. Kiran, P. M. M. Nabeel, J. Joseph, M. Sivaprakasam, and J. J. and M. S. Rahul Manoj, R. Kiran V, Nabeel. PM, "A Bi-modal Probe Integrated with A-mode Ultrasound and Force Sensor for Single-site Assessment of Arterial Pressure-Diameter Loop," in *IEEE International Symposium on Medical Measurements and Applications (MeMeA)*, 2020, pp. 1–6.
- [10] P. M. M. Nabeel *et al.*, "Local Pulse Wave Velocity: Theory, Methods, Advancements, and Clinical Applications," *IEEE Rev. Biomed. Eng.*, vol. PP, no. c, pp. 1–1, 2019.
- [11] B. E. Westerhof, I. Guelen, N. Westerhof, J. M. Karemaker, and A. Avolio, "Quantification of wave reflection in the human aorta from pressure alone: A proof of principle," *Hypertension*, vol. 48, no. 4, pp. 595–601, 2006.
- [12] G. Swamy, N. B. Olivier, and R. Mukkamala, "Calculation of Forward and Backward Arterial Waves by Analysis of Two Pressure Waveforms," *IEEE Trans. Biomed. Eng.*, vol. 57, no. 12, pp. 2833–2839, 2010.
- [13] J. P. Murgu, N. Westerhof, J. P. Giolma, and S. A. Altabelli, "Aortic Input Impedance in Normal Man: Relationship to Pressure Wave Forms," *Circ. J.*, vol. 62, no. 1, pp. 105–116, 1980.
- [14] C. D. Cantwell *et al.*, "Nektar++: An open-source spectral/hp element framework," *Comput. Phys. Commun.*, vol. 192, pp. 205–219, 2015.
- [15] P. H. Charlton, J. Mariscal Harana, S. Vennin, Y. Li, P. Chowienczyk, and J. Alastruey, "Modeling arterial pulse waves in healthy aging: a database for in silico evaluation of haemodynamics and pulse wave indexes," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 317, no. 5, pp. H1062–H1085, 2019.
- [16] E. Hermeling, K. D. Reesink, L. M. Kornmann, R. S. Reneman, and A. P. G. Hoeks, "The dicrotic notch as alternative time-reference point to measure local pulse wave velocity in the carotid artery by means of ultrasonography," *J. Hypertens.*, vol. 27, no. 10, pp. 2028–2035, 2009.