FRACTIONAL CALCULUS APPLIED TO MODEL ARTERIAL VISCOELASTICITY

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***Abstract*— Arterial viscoelasticity can be described using stress-relaxation experiments. To fit these curves, models with springs and dashpots, based on differential equations, were widely studied. However, uniaxial tests in arteries show particular shapes with an initial steep decay and a slow asymptotic relaxation. Recently, fractional order derivatives were used to conceive a new component called *spring-pot* that interpolates between pure elastic and viscous behaviors. In this work we modified a standard linear solid model replacing a dashpot with a *spring-pot* of order α. We tested the fractional model in human arterial segments. Results showed an accurate relaxation response during 1-hour with least squares errors below 1%. Fractional orders α were 0.2-0.4, justifying the extra parameter. Moreover, the adapted parameters allowed us to predict frequency responses that were similar to reported Complex Elastic Moduli in arteries. Our results indicate that fractional models should be considered as real alternatives to model arterial viscoelasticity.**

***Keywords* — Viscoelasticy, Stress-relaxation, Human arteries, Standard-linear solid, Fractional calculus.**

I. INTRODUCTION

Arteries, like other soft tissues exhibit viscoelastic behavior. In this context, the mechanical energy transferred to them is partly stored in a reversible form (elasticity) while other fraction is dissipated (viscosity). Getting insight into viscoelastic properties of arteries can help to identify their biomechanical structure and function, to study the progression and reversion pathologies that might affect them and even to predict their natural deterioration with age and the influence of cardiovascular circulation (Armentano *et al*., 2006; Fung, 1981).

Uniaxial stress-relaxation test can be used to study arterial wall mechanics. Arterial segments are stretched with a loading ramp that stops while true stress is registered. Measured stress in arteries describes a particular curve with a fast steep decrease and a very slow asymptotic relaxation (Hardung, 1952; Jager, 2005; Bergel, 1961). This temporal response to a step deformation in arterial segments can also be associated to their frequency response using complex elastic modulus E^*. In frequency domain, E^* exhibit a fast initial increase from static values, progressing to attain a plateau at higher frequencies (Westerhof and Noordergraaf, 1970). In that sense, arteries are relatively insensitive to strain rate in a wide frequency range.

Models based on ordinary differential equations were used to describe stress-relaxation experiments. They use mechanical analogies connecting springs and dashpots to ultimately represent material viscoelastic properties. The parameters of these components are adjusted using least-squares algorithms and they are eventually associated to some structural or functional properties of the described material.

The simplest model that predicts creep and stress-relaxation is the standard linear solid (SLS) with a parallel combination of a Maxwell arrangement (spring and dashpot in series) with a spring (Fung, 1981). Its temporal step response predicts a negative exponential function. Although this model showed several limitations, it was widely used as a conceptual unit to construct more complicated arrangements that better describe dynamic responses of several materials. Evidently, increasing the number of units (order of the model) blurs the conceptual meaning of each component.

Recently, some models based on fractional order differential equations were presented to describe cell and tissue biomechanics (Djordjevic *et al*., 2003; Koeller, 1984; Suki *et al*., 1994). These equations derive into fractional viscoelastic concepts. Briefly, if a spring represents a zero order element and a dashpot a first order element, a new component called *spring-pot* can be conceived with an intermediate order $1>\alpha>0$. Using α, the mechanical response can interpolate between pure elastic and viscous behaviors. Both temporal relaxation and frequency responses of a *spring-pot* follow power-law functions that seem to be naturally adapted to fit arterial requirements.

The aim of this work was to modify an SLS model, replacing a dashpot with a *spring-pot* of order $1>\alpha>0$ defined using fractional derivatives, to describe arterial viscoelasticity in-vitro. Uniaxial stress-relaxation was registered during 1-hour in human arteries at 2 stress levels and the parameters of the proposed model were adjusted. Finally, an estimation of the frequency response in arteries was presented and discussed.

