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A New Non-Equilibrium Thermodynamic Fractional Visco-Inelastic Model to Predict Experimentally Inaccessible Processes and Investigate Pathophysiological Cellular Structures

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Abstract: After remarking on non-equilibrium thermodynamics with internal variables, this paper highlights the importance of these variables to the study of biological systems. Internal variables can provide a more detailed description of biological processes that occur inside cells, tissues and organs. In order to introduce a fractional model on a visco-inelastic medium based on Kluitenberg's non-equilibrium thermodynamics, the origin of the complex dynamic modulus is shown by means of linear response theory. This research recalls our previous work to develop an ultrasound wave technique that allows us to investigate biological systems, and introduces the fractional visco-inelastic model and relative generalized relaxation time, to show that it is possible to obtain the Cole–Cole model in a particular case.

Keywords: non-equilibrium thermodynamics; fractional models; pathophysiological cellular structures

1. Introduction

The study of the matter around us can be addressed by considering it to be composed of an extremely large number of elements; with the smallest elementary particles of matter having the same properties as the material itself. Elemental particles obey the laws of classical mechanics, and knowledge of the positions and velocities of all the relevant particles at a specific moment may allow us also to predict their evolution. However, it is impossible to assign a specific position and velocity to all particles, because they are numerous. Only "average" observations can be made, which will then lead to the forecast of average effects due to the evolution observed and will obey probability laws as to which form should be determined. This approach is part of that discipline going under the name of classic statistical mechanics (or classical statistical physics). Statistical mechanics is characterized by a basic determinism, with respect to which probabilism is not substantial but depends on the (technical) impossibility of observing individual effects. In other words, statistical mechanics is deterministic and is accompanied by probabilistic predictions only due to our incapacity in respect of individual determinations. It is understood, therefore, that average observations greatly simplify the mathematical problem of formulating equations when it comes to an extraordinarily large number of instances. In addition, quantities that are not defined in the microcosm (such as entropy) are introduced, but they only make sense on a macroscopic scale [1,2]. It is possible, by contrast with this point of view, to develop a continuous vision of the material that seems contradictory to the molecular one, so that matter is considered as a continuous mathematics. It should be noted that for some hypotheses,

the two points of view can coexist if the macroscopic quantities introduced in the continuous vision are identified with the stabilizing averages of the corresponding molecular quantities. This means that the statistical averages of molecular actions are considered macroscopic magnitudes. In this light, statistical averages are calculated regardless of the structure of matter. As in the continuous mathematics, volume elements are introduced, meaning infinitesimal volumes, in order to apply the algorithms of mathematical analysis. However, volume elements, while being treated by infinitesimal calculus, when viewed in a model must be large enough to be able to follow the macroscopic changes due to the molecular mechanisms being studied [1]. Obviously, such molecular mechanisms are not directly observable, so they are referred to as internal or hidden processes, and the associated variables take the name of internal or hidden variables. Thus, to apply the theory of continuity, it is supposed that in an experiment the matter contained in a volume element reaches a balance in times of relaxation time order. The axiom regarding local equilibrium is thus formulated: "*for a sufficiently small deviation from equilibrium, a system can be divided into tiny (physical) volume elements, each of which can be regarded as a small homogeneous equilibrium system*" [1]. Moreover, from a macroscopic point of view, the length and time scale of these sub-systems are infinitesimally small, but from a molecular point of view they are still large. These observations confer a deterministic significance upon the average number of molecules because there are enough molecules in the sub-system. It is on this axiom that the thermodynamics of non-equilibrium is based. Of course, here we will not formulate the principles and will not describe the developments of non-equilibrium thermodynamics, but it is helpful to remember that it was systematically developed towards the middle of the last century by De Groot and Mazur [2]. Subsequently, other authors have dealt with these issues, some remaining faithful to basic ideas, others developing points of view discordant with the authors mentioned. Following the De Groot and Mazur school, a remarkable step forward was made by Kluitenberg, who introduced and developed non-equilibrium thermodynamics with internal variables, the theory to which we will refer [2–7]. This theory has been developed both in the mechanical continuous and electrodynamic fields. Theoretical results have been obtained that can be considered rheological determinants in the study of relaxation phenomena in any order, considering a finite number of elementary phenomena occurring in between. A theory has also been developed on the propagation of longitudinal, transverse and electromagnetic elastic waves (ultrasound) with internal variables. The introduction of the internal variable concept by Kluitenberg makes this theory particularly suitable for the study of biological phenomena in which the variables to be considered are multiple and the system is always out of equilibrium. Further development of this theory has been carried out by Farsaci et al. [8–15] who have determined a way to correlate the functions that appear in theory with experimentally measurable functions; in particular, with complex dynamic modules (loss and storage) measured in mechanical and dielectric relaxation phenomena. This allowed the experimental (indirect) evaluation of all the rheological functions of the theory and those related to the dielectric polarization phenomena as well as entropy production [16,17]. Such a result is very important as it allows the application of theory to visco-elastic and dielectric study (considered as such). In the latter case, it takes into account the electrical conduction phenomena that often occur. A special mention should be given to the applicability of these developments in the biological field. As we shall see later, this theory is particularly suitable to the study of several pathologies such as tumor evolution and disease prevention, as well as the development of new diagnostic techniques. The aim of this paper is twofold:

(i) To formulate a fractional model for dynamic complex modules in visco-inelastic media of order one, based on Kluitenberg's theory;

(ii) To show how this model can be applied to investigate biological and pathological tissues by using an ultrasound longitudinal wave as a probe.

