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Low frequency dielectric characteristics of human blood: A non-equilibrium thermodynamic approach

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ABSTRACT

In this paper we apply some recent results of non-equilibrium thermodynamic to human blood. In particular we focus our attention on dielectric α-dispersion region which presents some not clear aspects. In the contest of Kluitenberg's non-equilibrium thermodynamic theory we determine the phenomenological and state coefficients that appear in the aforementioned theory in the case of a harmonic perturbation. This is possible by invoking a classical linear response theory and correlating dielectric storage and loss moduli to the aforementioned coefficients. These coefficients allow us to determine the elastic and inelastic parts of the polarization P so as to study some dielectric effects of blood in the α dispersion region. By taking into account these results we ascribe some relevant polarization effects, as the dispersion aforementioned, to white blood cells in agreement to some authors as Abdalla. Moreover we determine the trend of entropy production observing more and more irreversibility as increasing of the frequency of perturbation.

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1. Introduction

In a biological tissue, takes place a plethora of complex biochemical and biophysical phenomena. As well-known, from the point of view of the energy involved in physical processes, they may be framed in two basic classes: conservative and dissipative phenomena. Of course a process where absolutely no energy is dissipated is an idealization and since in reality no phenomena are elementary: they are composed by both classes of phenomena.

It is evident that in the biological setting, e.g. in a tissue specimen, the energetic properties are difficult to be characterized, due to its inherent complexity. Indeed, the number of variables describing a system such as a biological tissue is very large and a reduction of this number means substituting the real system with an ideal one whose description is limited to the chosen variables. As a consequence, it is very difficult to identify the variables giving the best – or at least a sufficiently good – description of the system in study.

Modern theoretical methods of non-equilibrium thermodynamics (NET), by means of a suitable choice of the aforementioned variable, allow summarizing — and to some extent classifying — the characteristics of a material by means of a limited set of parameters called *phenomenological and state coefficients* [1]. Thus irreversible processes characterizing biological tissues may ideally be framed in the theory of NET.

These coefficients, fundamental in NET, have the role of relating entropy sources to irreversible processes that occur inside a medium. Thus, they summarize some physical phenomena occurring in the medium in study. Indeed, a central point of the formalism of NET is the definition of appropriate thermodynamic generalized forces (also called affinities) and fluxes in order 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 of those linear relationships are called *phenomenological coefficients* [1]. Of course, these coefficients (constant in time) are dynamically varying and they depend on the frequency spectrum of the excitations [2,3].

A more deep insight in the underlying phenomena is obtained by the Kluitenberg's thermodynamic theory by means of the introduction of *internal variables* associated to the internal degree of freedom [4–6]. These lead to particular linear relationships in which appear the *state and phenomenological coefficients*. Indeed, they allow to qualitatively discriminate among classes of phenomena, and to provide quantitative estimate.

Recently Farsaci et al. [7] proposed, a suitable extension of this theory an approximate form for those coefficients, which allows their measurement with standard techniques when the medium is subject to a harmonic perturbation [8].

A measurement of the frequency characteristics of biological tissues by taking into account detailed phenomena is an issue of biomedical interest since it may allow to better understand their physical properties,

Abbreviations: NET, non-equilibrium thermodynamics; RBCs, red blood cells; WBCs, white blood cells; MPs, micro-particles.

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and it might allow to perform comparison between physiological and pathological tissues [9]. Moreover, in recent years, starting from the observation that the physical behavior of many materials does not exactly follow the classical theoretical laws of dielectric (and mechanical), fractional physic theories (i.e. making use of the fractional calculus) have been developed. Thus, since many physiological tissues and pathological ones are characterized by fractal structures, it is possible to extend the NET approach by introducing a fractional dependence in the input–output physical relationships in the domain of frequency. This should be of particular utility in case of the analysis of those tissues that have a higher degree of self-organization (for example liver and tumor tissues) for which it is thought that a fractal description should more faithfully describe their growth and homeostatic structure [9].

Our approach consists in the possibility of studying the physical properties and irreversible phenomena that occur in biological tissues (physiological and pathological) by applying the Kluitenberg's NET theory [5,6]. Namely, we shall use some recent extensions of this theory that allow to infer its main characteristic parameters from experimental measures, overcoming a classical limit in the application of NET theory [7,10,11]. Application of this theory to the study of appropriate specimens of biological tissues, allows to determine, in some details, the amount of a single reversible and irreversible phenomenon occurring inside it, by subjecting the biological sample to harmonic perturbations.

It is of interest to observe that the experimental apparatus to be used for dielectric and ultrasound investigations allows for a possible in vivo investigation on biological tissues. In particular by using ultrasound wave the investigation can result in non-invasive, while in a dielectric case it can result in non-invasive if it is carried out on an exterior tissue. Moreover we developed an algorithm which enables to obtain the aforementioned mechanical coefficients only by the knowledge of the wave vector of ultrasound wave of perturbation (similar to ecography) [12]. This leads to a non-invasive method for the study of rheological properties of in vivo tissues (physiological and pathological) which can be used also as diagnostic.

