Evaluation of the human blood entropy production: a new thermodynamic approach

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Abstract In this paper, we follow the thermodynamic theory with internal variables of Kluitenberg evaluating the entropy production of red blood cell in saline solution and whole blood, respectively, when they are subjected to an ultrasound wave. From a thermodynamic point of view, blood is an open system; so to fully represent the entropy variation as function of frequency perturbation we employ phenomenological coefficients which allow us to qualitatively discriminate among classes of phenomena which cannot be observed in any other way. Therefore, a correlation between these coefficients and quantities experimentally measurable allows to a deeper knowledge of biological phenomena.

Keywords Blood · Entropy · Non-equilibrium thermodynamic · Red blood cells · Ultrasound

Sommario In questo lavoro, utilizzando la teoria termodinamica di Kluitenberg con variabili interne, viene valutata la produzione di entropia nel sangue intero e nei globuli rossi, quando questo viene perturbato con ultrasuoni in funzione della frequenza. Poiché da un punto di vista termodinamico, il sangue è un sistema aperto, determinare la variazione di entropia in funzione della frequenza è della massima importanza. A tale scopo vengono determinati i coefficienti fenomenologici da cui essa dipende, i

quali, inoltre, permettono di discriminare qualitativamente classi di fenomeni che altrimenti non vengono considerate. Pertanto, una correlazione tra questi coefficienti e le quantità sperimentalmente misurabili permette di approfondire la conoscenza dei fenomeni biologici.

Abbreviations

NET Non-equilibrium thermodynamics
RBCs Red blood cells
WBCs White blood cells
MPs Micro-particles

Introduction

Entropy is one of the most important physics concepts is entropy [1, 2]; it is connected with the second principle of thermodynamics and gives a measure of disorder of a system.

From a thermodynamic point of view, we can frame physical processes into two classes: reversible and irreversible. The characterization of these processes is related to the change of the entropy. In particular, a zero change of the entropy means that the process is reversible, while a change of the entropy different from zero means that the process is irreversible. So the entropy production can be considered as a measure of the irreversibility of a process. Unfortunately, all processes which occur in nature are irreversible and this implies great complications in their study. Another meaning of the increment of the entropy is its relation with an increment of disorder for an isolated system. In other words, an isolated system evolves spontaneously toward stages with greater entropy and with a greater level of disorder.

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The branch of the physics which studies these arguments is the so-called “non-equilibrium thermodynamics” (NET) [2]. Indeed, in the literature, there exist several approaches to this discipline which differ mainly in the choice of the variables to describe phenomena. In this paper, we follow the thermodynamic theory with internal variables of Kluitenberg [3–7] and we will evaluate the entropy production of a system when it is subjected to an ultrasound wave. Indeed, in previous papers, this has been done but the system was perturbed by an electric field or mechanical vibrations [8–16]. Moreover, we will apply the so-obtained results to biological systems such as blood.

Materials and methods

For that which regards the values of attenuation coefficient and dispersion we refer to the paper [17, 18].

A theoretical and experimental approach to the investigation of blood

From more than half a century, more and more researchers have approached the study of biological tissues applying some physical methods to the study and characterization of the evolution of the physiological and pathological states. In this contest, the difficulties to detect phenomena occurring at a cellular and intracellular level are huge since high is the number of variables to control during an experiment. On the other hand, if, during an experiment, the contribution of some variables was neglected the real system will be substituted with an ideal one in which the description of results obviously will be incomplete. However, the choice of the selected variables to control an experiment is function of the phenomenal object of study, and in many cases an accurate choice will give a sufficiently good description of the system. Obviously, it is very difficult to identify these variables; the way to follow for the choice of the variables that can be neglected in an experiment is to check their influences by conducting a sufficient number of experiments that show a very small contribution to the phenomenal object of study.

These clarifications allow to take into account many techniques, but we will refer to ultrasound investigation which is one of the most applied being a noninvasive technique and allows a possible *in vivo* investigation [17–22]. Generally such technique led to the determination of two parameters as function of the frequency of perturbation: attenuation and dispersion of the acoustic wave. The knowledge of these parameters allows the study of rheological properties of the medium and they can be regarded as a way for characterization of biological tissues. Here, it will remark that measure of the frequency

characteristic of biological tissues is an issue of biomedical interest since it may help to better understand their biological and pathological behavior. However, a more complete description can be performed by supporting this approach with thermodynamics. The latter is very difficult to be applied because of the inherent complexity of biological tissues which are characterized by a plethora of complex irreversible processes; so these can be framed into the framework of NET. Here we must take into account that biological materials are generally, from a thermodynamics point of view, an open system.