II. METHODS

A. Modeling

Springs, which represent the elastic component of a viscoelastic material, obey Hooke's Law:

$$\sigma(t) = E.\varepsilon(t)$$

where σ is the applied stress, E is the Young's modulus of the material and ε is the strain. Dashpots represent the viscous component of a viscoelastic material. In these elements, the applied stress varies with strain rate:

$$\sigma(t) = \eta.\frac{d\varepsilon(t)}{dt}$$

where η is viscosity of the dashpot component. In a SLS model, these components are connected as shown in left side of Fig. 1, resulting in the following differential equation

$$\frac{d\varepsilon(t)}{dt} = \frac{E_2}{\eta\left(E_1 + E_2\right)}\left[\frac{\eta}{E_2}\frac{d\sigma(t)}{dt} + \sigma(t) - E_1\varepsilon(t)\right] \quad (1)$$

The complex elastic modulus E^* is defined as the quotient between stress and strain in the frequency domain. Applying the Laplace transform to Eq. 1 and assuming null initial conditions, E^* results

$$E^*(s) = \frac{\sigma(s)}{\varepsilon(s)} = \left(E_1 + E_2\right)\frac{s + \frac{E_1E_2}{\eta\left(E_1 + E_2\right)}}{s + \frac{E_2}{\eta}} \quad (2)$$

where s is the complex Laplace variable. The step temporal response $g(t)$ of this model can be predicted using a unit step in strain and calculating the resulting stress as:

$$g(t) = E_1.u(t) + E_2.e^{-t/\tau}u(t) \quad (3)$$

where $\tau=\eta/E_2$ is the time constant of the exponential decay relaxation. Both frequency and step responses of the SLS model are shown in Fig 2.

The fractional order derivative α of a function $f(t)$ can be expressed following the classical definition attributed to Rienman and Liouville as

$$D^{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)}\frac{d}{dt}\int_0^t \frac{f(\theta)}{(t-\theta)^{\alpha}}d\theta$$

where Γ is the Euler gamma function. Accordingly, in the Laplace domain, the fractional operator results in

$$D^{\alpha} f(t) \xrightarrow{L} s^{\alpha}F(s) \quad (4)$$

where null initial conditions were assumed. Thus, a new component can be conceived with

$$\sigma(t) = \eta.D^{\alpha}\varepsilon(t)\,. \quad (5)$$

This element called *spring-pot* interpolates between a spring (α=0) and a dashpot (α=1). Replacing the dashpot with a *spring-pot*, a modified fractional order viscoelastic SLS (FOV-SLS) can be conceived (Fig. 1). Following Eq. 1, this new fractional model can be represented with a fractional order differential equation as

$$D^{\alpha}\varepsilon = \frac{E_2}{\eta(E_1 + E_2)}\left[\frac{\eta}{E_2}D^{\alpha}\sigma(t) + \sigma(t) - E_1\varepsilon(t)\right]. \quad (6)$$

Applying the Laplace transform and using Eq. 4, E^* results

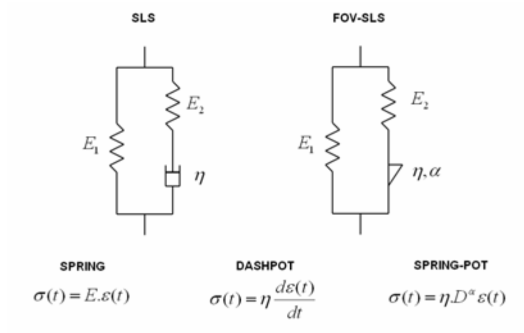

Fig. 1. Standard-linear solid model and the fractional order viscoelastic model.

$$E^*(s) = \left(E_1 + E_2\right)\frac{s^{\alpha} + \frac{E_1E_2}{\eta.(E_1 + E_2)}}{s^{\alpha} + \frac{E_2}{\eta}} \quad (7)$$

which is the analogy of Eq. 2. Again, the step response $g(t)$ can be calculated as

$$g(t) = E_1u(t) + E_2F_{\alpha}\left(-\frac{t^{\alpha}}{\tau}\right).u(t) \quad (8)$$

where the time constant is now $\tau = (\eta/E_2)^{1/\alpha}$ and F_{α} is the Mittag-Leffler function defined as

$$F_{\alpha}\left(z\right) = \sum_{k=0}^{\infty}\frac{z^k}{\Gamma\left(\alpha.k + 1\right)} \quad (9)$$

and its Laplace transform for $1 > \alpha > 0$ is

$$F_{\alpha}\left(-a.t^{\alpha}\right) \xrightarrow{L} \frac{s^{\alpha}}{s.(s^{\alpha} + a)}$$

Frequency and step responses of the SLS and the modified FOV-SLS models are shown in Fig 2.

