Finite-time simultaneous estimation of aortic blood flow and differentiation order for fractional-order arterial Windkessel model calibration ⋆

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Abstract: A fractional-order vascular model representation for emulating arterial hemodynamics has been recently presented as an alternative to the well-known integer-order arterial Windkessel. The model uses a fractional-order capacitor (FOC) to describe the complex and frequency-dependent arterial compliance. This paper presents a two-stage algorithm based on modulating functions for finite-time simultaneous estimation of the model's input and the fractional differentiation order. The proposed approach is validated using in-silico human data. Results show the prominent potential of this method for calibrating arterial models and enhancing cardiovascular mechanics research as well as clinical practice.

Keywords: Joint-estimation, Modulating functions, Windkessel model, Fractional derivative

1. INTRODUCTION

Generally, arterial models vary from being very simple but physically less interpretable to very complex but accurate. Arterial models can be divided into two main categories. The macro-scale-based models' class consists of low-dimensional modeling approaches. Macro models include zero-dimensional models (0-D) or lumped parametric models. They are very simple with small computational cost; however, they are weak in terms of physical interpretability, Bahloul and Laleg-Kirati (2020). Regarding the cardiovascular characterization, these models are usually applied to represent the hemodynamic determinants of the global arterial system. The most well-known lumped arterial parameter model is the arterial Windkessel, Frank (1899), which includes mono-compartment models and multi-compartment models, Malatos et al. (2016); Shi et al. (2011). Mathematically, macro models are usually based on ordinary differential equations (ODEs), and they represent the hemodynamic as a function of time only. The second class is the micro-scale-based models that can yield more accurate physical descriptions of the regional arterial system determinants compared to macro-scale one. These models are generally explored to represent the complex hemodynamic phenomenon of a particular region in the cardiovascular system. Typically, this category consists of high-dimensional modeling frameworks that include one-dimensional (1D), two-dimensional (2D), and three-dimensional (3D) models. To establish micro modeling of the entire arterial tree, complex geometrical and mechanical knowledge must be produced, resulting in huge computational complexity. Hence, it cannot be promptly executed in practice. Mathematically, macro models are based on partial differential equations (PDEs), and they represent the hemodynamic as a function of time and space, Ruan et al. (2018).

Commonly, the typical practical scenario is to have a class of models with interpretable parameters and manageable complexity. In the last three decades, fractional-order (non-integer) derivative has played a notable role in multiple fields, mainly modeling biological systems. Fractional-order models extend the concepts of differentiability and incorporate non-local and system memory effects through fractional-order space and time derivatives. These properties enable us to model aspects over various time and space scales without breaking the problem into smaller and smaller compartments. The most common modeling/simulation paradigm that can involve the above features is the so-called mesoscale-based model. The meso-scale-based model is more complicated than the macro-based model, but its complexity is still manageable. They are based on mathematical description forms with non-locality properties. Therefore, using fractional-order derivative tools, the parameters of the mesoscale based-model are usually physically interpretable. Mesoscale models are considered as key elements in multiscale characterization. The versatility and flexibility of fractional-order tools generated a belief that the future of

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computational modeling in bioengineering will undergo a paradigm shift in favor of mesoscale-based-model, Bahloul and Kirati (2021).

Regarding cardiovascular system modeling, the power-law behavior has been proved in the viscoelasticity characterization of an elastic aorta. The *in-vivo* and *in-vitro* experiment have shown that fractional-order calculus tools are more convenient to precisely represent the arterial dynamics; the viscoelasticity properties of the collagenous tissues in the arterial bed; the arterial blood flow, Perdikaris and Karniadakis (2014); Bahloul and Kirati (2019); red blood cell membrane mechanics, Craiem and Magin (2010) and the heart valve cusp, Doehring et al. (2005). Recently, we extended fractional-order derivative tools to the well-known arterial Windkessel paradigm by substituting the ideal capacitor, which accounts for the total arterial compliance, with a fractional-order capacitor. Our preliminary investigation confirmed that the fractional-order impedance is the right candidate for the accurate assessment of the aortic input impedance. Moreover, a strong correlation between the main hemodynamic determinants and the fractional differentiation order (α) has been proved, Bahloul and Laleg-Kirati (2020, 2018). The fractional order is used to describe the transition between viscosity and elasticity more accurately.