Indeed, a central point of formalism of NET is the definition of appropriate thermodynamic generalized forces (also called affinity) and fluxes to fully represent the entropy variation. Generalized forces and fluxes are connected by relationships, called phenomenological equations, which in many cases can be considered linear. The coefficients that appear in these are called phenomenological coefficients: they are constant in time and dynamically vary depending on the excitation frequency spectrum.

A deeper insight into the biological phenomena can be obtained by Kluitenberg’s thermodynamic theory by means of the definition of some other linear relationship, called state equations, in which appear the so-called state coefficients [3–7]. The theory is based entirely on the introduction of a set of so-called internal variables associated to internal degree of freedom of the medium by means of which a more complete description is possible. So it is clear that this theory is suitable for the study of phenomena that occur in biological tissues.

The applicability of this theory is based essentially on the analytical computation of these coefficients, the role of which is to determine values of internal variables introduced and, therefore, the entropy production [19, 23–25]. Moreover, these coefficients allow to qualitatively discriminate among classes of phenomena which cannot be observed in any other way. Therefore, a correlation between these coefficients and quantities experimentally measurable allows to a deeper knowledge of biological phenomena.

Thus, we have a more complete view since an experimental investigation will be supported by a thermodynamic one of irreversible processes.

Ultrasound mechanism of absorption, as above, is minimally invasive and leads to good results in prevention and treatment of pathology. It is based on time deformation (oscillations) of materials at atomic or molecular level; these are forced into vibrational motion about their equilibrium position. When a particle is displaced from this position it reacts by raising internal restoration forces that oppose to this displacement. The individual particles do not progress through the medium but their vibrations will propagate building a compression wave.

Since we treat with the blood, which normally is in liquid state, we will consider only a harmonic longitudinal wave. It is well known that such a wave is characterized by the complex wave vector $\underline{K} = \underline{K}_1 + i\underline{K}_2$ in which the real part $\underline{K}_1$ is connected to phase velocity and attenuation $\underline{K}_2$ to the rates at which the amplitude of the wave is reduced. Obviously, these two quantities vary with the frequency of perturbation giving precious information on the mechanism that occurs during the wave–blood interaction.

Indeed, there are several mechanisms which induce variation of $\underline{K}_1$ and $\underline{K}_2$ as well explained in Ref. [17, 18, 20–22]. These occur at a molecular and at a cellular level. By taking into account the blood model introduced in the next section, the attenuation at cellular level is attributed to the interaction between the cell surface (membrane) and the fluid in which they are suspended (plasma) [17], while the attenuation at the molecular level is attributed to intracellular and extracellular (plasma) mechanisms [17, 18, 20–22]. For what concerns the absorption mechanism at the cellular level, it is attributed to the viscous relative motion and to the thermal conduction due to the inhomogeneous regions of the blood and to the scattering phenomena [17]. At the molecular level, absorption is attributed to classical relaxation phenomena (viscosity and thermal conduction). In this paper, we investigate some rheological properties of human blood cell in saline solution and whole blood making a comparison between them; moreover, we will obtain important thermodynamic information through the knowledge of the wave vector only.

In detail, after the introduction of aforementioned phenomenological and state coefficients, we derive the relationships which correlate them to the wave vector $\underline{K}$, experimentally measurable with ultrasound techniques. This allows us to obtain a spectrum of the coefficients as function of the frequency of the ultrasonic wave. Therefore, since the coefficients are related to particular phenomena occurring inside the medium (blood) as elasticity, inelasticity, fluidity and viscosity [7], we obtain a description of these phenomena as function of frequency. This knowledge allows to determine the entropy production and has the role of relating entropy sources with irreversible processes that occur in the blood.