Finally, and as to analyze a FOV model with the same number of parameters as the SLS model, we removed the E_2 spring in Fig. 1 leaving only one spring (E_1) in parallel with a *spring-pot*. This last alternative was called FOV-Voigt model. Removing E_2 from Eq. 7, the simplified $g(t)$ results:

$$g(t) = E_1u(t) + \frac{\eta}{t^{\alpha}}u(t) \quad (10)$$

where the Mittag-Leffler function present in Eq. 8 was reduced to a simple power-law function.

B. Experimental Validation

To estimate the 4 parameters of the FOV-SLS model, uniaxial stress-relaxation experiments were conducted. Ascending aortic segments were harvested from four human donors (3 men and 1 women aging 42-51) deceased from causes not related to atherosclerosis. All vessel samples were obtained after acquiring the permissions required by current legislation and according to a protocol established and approved by the Ethics Committee of the Hospital Puerta de Hierro in Madrid.

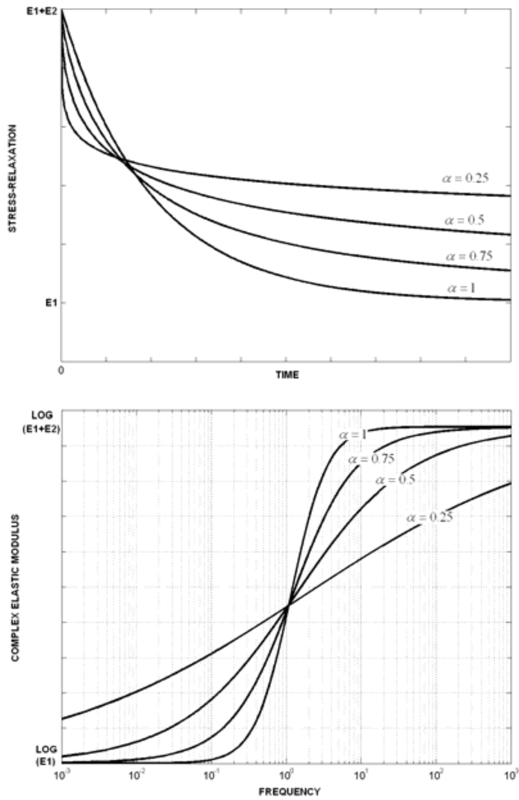

Fig. 2. Time and frequency effects of adjusting the fractional order model α. Up: Stress-relaxation curves. Down: Complex elastic modulus(E^*).

One representative specimen was extracted from each donor. Each specimen consisted of a circumferentially oriented T-bone strip of nominally 2mm width and 10mm length dissected using a custom-made steel cutting block. In-vivo diameter ranged from 24 to 35mm and specimen thickness from 2.00 to 2.25mm. Details of experimental devices are described elsewhere (Atienza *et al.*, 2007). Briefly, two stainless steel fixtures joined the arterial segments to the grips of an electromechanical tensile testing machine (Instron 5866) equipped with a 10N load cell. Specimens were enclosed in a PMMA transparent chamber and submerged in PBS solution heated by a thermostatic bath (Unitronic 6320200). The temperature of the vessel was 37ºC and controlled to 0.5ºC by a K-type thermocouple located in the chamber and close to the artery (<4mm). The elongation was measured by the machine's transducer, which gives a precision of 0.001mm.

In all cases, three preconditioning cycles preceded 1-hour relaxation phases at 2 stress levels: LOW (0.05MPa) and HIGH (0.1MPa). Stress levels were selected to match in-vivo physiological ranges. The loading and unloading rates were in all cases fixed to $0.03 mm.s^{-1}$. Data from 1-hour stress-relaxation portions were registered at a sampling rate of 10Hz and reduced to 0.5Hz using a decimation function based on an eighth-order lowpass Chebyshev Type I filter (decimate Matlab® function).