In order to calibrate fractional-order models, several estimation-based methods have been proposed in the literature. These methods can be classified into two categories: asymptotic such as observer-based methods, and non-asymptotic such as algebraic methods Belkhatir et al. (2018). Although asymptotic techniques are very reliable, they are computationally expensive and often depend on the initialization condition. In addition, in some cases, they are not robust against noise. However, non-asymptotic methods are generally efficient with manageable computation's complexity. Besides, they allow the joint and finite estimation of parameters and unknown input. In Bahloul and Kirati (2020), the authors proposed a finite-time estimation algorithm based on the so-called modulating functions (MFs) to jointly estimate the blood flow in a specific site of the arterial network, which regarded as the input of the model, and the two-element Windkessel model's parameters. In this paper, we enlarge our approach to the fractional-order two-element Windkessel model. The proposed algorithm consists of two stages to simultaneously estimate the fractional differentiation order and the input blood flow. The rest of the paper is organized as follows. Section 2 presents some preliminary results on the mathematical formulation of the fractional-order arterial Windkessel representation and the modulating functions. The two-stage-based modulating functions algorithm for the joint estimation of the input (arterial blood flow) and parameters is proposed in Section 3. Some numerical examples that illustrate the performance of the proposed algorithm are provided in Section 4 and a discussion of the results. Finally, the conclusion and future work are given in section 5.

2. PRELIMINARIES

2.1 Fractional Derivative

***Definition 1**, Lorenzo and Hartley (2008):* The initialized Rimeann-Liouville (R-L) fractional derivative is defined as:

$$D_t^\alpha f(t) = d_t^\alpha f(t) + \psi(f_i, -p, -t_0, 0, t), \quad t > 0, \tag{1}$$

where $\alpha = n - p$ with $n \in \mathbf{R}$ and $p, \alpha \in \mathbf{R}_+^*$. The terms $d_t^\alpha f(t)$ are the uninitialized α-th order Riemann-Liouville derivative and ψ is the initialization function given as follows:

$$\begin{cases} d_t^\alpha f(t) = \dfrac{d^n}{dt^n} \dfrac{1}{\Gamma(p)} \int_0^t (t-\tau)^{p-1} f(\tau) d\tau, \\ \psi(f_i, -p, -t_0, 0, t) = \dfrac{d^n}{dt^n} \dfrac{1}{\Gamma(p)} \int_{-t_0}^0 (t-\tau)^{p-1} f_i(\tau) d\tau, \end{cases} \tag{2}$$

where $\Gamma(.)$ is the gamma function and $f_i(t)$ is the initialization function defined for $t \in [-t_0, 0], t_0 \in \mathbf{R}_+$. This definition assumes that the history-function for $t \in (-\infty, -t_0)$ is zero.

2.2 Fractional-order arterial Windkessel

The concept of Windkessel representation was borrowed from electrical circuit analogy, where the electrical voltage corresponds to the arterial blood pressure, and the current corresponds to the blood flow through the arteries. Besides, the electrical resistor and capacitor represent vascular resistance and compliance, respectively. Fractional-order arterial Windkessel is similar to the standard Windkessel representation; however, instead of using an ideal capacitor, we employed a fractional-order capacitor (FOC) to represent the arterial compliance. FOC, which generalizes capacitors and resistors, displays a fractional-order behavior that can capture both elastic and viscous properties through a power-law formulation. The fractional differentiation order is employed to describe the transition between viscosity and elasticity more accurately. In the following, we represent the formulation of the fractional two-element Windkessel:

Based on the conservation mass, the arterial blood flow pumped from the heart to the arterial vascular bed (q_{in}) can be expressed as:

$$q_{in}(t) = q_{stored}(t) + q_{out}(t), \tag{3}$$

where q_{stored} is the blood stored in the arterial tree, and q_{out} corresponds to the flow out of the arterial system, which can be expressed as follows:

$$q_{out}(t) = \frac{1}{R_p} p_a(t). \tag{4}$$

where, R_P represent the peripheral vascular resistance and p_a corresponds to the aortic pressure. Regarding q_{stored}, typically using the conventional definition, it can be determined as the rate of flow by taking the first derivative of the volume equation for the time, whereas, in consideration of the fractional properties of both RBC and the collagenous tissues forming the arterial bed, we allow the differentiation order of the blood volume for time to be real ($\alpha \in [0\ 1]$) and hence applying the fractional-order derivative to this differential equation.

$$q_{stored}(t) = D_t^\alpha V(t) = \frac{d^\alpha V(t)}{dt^\alpha}, \tag{5}$$

$$q_{stored}(t) = \underbrace{\frac{d^{\alpha}V(t)}{d^{\alpha}p_a(t)}}_{C_\alpha} \frac{d^{\alpha}p_a(t)}{dt^{\alpha}}, \quad (6)$$

where C_α is a fractional order proportionality constant that can be defined as a fractional order compliance expressed in the unit of $[\text{l/mmHg} \cdot \text{sec}^{1-\alpha}]$. Substituting (4) and (6) into (3) yield:

$$q_{in}(t) = C_\alpha \frac{d^{\alpha}p_a(t)}{dt^{\alpha}} + \frac{1}{R_p} p_a(t). \quad (7)$$

Equation (7) can be written as:

$$y(t) + \tau D_t^{\alpha} y(t) = u(t), \quad (8)$$

where $u(t) = R_p q_{in}(t)$, $y(t) = p_a(t)$, and $\tau = R_p C_\alpha$.