This new approach introduces a new technique to characterize blood and its components from a rheological point of view. Moreover, it can be used in the physiological and pathological investigation of blood, as well as in diagnostics; it may contribute to the development of new methodologies and biomedical devices for diagnosis and prognosis of diseases as well as for monitoring the repressiveness of some diseases to therapeutic agents.

Mathematical model of the blood and basic axiom

Human blood contributes to 7 % of the body weight; its main roles are: carries the nutrients and molecular oxygen essential for the cellular metabolism and at same time it has an important thermoregulatory role. From the electrical point of view, the human blood is a very inhomogeneous solution composed of plasma and several kinds of cells; these cells called corpuscles or “formed elements” consist of erythrocytes (red blood cells, RBCs), leukocytes (white blood cells, WBCs), and thrombocytes (platelets). By volume, the RBCs constitute about 45 % of the whole blood, the plasma about 54.3 % and WBCs about 0.7 %.

RBCs have a biconcave disk shape and are small in size (7 μm); they are highly specialized cells that have no nucleus, no mitochondria and no endoplasmic reticulum, and provide as much space as possible for hemoglobin (4–5 mm). Hemoglobin is a globular protein, the main function of which is to transport oxygen from lungs to respiring tissues. WBCs differ from the RBCs because they always have a nucleus and their shape is usually spherical. There are two main groups of WBCs: phagocytes and lymphocytes. Phagocytes, which destroy invading microorganisms by phagocytosis, are characterized by the lobed nuclei and granular cytoplasm. Lymphocytes that destroy microorganisms by secreting antibodies are smaller than phagocytes and are recognized by large nucleus and only a small amount of cytoplasm. In the blood of all vertebrates, plasma consists principally of water and contains a wide variety of substances such as proteins, cholesterol, hormones, amino acids, glucose, salts, vitamins, and antibodies. Among these an important role is performed by the glucose sugar, selected as central carbohydrate for its metabolic and structural functions [26]. Its normal concentration is regulated by several hormones but in some metabolic disorders as well as in diabetes, glucose concentration in the blood can reach toxic levels responsible for the functional and structural alterations of the cells constituting the hematic tissue.

Our approach is based on the assumption (supported by experiments) that in biological tissue hidden mechanical phenomena occur to which corresponds internal degree of freedom which must be taken into account for a more detailed description.

So we consider the blood as a viscoanelastic fluid in which the three major micro-particles are suspended (RBCs, WBCs and MLPs which are lighter than RBCs and WBCs) and distributed in a homogeneous way [17].

This allows us to consider the blood as a continuum medium which obeys the continuum mechanics indefinite equations and Maxwell’s equation in the matter with a mass density ρ , which varies as a function of the blood’ elements under consideration. It easy to prove that, by

considering the blood as an incompressible fluid, the Lagrangian derivative $\frac{d\rho}{dt}$ of the mass density will result in zero. In other words, the mass density is almost constant for each fluid element during the motion. This is justified if we consider the mass density of the three major micro-particles of the blood (RBCs, WBCs, and MLPs).

Such an assumption is also in agreement with the basic axiom on the local and instantaneous equilibrium: 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.

Moreover, the length and timescale of these subsystems are infinitesimally small from a macroscopic point of view, but from molecular point of view they are still large, such that the subsystem contains enough molecules so that the average taken on the number of molecules has deterministic significance.

Since we will study the blood when it is subject to an external harmonic ultrasound perturbation, we assume that in this case the axiom of local and instantaneous equilibrium will be satisfied; this is true for a sufficiently low-intensity perturbation.

Remarks on Kluitenberg theory

Generally, it is assumed that the specific entropy s of an elastic dielectric is a function of the specific internal energy u , the strain tensor ε_{ik} :

$$s = s(u|\varepsilon_{ik}) \quad (1)$$

The new Kluitenberg's idea consists in the assumption that there is a vector field $\varepsilon_{ik}^{(1)}$ which plays the role of thermodynamic internal degree of freedom and which influences the strain. In the theory, it is assumed that the specific entropy (which we indicate with s) has the following functional dependence [7]

$$s = s\left(u\left|\varepsilon_{ik}\right|\varepsilon_{ik}^{(1)}\right) \quad (2)$$

From which it follows:

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

where it can be shown that by assuming there exists an R state at the constant temperature T_0 results in [7]:

$$\tau_{ik}^{(eq)}(T_0) = \tau_{ik(0)}^{(eq)} = 0$$

The tensor strain is additively composed of two parts $\varepsilon_{ik}^{(0)}$ and $\varepsilon_{ik}^{(1)}$

$$\varepsilon_{ik} = \varepsilon_{ik}^{(0)} + \varepsilon_{ik}^{(1)} \quad (3)$$

Moreover, it can be shown that the change of both $\varepsilon_{ik}^{(0)}$ and $\varepsilon_{ik}^{(1)}$ contributes to the entropy production and, therefore, they represent two irreversible processes.