Stress was normalized in each experiment to peak stress. For the estimation of parameters, we minimized the error between model step responses in Eq. 8 and measured true stress data. The curve fitting problem was solved in the least-square sense using Matlab® function based on the Levenberg-Marquardt algorithm. As the relaxation function for our FOV-SLS has a weak singularity at t=0, we computed values from the smallest positive time based on the sampling rate. Initial conditions for the parameters in all cases were: E_1=0.5, E_2 =0.5, η=1, α=0.5.

To evaluate the quality of fitting, percentage least-square errors (LSE) relative to the measured values were calculated as

$$LSE = \sqrt{\frac{\sum_{i=1}^{n}\left[\sigma_{measured}(i) - \sigma_{model}(i)\right]^2}{\sum_{i=1}^{n}\sigma_{measured}(i)^2}} \times 100\,. \quad (11)$$

III. RESULTS

All viscoelastic parameters are shown in Table 1 and a representative stress-relaxation experiment can be observed in Fig. 3. The fractional order of the *spring-pot* resulted in between 0.10 and 0.36. The elastic constant E_1 was greater than E_2 in all cases and (E_1+E_2) averaged ~1.05. Least-squares errors were always below 1%. For each viscoelastic parameter mean ±SD was calculated. A pooled frequency response was calculated using Eq. 7, normalized to static complex elastic modulus ($E^*(\omega)/E^*(0)$) and shown in Fig. 4. A clear power-law response can be visualized.

When the FOV-Voigt alternative model was tested using Eq. 10, the three parameters E_1, η, α did not significantly differ from the ones presented in Table 1, although fractional orders tended to be slightly lower and the viscous constants higher. With respect to the curve fitting quality, LSE did not vary significantly and remained below 1% in all cases.

TABLE I: Adjusted viscoelastic parameters from the FOV-SLS model after fitting 1-hour stress-relaxation curves.

Segment	Stress level	E_1	E_2	η	α	LSE (%)
PH45	LOW	0.68	0.39	2.14	0.23	0.15
	HIGH	0.64	0.49	1.80	0.18	0.20
PH56	LOW	0.56	0.48	5.54	0.11	0.39
	HIGH	0.61	0.48	1.54	0.16	0.53
PH68	LOW	0.67	0.38	1.88	0.22	0.30
	HIGH	0.62	0.51	1.95	0.36	0.22
PH76	LOW	0.80	0.19	3.76	0.10	0.38
	HIGH	0.69	0.33	2.77	0.23	0.24

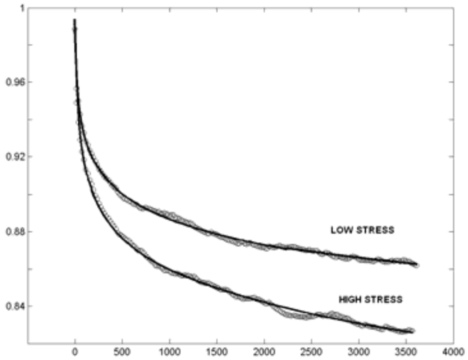

Fig. 3. Stress-relaxation results for LOW and HIGH stress levels. Circle dots for measured values and solid line for model adaptation.

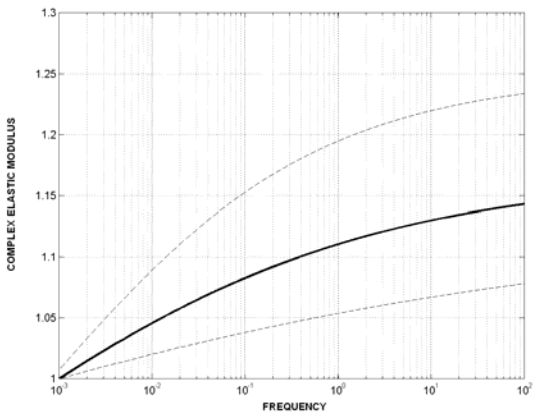

Fig. 4. Complex elastic modulus for pooled results. Solid line for mean values and dotted lines for min and max values.

III. DISCUSSION

In the present work a classical SLS model was modified to describe viscoelasticity in human arteries. A dashpot was replaced by a *spring-pot* that has a fractional order derivative in its definition. After adjusting the parameters, modeled stress-relaxation accurately matched experimental measurements with error below 1%. Moreover, particular properties of relaxations, as the initial steep decay and the slow asymptotic descent until stability were correctly predicted. Finally, frequency responses were estimated and came out similar to actual measurements observed in arteries. Our results show that fractional models should be considered as a plausible alternative to describe arterial viscoelasticity.