2.3 Modulating functions (MFs)

Definition 2: Let $\phi(t)$ be a function defined in the interval $[0, T]$. $\phi(t)$ is an MF of order n if it satisfies the following properties:

(P1) $\phi(t) \in C^n([0, T])$, where $C^n([0, T])$ denotes the space of n times differentiable functions over $[0, T]$.

(P2) $\phi^{(i)}(0) = \phi^{(i)}(T) = 0, i = 0, 1, ..., n-1$,

(P3) $D_t^{\alpha}\phi(t)$ exists, $\forall\ 0 \le \alpha \le n$,

(P4) $D_t^{\alpha}\phi(t)|_{t=0} = 0, \forall\ 0 \le \alpha \le n$.

In the following, we recall an important property, an integration by parts-like formula for initialized RL fractional derivative, that relates a MF with its fractional derivative of order α when integrated against a given function.

Lemma 2 , Belkhatir et al. (2018): Consider a function $f(t)$ and let $\phi(t)$ be a MF of order n, with $n \in \mathbf{N}^*$. Assume that the α-th initialized RL fractional derivative of $f(t)$, with $\alpha \in \mathbf{R}_+^*$, exists. Let the initialization function be a constant $f_0(t) = c_0$, defined for $t \in [-t_0, 0], t_0 \in \mathrm{R}_+$. Then, the following expression holds:

$$\begin{aligned} &\int_0^T D_t^{\alpha} f(t)\phi(T-t)dt = \int_0^T f(T-t) D_t^{\alpha}\phi(t)dt \\ &+ \frac{c_0}{\Gamma(1-\alpha)} \int_0^T \phi(T-t)(t+t_0)^{-\alpha}dt - c_0 D_t^{\alpha-1}\phi(T). \end{aligned} \quad (9)$$

3. MATERIALS & METHOD

3.1 Two-stage based Modulating functions algorithm

MF based-estimation is a non-asymptotic method that has been successfully used in parameters' identification for both integer order systems, Co and Ydstie (1990); Balestrino et al. (2000); Guo et al. (2014) and fractional order systems Liu et al. (2013); Wei et al. (2019). The basic idea of this method is to transform the estimation problem for an integer/fractional order differential equation into an algebraic problem of finding the solution of a set of equations. Thanks to its properties, the MF-based estimation approach is very fast and easy to implement. In addition, by dint of the integration by part criteria (*Lemma 2*) along with modulating function properties (P2-P4) in the *Definition 2*, the MF based method is considered robust against corrupting noises. In order to estimate the fractional differentiation order simultaneously with the input, a two-stages algorithm has been proposed by Belkhatir et al. (2018). The proposed algorithm combines the modulating functions method and the first-order Newton methods. Functionally, the two-stage algorithm is an iterative technique that consists of two steps. The first step solves the estimation problem of the input based on the MF technique at each iteration. The main logic of this step is to project the input into an appropriate set of basis functions. Considering the coefficient of the projection as unknown parameters that will be will be simultaneous with the vector of fractional differentiation orders. The second step solves a nonlinear system of equations using Newton's method to estimate the fractional differentiation orders.

Considering the following linear continuous-time non-commensurate fractional-order system:

$$y(t) + \sum_{i=1}^{N} a_i D_t^{\alpha_i} y(t) = u(t),\ t \in [0, T], \quad (10)$$

where $y(t) \in \mathbf{R}$ is the output, $u(t) \in \mathbf{R}$ is the input, $a_i \in \mathbf{R}$, for $i = 1, 2 \ldots, N$, are the parameters and $\alpha_i \in \wp = (n_{i-1}, n_i)$, with $n_i \in \mathbf{N}^*$ and $i = 1, 2, \ldots, N$ are the unknown fractional differentiation orders. They are assumed to be as follows: $0 < \alpha_1 < \alpha_2 < \cdots < \alpha_n$, i.e., $n_i < n_{i+1}$ for $i = 1, 2, \ldots, N-1$. We denote the vectors θ and α as: $\theta = (a_1\ a_2\ \ldots a_N)^{tr}$, $\alpha = (\alpha_1\ \alpha_2\ \ldots \alpha_N)^{tr}$ and its estimate as $\hat{\alpha} = (\hat{\alpha}_1\ \hat{\alpha}_2\ \ldots \hat{\alpha}_N)^{tr}$. $(\cdot)^{tr}$ denotes the transpose of the row vector. Considering the above fractional-order system (10), the estimation problem can be formulated as:

EP: *Given the output signal* $y(t)$ *for* $t \in [0, T]$ *and knowing the value of the vector* θ*, jointly find estimates* $(\widehat{u(t)}, \hat{\alpha})$ *for the unknowns: input signal* $(u(t))$ *and vector of fractional orders* (α)*.*

As the main concept of the MF based method is to write the fractional differential equation as a set of algebraic integral equations. Accordingly, to estimate the (input-parameters) simultaneously with the fractional differentiation orders, we need to decompose the input signal $u(t)$ in the space spanned by a set of known basis functions $\{\beta_i(t)\}_{i=1}^{V}$, as follow:

$$u(t) = \sum_{j=1}^{V} \xi_j \beta_j(t), \quad (11)$$

Expression (10) is rewritten as:

$$y(t) + \sum_{i=1}^{N} a_i D_t^{\alpha_i} y(t) = \sum_{j=1}^{V} \xi_j \beta_j(t),\ t \in [0, T], \quad (12)$$

where $\{\xi_j\}_{j=1}^{V}$, $V \in \mathbb{N}^*$, will be considered the unknown projection parameters that will be estimated jointly with the parameters, θ. Based on this projection, the estimation problem can be formulated as follows:

EP*: *Given the output signal* $y(t)$ *for* $t \in [0, T]$ *and knowing the value of the vector* θ*, jointly find estimates* $(\{\hat{\xi}_j(t)\}_{j=1}^{V}, \hat{\alpha})$ *for the unknown projection weights* $(\xi_j(t)\}_{j=1}^{V})$ *and vector of fractional orders* (α)*.* In what follows, the different steps within each stage of the proposed algorithm are presented to solve EP^*, and hence EP:

First stage: The main objective of this stage is to estimate the input via its projection weights (12), for a given fractional differentiation order of the output. Let's suppose that the fractional-order derivative of the output $y(t)$ is initialized with a constant initialization function $f_0(t) = c_0, t \in [-t_0, 0], t_0 > 0$. Multiply (12) by $\{\phi_m(t)\}_{m=1}^{M}$ (a set of linearly independent MFs) and integrate over a period $[0, T]$:

$$\int_0^T \phi_m(T-t)y(t)dt + \sum_{i=1}^{N} a_i \int_0^T \phi_m(T-t)D_t^{\alpha_i}y(t)dt = \sum_{j=1}^{V} \xi_j \int_0^T \phi_m(T-t)\beta_j(t)dt. \tag{13}$$

By applying *Lemma 2*, to the second integral of (13), we obtain:

$$\sum_{j=1}^{V} \xi_i A_{mj} = b_m(\alpha), \qquad m = 1 \,, .., M, \tag{14}$$

where

$$\begin{cases} A_{mj} = \int_0^T \phi_m(T-t)\beta_j(t)dt \\ b_m(\alpha) = \int_0^T \phi_m(T-t)y(t)dt + \sum_{i=1}^{N} a_i \tilde{A}_{mi}(\alpha) \end{cases} \tag{15}$$

where $\tilde{A}_{mi}(\alpha)$ is given by

$$\tilde{A}_{mi}(\alpha) = \int_0^T D_t^{\alpha_i}\phi_m(t)y(T-t)dt - c_0 D_T^{\alpha_i - 1}\phi(T) + \frac{c_0}{\Gamma(1-\alpha)} \int_0^T \phi_m(T-t)(t+t_0)^{-\alpha_i}dt, \tag{16}$$

For a given fractional differentiation order $(\hat{\alpha}^k)$, the finite estimate of the parameters and the projection weights of the input, $\hat{\xi} = (\hat{\xi}_1 \; \hat{\xi}_2 \ldots \; \hat{\xi}_V)^T$ can be found by solving the following linear system:

$$A\hat{\xi} = b(\hat{\alpha}^k) \tag{17}$$

Second stage: In order to estimate the fractional differentiation order an iterative computation method based on the *Newton update law* is adopted as follow:

An estimate α^k of the vector of fractional differentiation orders is computed iteratively using the following Newton update law:

$$\hat{\alpha}^{k+1} = \hat{\alpha}^k - \gamma[L'(\hat{\alpha}^k)]^{-1}J(\hat{\alpha}^k), \tag{18}$$

where γ is a regularization parameter, $\gamma \in (0, 1]$. $J(\hat{\alpha}^k) \in \mathbb{R}^N$ is given by

$$J(\hat{\alpha}^k) = L(\hat{\alpha}^k) - R = 0, \tag{19}$$

with $L(\hat{\alpha}^k) \in \mathbb{R}^N$, $R \in \mathbb{R}^N$ and for $j = 1, \ldots, N$

$$\begin{cases} L_j(\hat{\alpha}^k) = \sum_{i=1}^{V} \hat{\xi}_i \int_0^T \phi_{M+j}(T-t)\beta_i(t)dt \\ \qquad - \sum_{i=1}^{N} a_i(\hat{\alpha}^k)\tilde{A}_{ji}(\hat{\alpha}^k) \\ R_j = \int_0^T \phi_{M+j}(T-t)y(t)dt \end{cases} \tag{20}$$

The matrix $L'(\hat{\alpha}^k) \in \mathbb{R}^{N\times N}$ corresponds to the *Jacobian* matrix of $L(\hat{\alpha}^k)$ given as follow:

$$\begin{pmatrix} \frac{\partial L_1}{\partial \alpha_1}(\hat{\alpha}^k) & \frac{\partial L_1}{\partial \alpha_2}(\hat{\alpha}^k) & \cdots & \frac{\partial L_1}{\partial \alpha_N}(\hat{\alpha}^k) \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial L_N}{\partial \alpha_1}(\hat{\alpha}^k) & \frac{\partial L_N}{\partial \alpha_2}(\hat{\alpha}^k) & \cdots & \frac{\partial L_N}{\partial \alpha_N}(\hat{\alpha}^k) \end{pmatrix} \tag{21}$$

The system of equations (17) is solved in two stages using $\bar{M} = M + N$ linearly independent MFs. While in the first stage we use $M \geq N$ MFs to estimate the the projection weights of the input and their gradients with respect to α_j, in the second stage we use the remaining N MFs to estimate the fractional differentiation orders. At this stage we consider the reset of $MFs\{\phi_m(t)\}_{m=M+1}^{M+N}$. Then, from (17) and the solution of **stage 1** we have

$$L(\alpha) := A\xi(\alpha) = b(\alpha), \tag{22}$$

The components of the vector $L(\alpha)$ are given as follows, for $j = 1, 2, \ldots, N$

$$L_j(\alpha) = \sum_{i=1}^{N} \hat{a}_i(\alpha)\tilde{A}_{ji}(\alpha) \tag{23}$$

The iterative first-order Newton method is used to solve (22), with a solution at iteration k denoted $\hat{\alpha}^k$. The Newton update law is given in (18). At each iteration, (19) and (20) follow directly from (22) and (23).

Characterization of the Jacobian matrix Thanks to the MFs, we can exactly characterize the entries of the Jacobian matrix as given in the following lemma. Such explicit characterization reduces significantly the computational burden.

Lemma 3: The entries of the Jacobian matrix are analytically characterized as follows; for $\bar{i} = 1, \ldots, N, j = 1, \ldots, N$,

$$L'_{j\bar{i}} := \frac{\partial L_j}{\partial \alpha_{\bar{i}}}(\alpha) = \sum_{i=1}^{V} \frac{\partial \xi_i}{\partial \alpha_{\bar{i}}} \int_0^T \phi_{M+j}(T-t)\beta_i(t)dt - a_{\bar{i}} \frac{\partial A_{j\bar{i}}(\alpha)}{\partial \alpha_{\bar{i}}} \tag{24}$$

with $\frac{\partial A_{j\bar{i}}(\alpha)}{\partial \alpha_{\bar{i}}} := \frac{\partial A_{(M+j)\bar{i}}(\alpha)}{\partial \alpha_{\bar{i}}}$ is given by (25) and $\frac{\partial D^{\alpha_{\bar{i}}}\phi_m(t)}{\partial \alpha_{\bar{i}}}$ is computed using *Lemma 1*. The terms $\frac{\partial \xi_i}{\partial \alpha_{\bar{i}}}$ are estimated by solving the following linear system of equations:

$$A\hat{\xi}_d^j = b^j(\alpha) \tag{26}$$

where, for $j = 1, \ldots, N$, $i = 1, \ldots, V$, $m = 1, \ldots, M$,

$$\begin{cases} A_{mi} \text{ is given by (15)} \\ b^j = -a_j \frac{\partial \tilde{A}_{mj}(\alpha)}{\partial \alpha_j} \\ \left(\xi_d^j\right)_i = \frac{\partial \hat{\xi}(\alpha)}{\partial \alpha_j} \end{cases} \tag{27}$$

where $\frac{\partial A_{j\bar{i}}(\alpha)}{\partial \alpha_{\bar{i}}}$ is given by (25) and $\left(x_d^j\right)_i$ denotes the ith element of ξ_d^J.