For this purpose, it is first important to discuss some aspects of Kluitenberg's thermodynamic theory and clarify our point of view in order to deal with a complete, theoretical and experimental study of the problems associated with rheological relaxation phenomena. Moreover, we introduce a short description of linear response theory (LRT) in which complex dynamic modules, of which we will

formulate a fractional model, are defined [18]. The fractional model we are introducing may be of great use in the study of biological systems, in a theoretical context. Indeed, in recent decades the theoretical approach to the study of biological and non-biological phenomena has grown. Therefore, this research for an analytical expression of a complex dynamic module summarizes the system's rheological properties in a way that can be transferred to any model (Zener, Voigt, Mazwell ...) by providing information on the relaxation phenomena of the system studied [19]. It also provides analytical knowledge of all the rheological functions of the theory, especially the analytical determination of entropy production. Lastly, supposing that the system is perturbed by a longitudinal elastic wave (ultrasound), we determine the analytical expression of the wave vector in function of the fractional complex module previously obtained. The study of wave fluctuations (pressure waves, ultrasounds) at wave frequency variations provides a powerful method of investigation, especially in the biological field [20]. From a theoretical point of view, it is considered an elastic wave propagating in the medium in question. Therefore, it is possible to calculate the coefficients that appear in the rheological equation as a function of attenuation and phase velocity, by considering the indefinite equations of the continuous means, the symmetry properties of the tensors of stresses and deformations, and by introducing approximations on the predominant elastic behavior of the means at the appropriate frequencies. This process allows for a double experimental study, since the results obtained from the experimental data of direct measurements of phase velocity and wave attenuation (MATEC) can be compared to those obtained by measuring the dynamic modules L_1 and L_2, all of which are obviously frequency functions.

2. Methods

2.1. Remarks on Non-Equilibrium Thermodynamics with Internal Variables

The irreversibility of natural phenomena is the main reason for the difficulties arising in state thermodynamic models. Nevertheless, this condition is described well by the entropy function that is one of the more important concepts in physics [1]. Knowledge of the change of entropy allows us to separate physical processes into two classes: reversible and irreversible. The first is connected with no changes in entropy, while in the second entropy changes occur [1]. So entropy may be considered a measure of the irreversibility of a process and, moreover, is related to an increase of disorder for an isolated system. The branch of physics that studies these subjects is non-equilibrium thermodynamics (NET) [1,2]. Another problem for state thermodynamic models is the non-linearity of phenomena. However, although almost all physical phenomena show non-linearity, in many cases linear approximation is a good compromise as it gives results in accordance with the phenomena. On the other hand, there are mathematical difficulties in dealing with non-linearities that cannot be overcome analytically, but only by means of numerical methods. In line with our research on the study of some biological phenomena by means of techniques developed in the context of NET, in this paper we will refer to a linear approximation since this proved to be successful in the study of biological phenomena [13–15,21,22]. As mentioned above, entropy plays a fundamental role in the whole NET. Generally, the entropy S is considered as function of n extensive variables X_i (i = 1, 2, ..., n) [1,2]

$$s = s(X_1, X_2, \ldots, X_n), \tag{1}$$

By introducing generalized forces:

$$F_k = \frac{\partial s}{\partial X_k}, \tag{2}$$

called affinities, and related "fluxes":

$$J_k = \frac{dX_k}{dt} \tag{3}$$

the entropy production can be written:

$$\frac{ds}{dt} = \sum_k F_k J_k = \sum_k \frac{\partial s}{\partial X_k} \frac{dX_k}{dt} \tag{4}$$

Generally, the functional dependence between fluxes and affinities can be very complex and assumes a non-linear form. Here we admit, supported by a large number of phenomena, that these relations are linear:

$$J_i = \sum_k M_{ik} F_k \tag{5}$$

where M_{ik} are called phenomenological coefficients and it can be shown that they satisfy some symmetry relations [1,2]. Following Kluitenberg's theory, we will introduce a particular form of relation (5) in following sections. Here, we will make clear why we consider Kluitenberg's theory particularly suitable for the study of biological phenomena. Apart from the non-equilibrium status of biological phenomena, there are reasons that make the theory with internal variables fit for this purpose. These are related to the connection that can arise between internal variables and processes which occur inside biological tissues not being caused by external perturbation but only by internal phenomena. We do not go into the details of the theory, which can be found at ref. [3,7], but we focus our attention on internal variables. Moreover, no use is made of spring-dashpot models. The heat dissipation functions for ordinary viscous fluids and for Maxwell, Kelvin (Voigt), Poynting–Thomson, Jeffreys, Prandtl–Reuss, Bingham, Saint Venant, and Hooke media may be regarded as degeneracy of the more general expression that is derived [3,7]. Generally, the set of variables—strain tensor, internal energy, specific volume, entropy and temperature, for example—are sufficient to characterize the state of a thermoelastic medium or fluid. But, if more complicated phenomena occur as a chemical reaction, anelastic or plastic strain, dielectric and magnetic relaxation, the aforementioned set of variables is incomplete. For instance, if we consider a fluid mixture of n-chemical components, each with a concentration $C^{(K)}$ (K = 1, 2, ..., n), the local thermodynamic state is completely specified by internal energy u, the volume v and the additional scalar (macroscopic) thermodynamic variables $C^{(K)}$ (K = 1, 2, ..., n) [2]. Thus the entropy s is assumed:

$$s = s(u, v, C^{(1)}, C^{(2)}, \ldots C^{(n)}) \tag{6}$$

In hematology there are several examples of this kind: the ratio albumin–globulin, leukocytosis, leukemia, leukopenia. A generalization of Equation (6) can be taken into account by considering a medium for which the entropy depends on the internal energy, the tensor of total strain, and some tensorial variables Ω_{ik}. We shall assume that Ω_{ik} is a macroscopic quantity which we need in order to give a complete description of the state of the medium. Without specifying the physical nature of Ω_{ik} (we shall call it a hidden tensorial variable), we assume that it influences the mechanical properties of the medium and that it is a symmetrical tensor field. Hence we assume that [3,7]:

$$s = s(u, \varepsilon_{ik}, \Omega_{ik}) \tag{7}$$

where Ω_{ik} is the tensor of total strain. A further generalization from the aforementioned ideas is the assumption that there are several microscopic phenomena which influence the mechanical properties of the medium under consideration. Besides, the thermodynamic state of the medium may be described by the internal energy, total strain and "n" macroscopic internal variables. This also includes the possibility of scalar internal variables. So Equation (7) assumes the form:

$$s = s\left(u, \varepsilon_{ik}, \Omega_{ik}^{(1)}, \Omega_{ik}^{(2)}, \ldots \Omega_{ik}^{(n)}\right) \tag{8}$$

Before proceeding to describe the theory, we must recall our definition:

We define the entropy, the variables on which the entropy depends, the quantities which are obtained by partial differentiation of the entropy (such as the temperature) and the functions of these quantities (such as free energy) as thermodynamic variables. Thermodynamic variables on which entropy depends and from which substantial time derivatives occur in the first law of thermodynamics may be called external thermodynamic variables, because the values of these parameters can be prescribed by external influences. Additional variables on which the entropy depends, and from which substantial time derivatives do not occur, may be called internal thermodynamic variables.

It can be shown [7] that the strain tensor can be split in two parts $\varepsilon_{ik}^{(0)}$, which we call the elastic part, and $\varepsilon_{ik}^{(1)}$, the inelastic part, respectively. So we have:

$$\varepsilon_{ik} = \varepsilon_{ik}^{(0)} + \varepsilon_{ik}^{(1)} \tag{9}$$

Moreover it can be shown that the change of both $\varepsilon_{ik}^{(0)}$ and $\varepsilon_{ik}^{(1)}$ contributes to entropy production and, therefore, they represent two irreversible processes. The inelastic deformation can be due to several internal processes that occur simultaneously. Let us suppose that there occur "n" different types of microscopic phenomena giving rise to inelastic strain, and let us further assume that:

$$\varepsilon_{ik}^{(i)} = \sum_{h=1}^{n} \varepsilon_{ik}^{(h)} \tag{10}$$

where $\varepsilon_{ik}^{(h)}$ is the contribution to the inelastic strain of the h-th microscopic phenomenon. It can be shown [7] that the expression (8) specializes as:

$$s = s\left(u, \varepsilon_{ik}, \varepsilon_{ik}^{(1)}, \varepsilon_{ik}^{(2)}, \ldots \varepsilon_{ik}^{(n)}\right) \tag{11}$$

where we assume that partial inelastic strain tensors $\varepsilon_{ik}^{(h)}$ (h = 1, 2, ... , n) are related to n different microscopic phenomena. From expression (11) it is seen that $\varepsilon_{ik}^{(h)}$ (h = 1, 2, ... , n) plays the role of internal variables. Just the expression (11) allows the possibility of studying particular processes that occur, for example, in cancer tissues, since we can correlate every partially inelastic strain to a tumor cell [15]. The rheological properties of these tissues are altered and those mechanical changes are revealed as emergent properties at a macroscopic level. This is the case for leukocytosis, which is an abnormal increase in the number of white blood cells; leukemia which is a neoplastic proliferation of hematopoietic stem cells; or leukopenia, which is an abnormal reduction of circulating white blood cells, especially granulocytes. In these cases, the rheological properties of the blood change, and in particular this can change the partial inelastic strain associated to each anomalous phenomena (disease). Obviously, it is very difficult to investigate these pathologies by considering directly partial inelastic strain, because a direct measure of them is very hard. However, from a rheological point of view, these diseases may be investigated by means of ultrasound waves, as we shall show in the next sections for a particular case. Here, we will show a "technique" for approaching this type of investigation [23–25].