So we can introduce the viscous stress tensor $\tau_{ik}^{(vi)}$:

$$\tau_{ik}^{(vi)} = \tau_{ik} - \tau_{ik}^{(eq)} \quad (4)$$

where τ_{ik} is the stress tensor which occurs in indefinite equations.

Now if we assume that only one microscopic phenomenon occurs which gives rise to the inelastic strain, it is possible to introduce this contribution as the internal degree of freedom in the Gibbs relation and together with the first law of thermodynamics an explicit form of the entropy production can be obtained. From the so-obtained expression, taking into account the usual procedure of the NET, the following phenomenological equations can be obtained [7]:

$$\tau^{(vi)} = \eta_s^{(0,0)} \frac{d\varepsilon}{dt} \quad (5)$$

$$\frac{d\varepsilon^{(1)}}{dt} = \eta_s^{(1,1)} \tau^{(1)} \quad (6)$$

in which we neglect the cross effects.

These together with linearized state equations [7]

$$\tau^{(eq)} = a^{(0,0)}(\varepsilon - \varepsilon^{(1)}) = a^{(0,0)}\varepsilon^{(0)} \quad (7)$$

$$\tau^{(1)} = a^{(0,0)}\varepsilon - a^{(1,1)}\varepsilon^{(1)} \quad (8)$$

Lead to the so-called relaxation equation for scalar part τ of the stress tensor and the scalar part ε of the strain tensor:

$$\frac{d\tau}{dt} + R_0^{(\tau)}\tau = R_0^{(\varepsilon)}\varepsilon + R_1^{(\varepsilon)}\frac{d\varepsilon}{dt} + R_2^{(\varepsilon)}\frac{d^2\varepsilon}{dt^2} \quad (9)$$

where

$$\begin{aligned} R_0^{(\tau)} &= b^{(1,1)}\eta_v^{(1,1)} = 1/\sigma, & R_1^{(\varepsilon)} &= b^{(0,0)} + b^{(1,1)}\eta_v^{(1,1)}\eta_v^{(0,0)} \\ R_0^{(\varepsilon)} &= b^{(0,0)}(b^{(1,1)} - b^{(0,0)})\eta_v^{(1,1)}, & R_2^{(\varepsilon)} &= \eta_v^{(0,0)} \end{aligned} \quad (10)$$

in which $b^{(0,0)}$ and $b^{(1,1)}$ are the state coefficients related to elasticity and inelasticity phenomena, respectively, while $\eta_v^{(0,0)}$ and $\eta_v^{(1,1)}$ are phenomenological coefficients related to viscosity and fluidity phenomena, respectively [7].

Mathematical approach

Let $u(u1, u2, u3)$ be a displacement of the form

$$\begin{cases} u_1 = Ae^{i(kx - \omega t)} \\ u_2 = u_3 = 0 \end{cases} \quad (11)$$

It represents a longitudinal wave which propagates in the direction of x -axis. Here, ω is the angular frequency, A the amplitude of the wave and $K = K_1 + iK_2$ is the complex wave number where K_1 and K_2 are connected to phase velocity v_s

$$v_s = \frac{\omega}{k_1} \quad (12)$$

and to attenuation, respectively. By remembering the expression of the strain tensor

$$\varepsilon_{ik} = \frac{1}{2} \left(\frac{\partial u_i}{\partial x_k} + \frac{\partial u_k}{\partial x_i} \right) \quad (13)$$

it is easy to show from (11) and (13):

$$\begin{aligned} \varepsilon_{11} &= iAke^{i(kx-\omega t)} \\ \varepsilon_{\alpha\beta} &= 0, \quad \alpha \neq 1, \quad \beta \neq 1 \\ \varepsilon &= \frac{1}{3} \varepsilon_{ii} = \frac{1}{3} iAke^{i(kx-\omega t)} \end{aligned} \quad (14)$$

