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Molecular characterization of a peculiar blood clot fluidification by theoretical thermodynamic models and entropy production study

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ABSTRACT

In this paper we analyzed thermodynamic functions of blood clot perturbed with a harmonic mechanical waves in the context of the non equilibrium thermodynamic. At a frequency >650 Hz, the clot shows a trend of increasing entropy that confirm what discussed in our previous paper. In details, blood clot seems to tend towards a fluidification process. We hypothesize that the impact of the wave on the blood can trigger a cooperative event of breaking the bonds present inside the clot. This means that a "refractory" state or a threshold is exceeded, beyond which the fluidization starts, probably triggered by the activation of the enzymes. The event is further favored by the intervention of the water molecules that hydrolyze the ATP released by the red blood cells.

1. Introduction

Why is thermodynamics important in the study of biological systems? Generally, thermodynamics studies a macroscopic portion of an event objectively identifiable and describable within the complete validity of the principle of conservation of energy [1]. Such a portion called thermodynamic system is a more general notion than that of a mechanical system because it requires the full validity of the principle of energy conservation. Mechanical context explores only two forms of energy, the kinetic and the potential one. A system is described mechanically through a set of an extraordinarily large number of point, postulating that there is an interaction between points, and writing the equations of motion. It is understood the extremely large number of equations and to solve them it would be necessary to know the initial position and velocity for each point. This is practically impossible, and only an "average" description of the system may be done. This implies replacing the large number of freedom degrees with a smaller number of new degrees. In no one material system like in a biological system, such strategy is necessary. In a biological system the amount of "points" (i.e. of molecules) to be taken into consideration is very large; but what makes very impossible a detailed description is the nature of the interactions between molecules and therefore their mathematical expression. For example, in a single cell, the number of "particles", their diversity and the various types of mutual interaction are very complex; everything is even more difficult when referred to an aggregate of cells such as a tissue. As mentioned above, an average description considerably reduces the number of degrees of freedom. Since energy flows in all degrees of freedom, this description, seems to imply a loss of energy and therefore a violation of the conversion principle. Hence the need to introduce a new form of energy: the internal energy. All this suggests treating the system as a continuous medium definable by means of macroscopic functions such as density, density of force, strain tension, stress tensor, etc. and laws that link these parameters. In these laws there are phenomenological and state coefficients, which characterize the system and depend on the type of perturbation to which the system is subjected (as we will see later). In a previous paper, the aforementioned phenomenological and state coefficients have been determined in a system perturbed by a harmonic action of frequency ω [2]; in this paper we aim to obtain the macroscopic functions that appear in Kluitenberg thermodynamics as a function of the perturbation frequency, in the blood clot. Finally, their analytical expression will provide the possibility of determining the entropy production. Since the knowledge of these functions provides a new and more complete vision of the rheological characterization, allowing to highlight and study new phenomena that occur in the blood if disturbed by a harmonic action. The calculus of the entropy production is very important because it can be connected to the global evolution of physiological and pathological phenomena. Entropy can indicate the evolution of pathologies and help to evidence therapeutic effects. On the other hand, the macroscopic rheological functions allow one to observe and study physiological and pathological details generally not evident in common investigations. Also, this approach has been used by us in previous papers considering dielectric relaxation phenomena [3–7]. From a theoretical point of view the introduction of rheological functions is well known in the literature

Abbreviations: ATP, adenosine-5′-triphosphate; ADP, adenosine diphosphate.

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[1], but their experimental evaluation in the case of harmonic perturbation has not been determined so far, precluding the possibility of applying the theory to any biological system and not [3, 8–10]. In this paper, referring to experimental data obtained by Schmitt et al. [11], we will find the link between all rheological thermodynamic quantities and those that can be measured experimentally, in order to obtain the spectrum of rheological frequency functions in blood. All this highlights a well-known role of thermodynamics in the study of physiological, pathological and therapeutic phenomena and at the same time reveals its importance in the prevention of pathologies.

Future investigations about the use of these perturbations, generated by appropriate instruments, might provide novel therapeutic strategies not only for thrombolytic therapy but also in the prophylaxis of clot generation. In this context, a valid support is the rheological coagulation degree spectrum (Nu) which being correlated to the viscosity and fluidity coefficients of the blood, restricts and selects the field of application being strictly [2].