2.2. Rheological Differential Equation

We assume that only one microscopic phenomenon occurs inside the medium. So the Equation (11) becomes:

$$s = s\left(u, \varepsilon_{ik}, \varepsilon_{ik}^{(1)}\right)$$

From which the usual equations lead:

$$\begin{cases} \frac{1}{T} = \frac{\partial s\left(u,\varepsilon_{ik},\varepsilon_{ik}^{(1)}\right)}{\partial u} \\ \tau_{ik}^{(eq)} = -T\rho\frac{\partial s\left(u,\varepsilon_{ik},\varepsilon_{ik}^{(1)}\right)}{\varepsilon_{ik}} \\ \tau_{ik}^{(1)} = T\frac{\partial s\left(u,\varepsilon_{ik},\varepsilon_{ik}^{(1)}\right)}{\partial \varepsilon_{ik}^{(1)}} \end{cases}$$

where T is the temperature; ρ the mass density; $\tau_{ik}^{(eq)}$ is equilibrium stress tensor; and $\tau_{ik}^{(1)}$ is affinity stress tensor. The viscous stress tensor $\tau_{ik}^{(vi)}$ can be introduced:

$$\tau_{ik}^{(vi)} = \tau_{ik} - \tau_{ik}^{(eq)} \tag{12}$$

here, τ_{ik} is the stress tensor that occurs in indefinite equations. Now, assuming that the inelastic strain derives from only one microscopic phenomenon, it is possible to introduce this contribution as the internal degree of freedom in the Gibbs' relation. This assumption and the first law of thermodynamics allow an explicit form of entropy production. By considering the scalar part τ of the stress tensor and the scalar part ε of the strain tensor, one has for the entropy production [7]:

$$\sigma^{(s)} = \frac{1}{T}\left[\tau^{(vi)}\frac{d\varepsilon^{(0)}}{dt} + \left(\tau^{(vi)} + \tau^{(1)}\right)\frac{d\varepsilon^{(1)}}{dt}\right] \tag{13}$$

From the expression thus obtained, taking into account the usual procedure of non-equilibrium thermodynamics and assuming that the cross effect among viscous flow and inelastic flow are neglected, the following phenomenological equations can be obtained [7]:

$$\tau^{(vi)} = \eta_v^{(0,0)}\frac{d\varepsilon}{dt} \tag{14}$$

$$\frac{d\varepsilon^{(1)}}{dt} = \eta_v^{(1,1)}\tau^{(1)} \tag{15}$$

where $\eta_v^{(0,0)}, \eta_v^{(1,1)}$ are phenomenological coefficients, and we shall assume that they are constant in time. The coefficient $\eta_v^{(0,0)}$ (volume viscosity), which has the dimension of a viscosity, is connected to irreversible processes related to the change of ε, while $\eta_v^{(1,1)}$, which has the dimension of a fluidity, is related to change of $\varepsilon^{(1)}$ and the corresponding intensive variable $\tau^{(1)}$. However, Equations (14) and (15) are connected with irreversible changes of the strain. These, together with linear state Equations [7]:

$$\tau^{(eq)} = b^{(0,0)}\left(\varepsilon - \varepsilon^{(1)}\right) = b^{(0,0)}\varepsilon^{(0)} \tag{16}$$

$$\tau^{(1)} = b^{(0,0)}\varepsilon - b^{(1,1)}\varepsilon^{(1)} \tag{17}$$

lead to the so-called relaxation equation for trace τ of the stress tensor and trace ε of the strain tensor:

$$\frac{d\tau}{dt} + R_0^{(\tau)}\tau = R_0^{(\varepsilon)}\varepsilon + R_1^{(\varepsilon)}\frac{d\varepsilon}{dt} + R_2^{(\varepsilon)}\frac{d^2\varepsilon}{dt^2} \tag{18}$$

where:

$$\begin{array}{ll} R_0^{(\tau)} = b^{(1,1)}\eta_v^{(1,1)} = 1/\sigma & R_1^{(\varepsilon)} = b^{(0,0)} + b^{(1,1)}\eta_v^{(1,1)}\eta_v^{(0,0)} \\ R_0^{(\varepsilon)} = b^{(0,0)}\left(b^{(1,1)} - b^{(0,0)}\right)\eta_v^{(1,1)} & R_2^{(\varepsilon)} = \eta_v^{(0,0)} \end{array} \tag{19}$$

In which $b^{(0,0)}$ and $b^{(1,1)}$ are the state coefficients related to the elasticity and inelasticity phenomena, respectively. The importance of the phenomenological and state coefficients is that they characterize

the medium specifying the amount of the type of phenomena correlate for each of them. It is important to observe that their constancy is related to the time for each type of perturbation that acts on the medium. However, they vary with the change of the perturbation. For example, if the perturbation is of a harmonic type with frequency ω, then the coefficients will depend on ω which can be considered as parameter in the functional dependence of the coefficients. In this case we shall call $a^{(0,0)}, a^{(1,1)}, \eta_v^{(0,0)}, \eta_v^{(1,1)}$ dynamical coefficients.