3.2 Materials

The two-stage algorithm has been tested using in-silico data set that has been generated from a validated one-dimensional numerical model of the arterial network, by Willemet et al. (2015). This database consists of hemodynamic signals (e.g. pressure, flow and distension waveforms) at all arterial locations. It presents arterial hemodynamic of virtual healthy adult subjects in which the cardiac and arterial parameters vary within physiological ranges. This in-silico data set is able to mimic the major hemodynamic properties sensed *in-vivo*. For this study, we selected 3 virtual subjects with different arterial characteristics, as shown in table 1. The explored hemodynamic signals are measured at the level of the ascending aorta. To implement the fractional-order derivative of the output blood pressure signal, we assume that the initialization function $f_0(t) = 0$ for all $t \in (-\inf, 0]$ and we used the following *Grünwald–Letnikov* (GL) formula:

$$D_t^{\alpha} f(t) = \lim_{h\to 0} h^{-\alpha} \sum_{j=0}^{[\frac{t}{h}]} (-1)^j \binom{\alpha}{j} f(t-jh), \tag{28}$$

$$\frac{\partial A_{m\bar{i}}(\alpha)}{\partial \alpha_{\bar{i}}} = \int_0^T \frac{\partial D^{\alpha_{\bar{i}}}\phi_m(t)}{\partial\alpha_{\bar{i}}} y(T-t)dt - c_0 \frac{\partial D^{\alpha_{\bar{i}}-1}\phi_m(T)}{\partial \alpha_{\bar{i}}} + \frac{c_0}{\Gamma(1-\alpha_{\bar{i}})}\left[\Psi_0(1-\alpha_{\bar{i}})\int_0^T \phi_m(T-t)(t+t_0)^{\alpha_{\bar{i}}}dt - \alpha_{\bar{i}}\int_0^T \phi_m(T-t)(t+t_0)^{-1-\alpha_{\bar{i}}}dt\right] \quad (25)$$

where $h > 0$ is the time step, $\binom{\alpha}{j} = \frac{\Gamma(\alpha+1)}{\Gamma(j+1)\Gamma(\alpha-j+1)}$ and [.] means the integer part. For MF we have used the following polynomial modulating function

$$\phi_m(t) = t^{M+q+1-m}(T-t)^{q+m}, \quad (29)$$

where $m = 1, 2, 3, ..., M$, and M is the total number of MFs, q is an integer parameter. In this work, we choose a set of sinusoidal basis to decompose the input signal corresponding to the blood flow:

$$\beta_i(t) = \sin\frac{i\pi t}{T}, \quad (30)$$

where T is the upper limit of the interval where the modulating function is defined. To evaluate the proposed algorithm, we use relative error, $R.E$, as metric:

$$R.E.[\%] = \frac{||u-\hat{u}||_2}{||u||_2} \times 100\%. \quad (31)$$

4. RESULTS & DISCUSSION

Table 2 presents the parameters and metrics used in the proposed two-stage algorithm to simultaneously estimate the aortic blood flow and fractional parameter (α), which corresponds to the input and differentiation order of FOS (8), respectively. In addition, we present the relative error evaluated between the exact input and the estimated one and the estimate of the fractional differentiation order for three different subjects. The studied subjects have different stroke volumes (SV) ranging from 66.90 *ml* to 99.60 *ml*. The proposed algorithm has been tested in both noise-free and noisy cases. In the noise corrupted case, white Gaussian random noise with zero mean has been added to the input signal (10% of the original signal). Fig. 1 shows the reconstruction results of the input aortic blood flow in the absence of noise using a sinusoidal basis. It also presents the absolute value of the error between the exact input waveform and the estimated one. For all the subjects, only 10 projection weights were needed. For the *Subject 1* and *Subject 2* 12 modulating functions have been used and 100 iteration to jointly estimate the input and the fractional-differentiation order. For *Subject 3* 10 MFs and only 64 iterations were enough to achieve a minimum relative error ($R.E$). *Subject 3* presents the best performance based on the evaluation of $R.E$, which is equal to 9.94% in the noise-free case and around 11.31% in the noisy case. For the other subjects, $R.E$ is less than 13.5% in all cases. The $R.E$ is slightly bigger in the noisy cases than the noise-free ones. Comparing to the results presented in Bahloul and Kirati (2020), the two-stage algorithm applied to the fractional-order Windkessel model enhanced the reconstruction performance of the aortic blood flow, especially in the noisy case. Overall, the presented algorithm showed satisfactory robustness against noise. The estimate of fractional differentiation orders are 0.98, 0.96 and 1.01 for *Subject 1*, *Subject 2* and *Subject 3* respectively. It is worth noting that during the experiments, we noticed that the algorithm depends on a good guess of the unknown fractional differentiation order, which leads to numerical instabilities. To avoid this issue, we included a regularization parameter γ, known as *learning rate* in Machine Learning context. The γ parameter belongs to the interval $(0, 1]$, and it is used in the updating rule described by (18). Based on the above results and the extensive numerical investigations that we have conducted, it is worth noting the following observations:1) The total number and type of modulating functions influence the two-algorithm performance. In fact, in the noise-free case, we noticed a minimal number of MFs is required to get the best performance. Increasing the number of MFs does not lead to better performance and might increase the error. However, in the noisy case, increasing MFs enhances the estimation results. 2) The choice of the projection basis and the number of functions affect the algorithm's performance. We think this choice depends on the prior knowledge of some properties of the estimated input, such as smoothness and periodicity. In this study, we observe the oscillatory behavior within the blood flow waveform; hence we choose a set of sinusoidal bases to decompose the input signal.3) Some numerical issues have been encountered in solving the linear problem using least square methods for a specific number of modulating functions and projection weights. This observation can be explained by the fact that the condition number of the matrix inverse depends on the nature and number of modulating functions and the real data, which may cause scarcity and numerical issues.