1.1. Stress and strain

It is well known that, Rheology studies the stress as function of strain. From the mechanics point of view of the continuous media, the internal tension state relative to a point is represented by two symmetrical double tensors called Cauchy stress tensor and strain tensor. From the thermodynamic point of view the internal stress state is studied assuming the specific entropy as a function of both the specific internal energy u and the strain described by the (double symmetric) strain tensor ε_{ik}. That is, said s the specific entropy, will be:

$$s = s(u, \varepsilon_{ik}) \tag{1}$$

and

$$\frac{1}{T} = \frac{\partial s}{\partial u} \tag{2}$$

$$\tau_{ik} = -T\rho \frac{\partial s}{\partial \varepsilon_{ik}} \tag{3}$$

where T is the temperature we supposed to be constant, ρ the mass density and T_{ik} the symmetrical stress tensor. However, through simple reflections we are convinced that, for a thermodynamic description the set of variables introduced is incomplete to study more complex phenomena such as chemical reactions, inelastic deformations, relaxation phenomena, etc. We will not go into details of the complete theory for which we refer to the bibliography [16] we only highlight some aspects that make the theory a very important method of investigation to study biological materials because new rheological functions are introduced describing relaxation phenomena not considered in a classical description. In a previous work we have explained what we mean by elastic deformation, inelastic, viscous, etc. [16]. Bearing in mind this, supposing that in a medium "n" microscopic phenomena originate "n" inelastic deformations described by the tensors and $\varepsilon_{ik}^{(h)}$ (h = 1,2,3 … n) it demonstrates [16] that the deformation tensor ε_{ik} can be considered as the contribution of an elastic part $\varepsilon_{ik}^{(in)}$ such that:

$$\varepsilon_{ik} = \varepsilon_{ik}^{(0)} + \varepsilon_{ik}^{(in)} \tag{4}$$

$$\varepsilon_{ik}^{(in)} = \sum_{h=1}^{n} \varepsilon_{ik}^{(h)} \tag{5}$$

being $\varepsilon_{ik}^{(h)}$ the contribution of the h-th microscopic phenomenon to inelastic deformation. Such a split of the strain tensor is possible [2, 5, 7, 8] introducing, in the functional dependence of the entropy, some symmetric tensor variables Ω_{ik} and identifying these variables with the strain tensor in a particular state of the system [2, 8]. In this paper, to study the biological tissues we suppose that the microscopic phenomenon occurring in the medium is identified by a single inelastic strain tensor that we indicate with $\varepsilon_{ik}^{(1)}$, to avoid complicating the mathematical formalism. The Eq. (1) will be written:

$$s = s\left(u, \varepsilon_{ik}, \varepsilon_{ik}^{(1)}\right) \tag{6}$$

where we use the same symbol s for the new functional dependency. In analogy with the Eqs. (29) and (3) we obtain [2]:

$$\frac{1}{T} = \frac{\partial s\left(u\middle|\varepsilon_{ik}\middle|\varepsilon_{ik}^{(1)}\right)}{\partial u} \tag{7}$$

$$\tau_{ik}^{(eq)} = -T\rho \frac{\partial s\left(u\middle|\varepsilon_{ik}\middle|\varepsilon_{ik}^{(1)}\right)}{\varepsilon_{ik}} \tag{8}$$

$$\tau_{ik}^{(1)} = T \frac{\partial s\left(u\middle|\varepsilon_{ik}\middle|\varepsilon_{ik}^{(1)}\right)}{\partial \varepsilon_{ik}^{(1)}} \tag{9}$$

where τ_{ik} is the equilibrium stress tensor and $\tau_{ik}^{(1)}$ is affinity stress tensor. The viscous stress tensor $\tau_{ik}^{(vi)}$ is then introduced and defined as:

$$\tau_{ik}^{(vi)} = \tau_{ik} - \tau_{ik}^{(eq)} \tag{10}$$

τ_{ik} is the stress tensor that appears in the indefinite equations. If $\tau_{ik}^{(vi)} = 0$, i.e. there are no viscous phenomena, it results:

$$\tau_{ik} = \tau_{ik}^{(eq)} \tag{11}$$

Considering only shear strain and stress it demonstrates [16] that the entropy production per unit of time is:

$$\sigma^{(s)} = \frac{1}{T}\left(\tau_{ik}^{(vi)} \frac{d\varepsilon_{ik}}{dt} + \tau_{ik}^{(1)} \frac{d\varepsilon_{ik}^{(1)}}{dt}\right) \tag{12}$$

where, we used the Einstein convention for repeated indexes. For our purposes we consider the case in which only one component of the deformation and stress tensor is different from zero and we indicate them with ε and τ. In this case Eq. (12) is:

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

From Eq. (13) and in linear approximation we obtain the following phenomenological and state equations [16].

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

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

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

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

where $a^{(0,0)}$ and $a^{(1,1)}$ are coefficients of state respectively related to elastic and inelastic phenomena, while $\eta_s^{(0,0)}$ and $\eta_s^{(1,1)}$ are phenomenological coefficients respectively related to viscous and fluidity phenomena. We have neglected cross effects between viscous and inelastic flows. From this equation it is shown that it is possible to derive the