It can be proved that for a fluid (such as blood) it is reasonable to assume that ρ is constant for each element so as to verify the basic axioms on local and instantaneous equilibrium [1]. Thus, we assume that the mass density ρ is constant. It is seen from Equation (17) that sudden change in $\varepsilon^{(1)}$ is impossible, while from Equation (16) it follows that sudden change in $\varepsilon^{(0)}$ is possible.

2.3. Remarks on Linear Response Theory

Here we will recall how to define the Complex Dynamic Modulus, because the introduction of its fractional form is the principal ambition of this work. Since we are studying relaxation phenomena, we assume as perturbation of the system an extensive variable $f(t)$ (cause) and the relative intensive variable $g(t)$ as response (effect). For a linear system, it can be shown that the following convolution relation is valid [19]:

$$g(t) = f(t) \otimes h(t) \tag{20}$$

where:

$$f(t) \otimes h(t) = \int_{-\infty}^{+\infty} f(t_1) h(t - t_1) dt_1 \tag{21}$$

From Equation (12), and taking in account convolution theorem, it follows:

$$FT\{g(t)\} = FT\{f(t)\} FT\{h(t)\} \tag{22}$$

where the symbol $FT\{\ldots\}$ is the Fourier transform. We have:

$$FT\{g(t)\} = G(\omega) = \int_{-\infty}^{+\infty} e^{-i\omega t} g(t) dt; FT\{f(t)\} = F(\omega) = \int_{-\infty}^{+\infty} e^{-i\omega t} f(t) dt \tag{23}$$

$$FT\{h(t)\} = H(\omega) = \int_{-\infty}^{+\infty} e^{-i\omega t} h(t) dt$$

where $H(\omega)$ is the transfer function. From relations (20)–(23) one has:

$$H(\omega) = \frac{G(\omega)}{F(\omega)} \tag{24}$$

and therefore:

$$h(t) = FT^{-1}\{H(\omega)\} = FT^{-1}\left\{\frac{G(\omega)}{F(\omega)}\right\} \tag{25}$$

where $FT^{-1}\{\ldots\}$ is the inverse Fourier transform. If we take into account the hypotheses for which the relaxation Equation (18) is valid, and we consider a harmonic deformation as input [18]:

$$\varepsilon(t) = \varepsilon_0 e^{i\omega t} \tag{26}$$

where ε_0 is the amplitude of the oscillation and ω its angular frequency, it can be shown that to a harmonic input corresponds a harmonic output of the same frequency, but with different amplitude and phase, which depend on the angular frequency of input. Therefore, the output will be [18]:

$$\tau(t) = \tau_0(\omega)e^{i(\omega t+\delta(\omega))} \tag{27}$$

where $\delta(\omega)$ is a phase lag. By applying Equations (20)–(25) to this case, one has:

$$L^*(\omega) = \frac{\tau_0(\omega)}{\varepsilon_0}e^{i\delta(\omega)} \tag{28}$$

and the complex quantity is introduced:

$$L^*(\omega) = L_1(\omega) + iL_2(\omega) \tag{29}$$

with the real and imaginary parts given by:

$$L_1 = \frac{\tau_0(\omega)}{\varepsilon_0}\cos\delta(\omega) \tag{30}$$

$$L_2 = \frac{\tau_0(\omega)}{\varepsilon_0}\sin\delta(\omega) \tag{31}$$

These functions are very important for studying the aforementioned relaxation phenomena. In a physical contest, L_1 and L_2 are called storage modulus and loss modulus, respectively [17], and it is possible to show that they are related to not-dissipative phenomena and dissipative phenomena, respectively. Moreover, these two quantities are experimentally measurable as functions of angular frequency of input.

2.4. Ultrasound Wave Approach: Summary of Previous Results

Here, we summarise our previous results showing where we can apply the fractional model, which we will obtain in the next section, and how important it is for determine an analytical expression of all thermodynamic functions. In previous papers [21], by assuming that a longitudinal wave

$$\begin{cases} u_1 = Ae^{i(kx-\omega t)} \\ u_2 = u_3 = 0 \end{cases} \tag{32}$$

perturb a medium (blood), where $u(u_1,u_2,u_3)$ is a vector displacement which propagates in the direction of x-axis; A the amplitude of the wave; and $K = K_1 + iK_2$ is the complex wave number, where K_1 is

$$K_1 = \frac{\omega}{v_s} \tag{33}$$

in which v_s is the phase velocity and K_2 is attenuation. So, taking into account Kluitenberg's theory and the characteristic of longitudinal waves, we obtain the following expression for phenomenological and state coefficients as functions of the wave vector $K(\omega)$ and for entropy production [21]:

$$\begin{aligned} b^{(0,0)} &= 3\rho\omega\left[\frac{\frac{2K_1K_2}{\sigma}+\omega\left(K_1^2-k_2^2\right)}{\left(K_1^2+k_2^2\right)^2}\right]-\frac{L_{2R}}{\omega\sigma} \\ b^{((1,1))} &= \frac{\left[3\rho\omega\left(\frac{2K_1K_2}{\sigma}+\omega\left(K_1^2-k_2^2\right)\right)-R_0^{(\varepsilon)}\frac{\left(K_1^2+k_2^2\right)^2}{\sigma}\right]^2}{\frac{1}{\sigma}\left(\omega^2+\frac{1}{\sigma^2}\right)\left[6\rho\omega K_1K_2-\frac{L_{2R}}{\omega}\left(K_1^2+k_2^2\right)^2\right]} \end{aligned} \tag{34}$$

$$\eta_v^{(1,1)} = \frac{\frac{1}{\sigma}\left(\omega^2 + \frac{1}{\sigma^2}\right)\left[6\rho\omega K_1 K_2 - \frac{L_{2R}}{\omega}\left(K_1^2 + k_2^2\right)^2\right]}{\left[3\rho\omega\left(\frac{2K_1K_2}{\sigma} + \omega\left(K_1^2 - k_2^2\right)\right) - R_0^{(\varepsilon)}\frac{\left(K_1^2+k_2^2\right)^2}{\sigma}\right]^2}$$

$$\eta_v^{(0,0)} = \frac{L_{2R}}{\omega}$$

$$\begin{aligned}\sigma^{(s)} = \frac{A^2}{3T}e^{-2k_2x}\Big\{&\left(\eta_s^{(0,0)}\omega^2k_1^2 + \eta_s^{(1,1)}k_2^2\Gamma^2\right)\cos^2\beta + \left(\eta_s^{(1,1)}\Gamma^2k_1^2 + \eta_s^{(0,0)}k_2^2\omega^2\right)\sin^2\beta \\ &-2k_1k_2\sin\beta\cos\beta\left(\eta_s^{(0,0)}\omega^2 - \eta_s^{(1,1)}\Gamma^2\right)\Big\}\end{aligned} \tag{35}$$

where σ is the relaxation time and L_{2R} the relaxed value of L_2 [19] and

$$\beta = k_1x - \omega t \text{ and } \Gamma = b^{(0,0)} - b^{(1,1)}\left(1 - \frac{L_1}{b^{(0,0)}}\right).$$

Moreover, the following expression is for rheological (internal variables) functions [22]:

$$\varepsilon = RK\sin(\omega t + \delta) \tag{36}$$

$$\tau = \lambda\sin(\omega t + \zeta) \tag{37}$$

$$\tau^{(vi)} = \eta_v^{(0,0)}\frac{d\varepsilon}{dt} = \eta_v^{(0,0)}RK\omega\cos(\omega t + \delta) \tag{38}$$

$$\tau^{(eq)} = \tau - \tau^{(vi)} = \lambda\sin(\omega t + \zeta) - \eta_v^{(0,0)}RK\omega\cos(\omega t + \delta) \tag{39}$$

$$\varepsilon^{(0)} = \frac{1}{b^{(0,0)}}\left[\lambda\sin(\omega t + \zeta) - \eta_v^{(0,0)}RK\omega\cos(\omega t + \delta)\right] \tag{40}$$

$$\varepsilon^{(1)} = \varepsilon - \varepsilon^{(0)} = RK\sin(\omega t + \delta) - \frac{1}{b^{(0,0)}}\left[\lambda\sin(\omega t + \zeta) - \eta_v^{(0,0)}RK\omega\cos(\omega t + \delta)\right] \tag{41}$$

$$\tau^{(1)} = \frac{1}{\eta_v^{(1,1)}}\left[RK\omega\cos(\omega t + \delta) - \frac{1}{b^{(0,0)}}\left[\lambda\omega\cos(\omega t + \zeta) + \eta_v^{(0,0)}RK\omega^2\sin(\omega t + \delta)\right]\right] \tag{42}$$

where:

$$u_1 = Ae^{-k_2x}\cos(k_1x - \omega t) \tag{43}$$

$$\begin{gathered}u_2 = u_3 = 0 \\ R = -\frac{1}{3}Ae^{-k_2x} \quad K = \sqrt{m^2 + n^2} = \sqrt{k_1^2 + k_1^2} \quad m = (k_2\sin k_1x - k_1\cos k_1x)\end{gathered} \tag{44}$$

$$n = (k_1\sin k_1x + k_2\cos k_1x) \quad \delta = \arctan\frac{n}{m} \tag{45}$$

$$\alpha_1 = RK\left(R_0^{(\varepsilon)} - \omega^2R_2^{(\varepsilon)}\right) \quad \beta_1 = RKR_1^{(\varepsilon)}\omega \quad \alpha = \alpha_1\cos\delta - \beta_1\sin\delta \tag{46}$$

$$\beta = \alpha_1\sin\delta + \beta_1\cos\delta \quad P = \frac{\alpha\sigma + \beta\omega\sigma^2}{1 + \omega^2\sigma^2} \quad Q = \frac{\beta\sigma - \alpha\omega\sigma^2}{1 + \omega^2\sigma^2} \quad \varsigma = \arctan\frac{Q}{P} \tag{47}$$