The proposed fractional order viscoelastic SLS (FOV-SLS) model has an additional parameter with respect to classical SLS model approach. The *spring-pot* order range ($1>\alpha>0$) allows adjusting time and frequency domain responses in an intermediate sense between pure elastic and viscous behaviors (Fig. 2). This extra parameter in the proposed model offers more versatility to fit arterial wall mechanical requirements. In fact, if $\alpha=1$, both models would match.

However, we found that α values were around 0.1~0.3, revealing a more pronounced elastic than viscous behavior. Others have found similar fractional orders in aortic valve cusps and pulmonary tissues (Doehring *et al.*, 2005; Suki *et al.*, 1994). Our results are coherent with observed stress-relaxation curves (Fig. 3). While the traditional SLS model predicts exponential decays, FOV-SLS includes a combination of power-law functions represented by the Mittag-Leffler summation in Eq. 9. As seen in Fig. 3, the proposed fractional model could naturally match 1-hour stress-relaxation curves in all specimens with LSE below 1%. This might suggest that relaxation curves in arteries are better described with power-law rather than exponential functions (Fung, 1981). In fact, fractional order components were related to fractal-like structures that might be associated to complex collagenous arrangements, present in arterial tissues (Doehring *et al.*, 2005).

The proposed FOV model has 4 parameters while the classical SLS model has only 3. To analyze the relevance of this extra free parameter in the fitting quality observed in Fig. 3 (and verified in LSE results in Table 1) we also fitted a FOV-Voigt model removing the spring E_2 from FOV-SLS arrangement. No perceptible differences were seen in curve fitting and LSE values remained in all cases below 1%. As can be seen in Eq. 10, the FOV-Voigt model has a singularity for $t=0$. Measurements and model differences were more pronounced near that initial time evaluation. However, power-law relaxations observed in Fig. 3 were naturally represented with $t^{-\alpha}$ functions present in Eq. 10, confirming that with only 3 parameters a FOV model might show fitting improvements with respect to classical exponential decay models.

The main goal of our experiments was to validate the relaxation curves in human arterial segments predicted by the FOV-SLS model. Stress-relaxation test include a loading ramp and 1-hour relaxation stages. We only used relaxation stages to fit viscoelastic parameters, although the whole mechanical process partly started during the ramp portion of the curve. In that sense, the loading ramp was neglected with respect to 1-hour relaxation times. In fact, biological tissues proved to be relatively insensitive to strain rates (Doehring *et al.*, 2004), supporting our methodology.

The frequency response of a material can be analyzed using the complex elastic modulus E^*. Pooling all the specimens, we constructed a single frequency response to estimate E^* (Fig. 4). A clear power-law response is evidenced in the range 0-100Hz. This result is similar to actual measurements in arteries (Hardung, 1952). Even though others have tried to generalize Voigt models, incorporating several combinations of spring-dashpot units (Westerhof and Noordergraaf, 1970), our approach with only one *spring-pot* correctly matched the frequency morphology in arteries. Moreover, the particular profile of curves in Fig. 4 can also be found using the FOV-Voigt alternative with only 3 parameters. In time domain, a *spring-pot* defines a $t^{-\alpha}$ relaxation curve while in frequency domain E^* incorporates ω^{α} components. These are both typical responses in arteries that now seem to be naturally fitted with fractional models.

Moreover, the 4 parameters of the FOV-SLS might be associated to inherent properties of the observed relaxation curves. Observing Fig. 2, E_1 and E_2 are connected to peak and asymptotic stress values. On the other hand, η and α defining the *spring-pot*, characterize the decay shape. The order α is maybe the most relevant parameter to be analyzed. If we assume that, in arteries, smooth muscle cells can stretch collagenous fibres, vascular activation can modify local viscoelastic response of the arterial wall (Armentano *et al.*, 2006). Then, the fractional order α could be associated to smooth muscle activity, modulating viscoelasticity in arteries. In-vitro orders in this work tended to show a small viscous effect. Further studies should be conducted to validate this hypothesis, activating vascular smooth muscle and analyzing the tendencies of the parameters.

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