Besides we want to stress another novelty in our approach that consists in the potentiality to investigate the change in the qualitative and quantitative states and in the phenomenological coefficients (i.e. how the underlying physical phenomena are influenced) of pathological samples with respect to physiological ones and how they change in pathological samples before and after the delivery of drugs. This may contribute to the development of new methodologies and biomedical devices for the diagnosis and prognosis of diseases, as well as for monitoring the responsiveness of some diseases to the therapeutic agents (result starts to develop).

This knowledge will impact not only on basic science of medicine and biophysics, but it might have a substantially rapid translation in terms of development of computer tools and physical devices to aid medical doctors in both diagnosis and the response to therapeutic drugs, as well as in monitoring the "natural" evolution of these diseases, in cases where treatment is, unfortunately, not feasible. Generally, one of the aims of clinical research is to individuate targets of diseases that may better represent several stages of illness. The necessity of clinics to have the use of a panel of targets for the diagnosis, prognosis and therapy is always present.

Moreover, the correlation between the mechanical and electric properties with the genetic content of samples, might give a contribution toward the design of tailored therapies, which are significantly more effective and less expensive.

Finally we will remark that our approach is a thermodynamic one and it don't take into account fitting problems. It regards only the introduction and the determination of thermodynamic function, as the entropy, polarization, internal energy, stress tensor……

We are conscious of the difficulties to adapt the mathematical model of the aforementioned theory to the very complex phenomena that occur in biological tissues, but in the next section we will show an application of this approach to human blood and the new information that can be obtained.

Unfortunately our results don't have any direct experimental confirmation, because they consist of obtaining the expression of some fundamental thermodynamic entity as a function of the frequency of perturbation. In particular we obtained the following results:

1. analytical expression of elastic and inelastic polarization vector ($P^{(0)}$, $P^{(1)}$);
2. analytical expression of elastic and inelastic state coefficients $a^{(0,0)}$, $a^{(1,1)}$ characteristic of the medium;
3. analytical expression of coefficient $L^{(1,1)}$ and coefficient $L^{(0,0)}$ related to irreversible processes due to displacement current associated to temporal variation of the inelastic part of polarization $P^{(1)}$ and to temporal variation of vector P respectively;
4. analytical expression of inelastic electric field $E^{(1)}$ related to temporal variation of the inelastic part of polarization $P^{(1)}$;
5. analytical expression of entropy production.

No results of this kind exist in literature. This will be clear in the next sections.

2. Material and methods

2.1. Human blood

Human blood is a complex biological system, important for its physiological function to deliver oxygen and nutrients as well as vitamins and metabolites to each part of the body.

The peculiarity of this tissue, to be able to reach every part of the body and its easy accessibility as a biological sample for analysis, makes the acquisition of precise knowledge of biological and electrical properties of blood and its constituents of great importance in medicine and biology for rapid diagnosis and new therapy-methods. In particular, the use of blood as a diagnostic medium of human diseases represents not only a noninvasive method of analysis, but also a distinctive signal of human health because changes in its physiology even produce changes in the blood electrical properties [13,14]. When blood is exposed to an alternating electric field various mechanisms of polarization can be realized and effectively measured using the dielectric spectroscopy. In general, the dielectric properties of the blood vary significantly from those of other biological tissues [15–17].

From the electric point of view, blood is considered as a heterogeneous medium essentially constituted of 55% plasma and 45% cells such as red blood cells (RBCs), white blood cells (WBCs) and platelets all of which with different functions and structures. Plasma in turn contains many different micro-particles (MPs) such as proteins, salts, hormones, antibodies and glucose, whose contribution to the dielectric increment in comparison with whole blood is around 1% and could be considered negligible. Differently from RBCs, biconcave anucleated cells containing hemoglobin molecules, which make up 99% of the total blood cells and are the dominant contributors of the dielectric increment [18,19].

However, in consequence of some molecular diseases (such as diabetes mellitus disorder, hyper-cholesterolemia, hyper-uric acid) or during drug therapies (such as chemotherapy or the regular intake of psychiatric drugs) the blood constituents may vary and alter the electric properties of the blood [13,20]. In consequence of this, the study of the electrical properties of the blood requires much attention but if understood they can give significant contributions to medicine and human health. In general, blood shows three distinct dielectric dispersion regions represented by α, β, and γ. The α dispersion is a matter of controversy, it occurs within a frequency range between 1 Hz and 10^4 Hz [16] and seems associated with the diffusion process of ions [21,22]. The β dispersion arises within the range of 10^4 Hz to 10^7 Hz, it occurs as a result of the dielectric properties of the cell membrane and its interaction with the extra- and intracellular matrices. Other contributions to the β dispersion

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