It is very important in our approach to take into account the well known relations between the complex wave vector K and the complex longitudinal dynamic modulus L^* (see Equations (30) and (31)):

$$K_1 = \omega\sqrt{\frac{\rho\left(\sqrt{L_1^2 + L_2^2} + L_1\right)}{2\left(L_1^2 + L_2^2\right)}} \quad K_2 = \omega\sqrt{\frac{\rho\left(\sqrt{L_1^2 + L_2^2} - L_1\right)}{2\left(L_1^2 + L_2^2\right)}} \tag{48}$$

$$L_1 = \frac{\rho\omega^2\left(K_1^2 - k_2^2\right)}{\left(K_1^2 + k_2^2\right)^2} \quad L_2 = \frac{2\rho\omega K_1K_2}{\left(K_1^2 + k_2^2\right)^2} \tag{49}$$

since we will formulate a fractional model for the modulus L^*. These relations allow us to obtain an analytical expression of the aforementioned coefficients and rheological functions, as we will see in the next section.

3. Results

After this review, we are able to introduce our new point of view on the fractional approach.

Fractional Visco-Inelastic Model

Fractional calculus can be considered a further approach, together with NET with internal variables, to the study of biological systems. We do not describe this calculus, for which we point to references [20,26]. However, we observe that fractional calculus extends the number of phenomena that occur inside a complex biological system, since it is able to investigate a larger space–time scale on which a model can be formulated. From a physical point of view, to formulate a fractional model it is necessary to introduce a fractional differential equation that has a number of parameters. Several models have been formulated (Cole–Cole, Cole–Davidson, etc.) with a certain number of parameters, but they are based on an adaptive empirical approach. Our point of view is different, because it is based on thermodynamic considerations. In fact, it is a fractional reformulation of Kluitenberg's theory with internal variables. Obviously, two fractional differential equations related to distinct models differ only in terms of the parameters which appear if the fractional order derivative is the same. The parameters which appear in the proposed fractional differential equation are not just of the fractional derivative, since there are other multiplicative functions with a well known physical meaning in the context of visco-inelastic Kluitenberg characterization of the media.

Clearly, a model with a minimum number of parameters is undoubtedly better. Here, we introduce a fractional visco-inelastic model with two fractional parameters. The coefficients appearing as multiplicative factors in the fractional differential equation can be evaluated by also using a method described in a previous article [8]. In accordance with NET, we enunciate a fractional differential equation for a visco-inelastic medium of order one (approximation with only one relaxation time) in agreement with Kluitenberg's theory:

$$\tau + \left(\frac{1}{k_0}\right)^{\beta} \frac{d^{\beta}\tau}{dt^{\beta}} = \left(\frac{h_0}{k_0}\right)\varepsilon + h_1\left(\frac{1}{k_0}\right)^{\beta} \frac{d^{\beta}\varepsilon}{dt^{\beta}} + h_2 k_0 \left(\frac{1}{k_0}\right)^{\alpha} \frac{d^{\alpha}\varepsilon}{dt^{\beta}} \tag{50}$$

$$0 < \beta \leq \alpha \leq 1$$
$$h_i = R^{(\varepsilon)}_{(i)} \quad (i = 0, 1, 2) \quad k_0 = R^{(\tau)}_{(0)} = \tfrac{1}{\sigma}$$

where we indicate with h_i and k_0 expressions (19) which are related to the phenomenological and state coefficients by equations.

Equation (50) is different from the usual fractional differential equations because the coefficients which appear have a particular meaning in the NET. They can be expressed as a frequency spectrum, as shown by Equations (34) and (19). We will also see that they can be expressed by means of the fractional expression of L^*.

Now, considering $\varepsilon = \varepsilon_0 e^{i\omega t}$ as the extensive variable (cause) and $\tau = \tau_0 e^{i(\omega t + \delta)}$ as the intensive one (effect), Equation (50) becomes:

$$\tau_0 F\left\{e^{i(\omega t+\delta)}\right\}\left[1 + (i\omega\sigma)^{\beta}\right] = \varepsilon_0 F\left\{e^{i\omega t}\right\}\left[h_0\sigma + h_1(i\omega\sigma)^{\beta} + h_2\frac{1}{\sigma}(i\omega\sigma)^{\alpha}\right]$$

where the following important relation between the Fourier transform $F\{\ldots\}$ and fractional derivative $\frac{d^{\rho}}{dt^{\rho}}$ has been used [26]:

$$F\left\{\frac{d^{\rho}m(t)}{dt^{\rho}}\right\} = (i\omega)^{\rho} F\{m(t)\}$$

It is easy to show that the complex dynamic modulus (28) is:

$$L^* = \frac{F\left\{\tau_0 e^{i(\omega t+\varphi)}\right\}}{F\left\{\varepsilon_0 e^{i\omega t}\right\}} = \frac{\left[h_0\sigma + h_1(i\omega\sigma)^\beta + h_2\frac{1}{\sigma}(i\omega\sigma)^\alpha\right]}{1+(i\omega\sigma)^\beta} \tag{51}$$

where we define

$$s = \sigma^\beta \tag{52}$$

as the generalized relaxation time. This reduces to classical relaxation time if $\beta = 1$.