If we substitute Eq. (14)₃ in (9), the integration of the so-obtained differential equation leads to the solution:

$$\tau = \frac{1}{3} A^{(*)} e^{i(kx-\omega t)} + ce^{R_0^{(e)}/\omega} \quad (15)$$

where

$$A^{(*)} = \frac{Ak(iR_0^{(e)} + \omega R_1^{(e)} - \omega^2 R_2^{(e)})}{R_0^{(\tau)} - i\omega} \quad (16)$$

We neglect the second term of Eq. (15) because it can be proved that it represents a transitory phenomena; Eq. (15) becomes

$$\tau = \frac{1}{3} A^{(*)} e^{i(kx-\omega t)} \quad (17)$$

By substituting Eqs. (17) and (11) in the indefinite equation

$$\rho \frac{\partial^2 u_1}{\partial t^2} = \frac{\partial \tau}{\partial x} \quad (18)$$

after some manipulations it follows:

$$K_1^2 = 3\rho\omega^2 \frac{R_0^{(\tau)} R_0^{(e)} + \omega^2 (R_1^{(e)} - R_0^{(\tau)} R_2^{(e)})}{(R_0^{(e)} - \omega^2 R_2^{(e)}) + \omega^2 R_1^{(e)^2}} \quad (19)$$

$$K_1 K_2 = \frac{2}{3} \rho\omega^3 \frac{R_0^{(\tau)} R_1^{(e)} - R_0^{(e)} + \omega^2 R_2^{(e)}}{(R_0^{(e)} - \omega^2 R_2^{(e)}) + \omega^2 R_1^{(e)^2}} \quad (20)$$

and from these by solving with respect to $R_0^{(e)}$ and $R_1^{(e)}$:

$$R_0^{(e)} = \omega^2 R_2^{(e)} + \frac{3\rho\omega^2}{(K_1^2 + k_2^2)^2} [R_0^{(\tau)} (K_1^2 - k_2^2) - 2\omega K_1 K_2] \quad (21)$$

$$R_1^{(e)} = \frac{3\omega\rho}{(K_1^2 + k_2^2)^2} [\omega(K_1^2 - k_2^2) + 2R_0^{(\tau)} K_1 K_2] \quad (22)$$

These last two are functions of the experimentally known K_1 , K_2 and ω , and of the unknown functions $R_0^{(\tau)}$ and $R_2^{(e)}$. So for an experimental evaluation of $R_0^{(e)}$ and $R_1^{(e)}$, it is necessary to have knowledge of $R_0^{(\tau)}$ and $R_2^{(e)}$. By taking into account the linear response theory, we remember the following relations

$$L_1 = \frac{\rho\omega^2 (K_1^2 - k_2^2)}{(K_1^2 + k_2^2)^2} \quad (23)$$

$$L_2 = \frac{2\rho\omega K_1 K_2}{(K_1^2 + k_2^2)^2} \quad (24)$$

where L_1 and L_2 are storage and loss longitudinal moduli, respectively. By evaluating the relaxed value $L_{2R} = L_2(\omega_R)$ and taking into account the relaxation time σ , we can put

$$\begin{cases} R_2^{(e)} = \frac{L_{2R}}{\omega} \\ R_0^{(\tau)} = \frac{1}{\sigma} \end{cases} \quad (25)$$

The position (25) allows to a complete experimental indirect evaluation of $R_0^{(e)}$ and $R_1^{(e)}$. Now if we solve the system of Eqs. (19) and (20) with respect to $b^{(0,0)}$, $b^{(1,1)}$, $\eta_v^{(0,0)}$ and $\eta_v^{(1,1)}$, we obtain:

$$\begin{aligned} b^{(0,0)} &= 3\rho\omega \left[\frac{2K_1 K_2}{\sigma} + \omega(K_1^2 - k_2^2) \right] - \frac{L_{2R}}{\omega\sigma} \\ b^{(1,1)} &= \frac{\left[3\rho\omega \left(\frac{2K_1 K_2}{\sigma} + \omega(K_1^2 - k_2^2) \right) - R_0^{(e)} \frac{(K_1^2 + k_2^2)^2}{\sigma} \right]^2}{\frac{1}{\sigma} \left(\omega^2 + \frac{1}{\sigma^2} \right) \left[6\rho\omega K_1 K_2 - \frac{L_{2R}}{\omega} (K_1^2 + k_2^2)^2 \right]} \\ \eta_v^{(1,1)} &= \frac{\frac{1}{\sigma} \left(\omega^2 + \frac{1}{\sigma^2} \right) \left[6\rho\omega K_1 K_2 - \frac{L_{2R}}{\omega} (K_1^2 + k_2^2)^2 \right]}{\left[3\rho\omega \left(\frac{2K_1 K_2}{\sigma} + \omega(K_1^2 - k_2^2) \right) - R_0^{(e)} \frac{(K_1^2 + k_2^2)^2}{\sigma} \right]^2} \\ \eta_v^{(0,0)} &= \frac{L_{2R}}{\omega} \end{aligned} \quad (26)$$

It is easy to obtain the expression for entropy production [...]

$$\sigma^{(s)} = \frac{1}{T} \left[\eta_s^{(0,0)} \left(\frac{dy}{dt} \right)^2 + \eta_s^{(v)} \tau^{(1)^2} \right] \quad (27)$$

In fact taking into account Eqs. (5)–(8) and (26), one obtains:

$$\begin{aligned} \sigma^{(s)} &= \frac{A^2}{3T} e^{-2k_2 x} \left\{ (\eta_s^{(0,0)} \omega^2 k_1^2 + \eta_s^{(1,1)} k_2^2 \Gamma^2) \cos^2 \beta \right. \\ &\quad + (\eta_s^{(1,1)} \Gamma^2 k_1^2 + \eta_s^{(0,0)} k_2^2 \omega^2) \sin^2 \beta \\ &\quad \left. - 2k_1 k_2 \sin \beta \cos \beta (\eta_s^{(0,0)} \omega^2 - \eta_s^{(1,1)} \Gamma^2) \right\} \end{aligned} \quad (28)$$

Fig. 1 Coefficient $b^{(0,0)}$ (Eq. (26)₁) for both RBCs and whole blood in the frequency range 0–70 MHz at 37 °C

Fig. 2 Coefficient $b^{(1,1)}$ (Eq. (26)₂) for both RBCs and whole blood in the frequency range 0–70 MHz at 37 °C

where

$$\beta = k_1 x - \omega t \quad \text{and} \quad \Gamma = b^{(0,0)} - b^{(1,1)} \left(1 - \frac{L_1}{b^{(0,0)}} \right) \quad (29)$$

Now we are able to evaluate the functions (26) and the entropy production (28) for human RBCs in saline with the total hemoglobin concentration of 15 g/dL at 37 °C and for whole human blood with an average total hemoglobin concentration of 15 g/dL at 37 °C and compare these functions. Our results are plotted in Figs. 1, 2, 3, 4, 5 and 6.

Results and conclusions

In this section, we analyze the coefficient aforementioned both for RBCs in saline solution and whole blood. In particular, we will compare viscoelastic properties of the

samples and connect these to specific interaction between blood components.

In that which follows, we introduce the suffix “s” and “w” to refer to RBCs in saline and whole blood, respectively.

We start with Fig. 1 in which it is plotted coefficient $b^{(0,0)}$ (Eq. (26)₁) for RBCs in saline and whole blood, respectively. By remembering that $b^{(0,0)}$ is related to elastic phenomena (we justify further on this terminology) we note that below the frequency of approximately 4×10^7 Hz both RBCs and whole blood show a peak, but the whole blood has more elastic behavior and this characteristic is preserved in the total frequency range considered. A general decrease of the elastic behavior is observed at the frequency higher than 4×10^7 Hz; in this range, the highlighted differences between RBCs and whole blood might be due to plasma, WBCs and platelets, respectively, or all the components.

Fig. 3 Coefficient $\eta_s^{(1,1)}$ (Eq. (26)₃) for both RBCs and whole blood in the frequency range 0–70 MHz at 37 °C

We think that this difference is mainly due to plasma and its several components [17].