Table 1. Hemodynamic determinants of 3 virtual subjects. T_c denotes the cardiac period, SV corresponds to the stroke volume, SP, DP are the systolic and diastolic blood pressure and τ is the time constant.

Subject \ Parameter	T_c [sec]	SV [ml]	SP [mmHg]	DP [mmHg]	τ
Subject 1	0.83	66.40	98.04	67.22	1.26
Subject 2	0.83	83.00	105.07	78.52	1.53
Subject 3	0.95	99.60	103.93	69.25	1.38

5. CONCLUSION

The estimation of the aortic blood flow and the hemodynamic determinants is of great importance in diagnosing and treating the cardiovascular system. This paper investigated the use of a hybrid approach that combines the modulating functions' algebraic method and the first-order iterative Newton's technique to estimate the aortic blood flow and jointly calibrating the fractional-order Windkessel model. The validation result using in-silico dataset for human adult shows a good reconstructing performance of the aortic blood flow and provide an acceptable estimate

Table 2. Metrics used in the two-stage algorithm to estimate the blood flow signal and fractional differentiation order estimate, $\hat{\alpha}$.

	Subject 1		Subject 2		Subject 3	
Metrics						
Noise	0%	10%	0%	10%	0%	10%
Iterations	100		101		64	
M	12		12		10	
V	10		10		10	
γ	0.3		0.2		0.1	
R.E. [%]	11.77	13.51	11.19	12.69	9.94	11.31
Fractional differentiation order estimate						
$\hat{\alpha}$	0.98	0.98	0.96	0.96	1.01	1.01

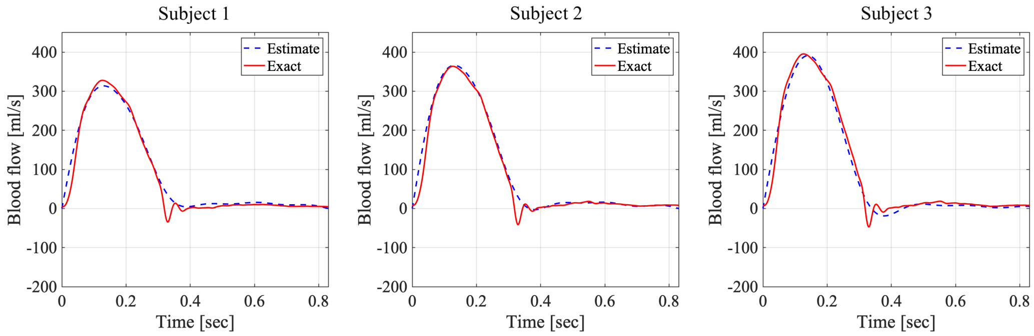

Fig. 1. Estimated aortic blood flow in noise-free for three different subjects using sinusoidal basis.

of the fractional-differentiation order. The algorithm has been tested in the noisy case and presented satisfying robustness against noise. The extensive conducted numerical simulations showed the sensitivity of the proposed method to the choice of the total number of modulating functions and projection weights of the basis used to estimate the input. In addition, the choice of the initial value of the fractional differentiation order is very critical and affects the convergence and accuracy of the estimation. In the future further investigations should be conducted to resolve any numerical issues and refine the tuning of the methods metrics. Additionally, we plan to validate the proposed algorithm using real human hemodynamic data with different physiological conditions. This phase should be directed closely with specialists in the cardiology field to explain and better analyze the obtained results.