By separating the real and imaginary part of Equation (51), one has:

$$L_1 = \frac{h_0\sigma + (\omega\sigma)^\beta \cos\beta\frac{\pi}{2}(h_1+h_o\sigma) + h_2\omega^\alpha\sigma^{\alpha-1}\cos\alpha\frac{\pi}{2} + h_1(\omega\sigma)^{2\beta} + h_2\omega^{\alpha+\beta}\sigma^{\alpha+\beta-1}\cos\left[(\alpha+\beta)\frac{\pi}{2}\right]}{1+2(\omega\sigma)^\beta\cos\beta\frac{\pi}{2}+(\omega\sigma)^{2\beta}} \tag{53}$$

$$L_2 = \frac{(\omega\sigma)^\beta \sin\beta\frac{\pi}{2}(h_1-h_o\sigma) + h_2\omega^\alpha\sigma^{\alpha-1}\sin\alpha\frac{\pi}{2} + h_2\omega^{\alpha+\beta}\sigma^{\alpha+\beta-1}\cos\left[(\alpha-\beta)\frac{\pi}{2}\right]}{1+2(\omega\sigma)^\beta\cos\beta\frac{\pi}{2}+(\omega\sigma)^{2\beta}} \tag{54}$$

Here four parameters, h_0, h_1, h_2, and σ, appear (which have a particular meaning in Kluitenberg's theory) as well as α, β. These can be determined by fitting the experimental data. This can be done, but it is possible to attempt a fit, the first time, with only the three parameters α, β and σ and take into account, incrementally, the other parameters if the first three are not sufficient for a good fit. If, for example, we obtain a good fit with three parameters α, β and σ, we can evaluate the expressions of h_0, h_1, h_2 obtained by using a method described in a previous paper [8].

If, after the fit, we substitute Equation (53) for Equation (48) and the expression obtained in Equations (34)–(47), we obtain an analytical form of these functions. Indeed, here we assume experimental knowledge of L_1 and L_2; this is the case in which we perturb the medium with a harmonic strain (26). But we will utilize Equations (53) in a different way. In fact, by perturbing the medium with a harmonic ultrasound longitudinal wave (32) and measuring the complex wave vector K, by means of the well known Equation (49), it is possible to obtain L_1 and L_2 and fit these values by means of Equations (53) and repeat the aforementioned procedure. Finally, it is easy to show that from Equation (51) the well known Cole–Cole expression can be deduced in a particular case:

$$L^* = \frac{L_R + L_U(i\omega\sigma)^\beta}{1+(i\omega\sigma)^\beta}$$

If we put $h_0\sigma = L_R$, $h_1 = L_U$ and $h_2 = 0$.

4. Conclusions

The approach introduced in this paper constitutes an advancement in the theoretical study of biological systems, in particular for fluid systems (such as blood), since the longitudinal wave is used as a probe. Its most important aspect is in the use of internal variables. These allow a more detailed description of the phenomena occurring inside the biological system, since an opportune variable can be associated with each process. This may help us to understand the evolution of a (physiological or pathological) phenomenon and, moreover, to test a therapeutic approach. Our technique can be applied in several cases since it is not invasive because ultrasound waves are non-invasive. But the most significant contribution of this approach is the knowledge of the phenomena associated with each phenomenological and state coefficient and with internal variables. These can highlight the evolution of pathologies that cannot be demonstrated with evidence in other investigations. In fact, as shown in several previous papers [8,21,22,27], these coefficients are specific for each system and this technique can be considered a new method of characterization. It is like watching a phenomenon with a magnifying glass, or splitting up a phenomenon into its components. Moreover, this knowledge can be used for the prevention, for example, of tumor pathologies: phenomena, which do not appear by

using classical techniques of investigation, can be identified by the aforementioned coefficients, since a process is associated with each of them that can characterize the system [13]. Generally, coefficients are considered constant and it is a novelty to represent their spectrum as a function of the frequency. In our case, in which the ultrasound wave is used as a probe, the aforementioned spectrum can be used to correlate a specific process to the frequency at which it occurs. This result may also be used for therapeutic interaction with the system. The model introduced here may be considered as a dual value: it may be used as prevention and as a therapeutic technique. First, we argue that the importance of an analytical expression of function which describes a phenomenon is well known. In our case the knowledge of an analytical form of a complex dynamic longitudinal modulus or a complex wave vector contribute in a consistent way to a theoretical study of phenomena that cannot be approached experimentally. Moreover, the model can predict processes which are not experimentally accessible and, as stated above, can be investigated as phenomena that do not appear in classical models from a theoretical point of view.

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