The coefficient $b^{(1,1)}$ related to inelastic phenomena (Eq. (26)₂) is plotted in Fig. 2, and no significant differences are observed between RBCs and whole blood for all frequencies. In detail, the whole blood shows a lesser inelasticity than RBCs with a decrement of inelasticity for both samples, but we can observe that there is an appreciable change around the frequency of 4×10^7 Hz where elastic component shows a peak (see Fig. 1). Moreover, it is important to observe that inelastic component is predominant in both the solutions (see Fig. 5). These findings suggest that the platelets, WBCs and plasma do not influence the inelastic properties of the blood and, therefore, what observed is mainly due to the presence of RBCs.

In Fig. 3, the coefficient $\eta_v^{(1,1)}$ for RBCs and whole blood (Eq. (26)₃) is plotted. The meaning of this coefficient is related to fluidity and taking into account Eq. (10)₁ we note an inverse proportionality between it and the coefficient $b^{(1,1)}$. Therefore, for this coefficient the same consideration applied to $b^{(1,1)}$ can be performed but with inverse results, i.e., the greater inelastic behavior for $b^{(1,1)}$ became lesser behavior for $\eta_v^{(1,1)}$, etc.

In Fig. 4, where we plot the coefficient $\eta_v^{(0,0)}$ (Eq. (26)₄) related to viscous phenomena, we note, as it is intuitive, that whole blood shows a greater viscosity with respect to RBCs in all ranges of frequencies (opposite to the coefficient $\eta_v^{(1,1)}$ related to fluidity). We associate this behavior mainly to the presence of the WBCs and platelets.

From a thermodynamic point of view, the more important result is represented in Fig. 6, in which the trend of entropy production (Eq. (28)) is plotted. But before commenting on Fig. 6, we will remember some thermodynamic

Fig. 4 Coefficient $\eta_s^{(0,0)}$ (Eq. (26)₄) for both RBCs and whole blood in the frequency range 0–70 MHz at 37 °C

results of Kluitenberg's theory for a better physical approach to biological irreversible processes.

In particular, we remind that the level of irreversibility of a phenomena is described by the level of entropy production in the mathematical expression of which appear both the coefficients $b^{(0,0)}$ and $b^{(1,1)}$ related to irreversible phenomena (see Eqs. (28), (29)). However, in some cases it occurs that the coefficient $b^{(0,0)}$ does not appear in the expression of the entropy production or it is small enough to be negligible. This means that in these cases this coefficient is related to reversible phenomena (this is the motivation for which it is called “elastic” coefficient). Now, by observing Fig. 5, we note that $b^{(0,0)}$ is smaller than $b^{(1,1)}$ and, therefore, it is negligible in the valuation of the entropy production. This means that inelastic phenomena

Fig. 5 Coefficients $b^{(0,0)}$, $b^{(1,1)}$, $\eta_s^{(1,1)}$, $\eta_s^{(0,0)}$ for both RBCs and whole blood in the frequency range 0–70 MHz at 37 °C

Fig. 6 Trend of entropy production (Eq. (26)) for both RBCs and whole blood in the frequency range 0–70 MHz at 37 °C

are predominant for both RBCs and whole blood and, therefore, they are the major source of irreversibility together with viscous phenomena.

By observing Fig. 6, we note that entropy production in RBCs is lesser with respect to whole blood. This means that the whole blood is more orderly than RBC, i.e., complex chemical substances have a greater degree of order of the components. These conclusions are based on the hypothesis that the system is isolated. Obviously, this is approximately true but for both the systems in equal measure.

Last but not least, our comparative study on the rheological properties of whole blood and RBCs highlights a peculiar entropy difference between the two systems. Curiously, despite the increased complexity of the whole blood, the entropy value for this system is less than that

observed for RBCs in saline. Then, in the course of time, embedding of RBCs in a complex medium such as blood in which there are RBCs, WBCs, platelets and other proteins has contributed greatly to the reduction of the disorderliness of tissue.

In other words, during the evolution, the increased complexity of the blood not only has improved the functionality of the transport and release of oxygen, but also shows a positive contribution to the “life” of the blood system. We note that we have focused our investigation on the study of some properties of the blood, but obviously this methodology can be applied to every medium with viscoelastic characteristics. We have done this in a previous paper but considering ultrasound transversal wave [13].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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