REFERENCES

Bahloul, M.A. and Kirati, T.M.L. (2019). Two-element fractional-order windkessel model to assess the arterial input impedance. In *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, 5018–5023. IEEE.

Bahloul, M.A. and Kirati, T.M.L. (2020). Finite-time joint estimation of the arterial blood flow and the arterial windkessel parameters using modulating functions. *IFAC-PapersOnLine*, 53(2), 16286–16292.

Bahloul, M.A. and Kirati, T.M.L. (2021). Fractional-order model representations of apparent vascular compliance as an alternative in the analysis of arterial stiffness: an in-silico study. *Physiological Measurement*, 42(4), 045008.

Bahloul, M.A. and Laleg-Kirati, T.M. (2018). Arterial viscoelastic model using lumped parameter circuit with fractional-order capacitor. In *2018 IEEE 61st International Midwest Symposium on Circuits and Systems (MWSCAS)*, 53–56. IEEE.

Bahloul, M.A. and Laleg-Kirati, T.M. (2020). Assessment of fractional-order arterial windkessel as a model of aortic input impedance. *IEEE Open Journal of Engineering in Medicine and Biology*, 1, 123–132.

Balestrino, A., Landi, A., and Sani, L. (2000). Parameter identification of continuous systems with multiple-input time delays via modulating functions. *IEE Proceedings-Control Theory and Applications*, 147(1), 19–27.

Belkhatir, Z., N'Doye, I., and Laleg-Kirati, T.M. (2018). Estimation methods for fractional-order systems: Asymptotic versus nonasymptotic approaches. In *Fractional Order Systems*, 451–475. Elsevier.

Co, T. and Ydstie, B. (1990). System identification using modulating functions and fast fourier transforms. *Computers & chemical engineering*, 14(10), 1051–1066.

Craiem, D. and Magin, R.L. (2010). Fractional order models of viscoelasticity as an alternative in the analysis of red blood cell (rbc) membrane mechanics. *Physical biology*, 7(1), 013001.

Doehring, T.C., Freed, A.D., Carew, E.O., and Vesely, I. (2005). Fractional order viscoelasticity of the aortic valve cusp: an alternative to quasilinear viscoelasticity. *Journal of biomechanical engineering*, 127(4), 700–708.

Frank, O. (1899). Die grundform des arteriellen pulses. z. biol. 37: 483-526. *English translation by Sagawa Ketal (1990) J Mol Cell Cardiol*, 22, 253–277.

Guo, Q., Perruquetti, W., and Gautier, M. (2014). Online robot dynamic identification based on power model, modulating functions and causal jacobi estimator. In *2014 IEEE/ASME International Conference on Advanced Intelligent Mechatronics*, 494–499. IEEE.

Liu, D.Y., Laleg-Kirati, T.M., Gibaru, O., and Perruquetti, W. (2013). Identification of fractional order systems using modulating functions method. In *2013 American Control Conference*, 1679–1684. IEEE.

Lorenzo, C.F. and Hartley, T.T. (2008). Initialization of fractional-order operators and fractional differential equations. *Journal of computational and nonlinear dynamics*, 3(2).

Malatos, S., Raptis, A., and Xenos, M. (2016). Advances in low-dimensional mathematical modeling of the human cardiovascular system. *J Hypertens Manag*, 2(2), 1–10.

Perdikaris, P. and Karniadakis, G.E. (2014). Fractional-order viscoelasticity in one-dimensional blood flow models. *Annals of biomedical engineering*, 42(5), 1012–1023.

Ruan, Y., Guo, Y., Zheng, Y., Huang, Z., Sun, S., Kowal, P., Shi, Y., and Wu, F. (2018). Cardiovascular disease (cvd) and associated risk factors among older adults in six low-and middle-income countries: results from sage wave 1. *BMC public health*, 18(1), 778.

Shi, Y., Lawford, P., and Hose, R. (2011). Review of zero-d and 1-d models of blood flow in the cardiovascular system. *Biomedical engineering online*, 10(1), 33.

Wei, Y.Q., Liu, D.Y., and Boutat, D. (2019). Innovative fractional derivative estimation of the pseudo-state for a class of fractional order linear systems. *Automatica*, 99, 157–166.

Willemet, M., Chowienczyk, P., and Alastruey, J. (2015). A database of virtual healthy subjects to assess the accuracy of foot-to-foot pulse wave velocities for estimation of aortic stiffness. *American Journal of Physiology-Heart and Circulatory Physiology*, 309(4), H663–H675.