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Gaussian distribution of relaxation through human blood

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ABSTRACT

The complicated structure of human blood has been characterized based on relaxation time, τ, and the Cole–Cole parameter, α, obtained from dielectric measurements. As previously reported by different authors, the experimental data show net deviation from the classical Debye model with certain distribution of relaxation times (D_τ). Plots of α versus width of the relaxation rate distribution of micro-particles inside the blood show that D_τ drastically affects the dielectric properties of the fluid. The mathematical function of D_τ is found to be Gaussian and we find that the α values of normal blood have net lower magnitude than that of diabetic blood. These results suggest that glucose in blood increases the broadness of the parameter α, which have significant importance in diabetic-biosensor manufacture.

1. Introduction

Recently [1], measuring the complex permittivity in blood and human tissue in general has become a common practice with several clinical applications. For example, different applications based on bioimpedance use the technique of fitting the measured complex permittivity data to a model described by the Cole equation and estimating the Cole parameter [2] in skin tumor (cancer) detection [3], respiration monitoring, determined cardiac stroke volume, and cardiac output by means of impedance cardiography [22] and assessment of body composition [4]. Although the complex permittivity, ε^*, of human blood has been long studied, some important questions still remain to be answered. One of those is: how does the distribution of different micro-particles (MPs) through the blood affect the physical behavior of ε^*? What is the mathematical shape of this distribution? For example, in order to characterize the distribution of red blood cells (RBCs), white blood cells (WBCs), micro-light blood particles (MLPs, which are lighter than RBCs and WBCs), and other micro-particles, dielectric measurements are considered as one of the most effective methods. In reality the dielectric relaxation process of normal and diabetic blood has been observed since early times [5–8]. This relaxation process is described to be almost Debye-type [9], i.e., the Cole–Cole parameter α [10] is unity or slightly smaller than unity, and it has been reported that the relaxation time of water molecules, α_{water}, is found to be about 8.27×10^{-12} s at 25 °C [11]. The relaxation time, τ, of micro-particles in human blood obtained by dielectric measurements is defined as the periodic oscillation time of a micro-particle suspended in the serum. However, several hundreds of millions of these MPs are distributed through the serum within a few drops of the human blood. Each micro-particle has its own mass and hence its own inertia. When these MPs are subjected to an AC electric field, they form dipoles that oscillate with the frequency of the external field. The inertia distribution results in different relaxation rate distributions (D_τ) throughout the polarized liquid. As the fluid becomes more inhomogeneous, the width of D_τ increases.

The relaxation process due to free RBCs, WBCs, and MLPs is generally expressed by the Cole–Cole equation, where the relaxation curve is broader than that of the Debye-type.

The relaxation strength, $\Delta\varepsilon=\varepsilon_{DC}-\varepsilon_\infty$, τ, and the parameter for the shape of relaxation curve, α, are dependent on the distribution of different charges throughout the polarized liquid [10].

Fricke and Morse (FM) [12] are the pioneers who successfully developed models for the electrical and dielectric properties of living tissues, which can be applied to the human blood. One of these models describes the Debye relaxation process, which is characterized by only a single characteristic time constant and thus, corresponds to a single dispersion. Since 1925, the FM model has been widely used and after many decades some authors are still using it [13,23]. This is because it can simply describe qualitatively the dispersion in the α dispersion region as defined by Schwan [14] in 1957 (α dispersion is not to be confused with the Cole parameter α under investigation here; the same notation is kept for convenience). However, since the first studies of the FM model, scientists have observed that this capacitive FM model is not accurate enough to fit experimental results in fluid-suspension studies of, for example, the human blood [10]. Moreover, calculations using the

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FM model lead to values higher than those from the experimental results. For example, in the Cole–Cole plot (the imaginary part of permittivity versus the real part), both the FM model and the experimental results produce a semicircle but the center is not on the real axis. In the literature, this fact is known as "depressed semicircles" (DS). Cole and Spencer [10] introduced a mathematical expression to describe the DS-experimental values with the parameter α. This so-called Cole equation, where the parameter α is an exponent of the imaginary quantity $j\omega\tau$, is described as

$$\varepsilon^* = \varepsilon_\infty + \frac{(\varepsilon_{DC}-\varepsilon_\infty)}{1+(j\omega\tau)^\alpha} \quad (1)$$

where ε^* is the complex impedance at frequency $f=\omega/2\pi$, j is the complex number $j=\sqrt{-1}$, ε_∞ is the dielectric constant at very high values of the frequency (the real part of the complex ε^*), ε_{DC} is the dielectric constant under DC conditions (zero frequency), τ is the relaxation time of the dipoles (where each micro-particle represents an electric dipole), and α is a parameter ranging between 0 and 1 with dimensionless units (Cole parameter).

The present work suggests that the highly disordered structure of blood with freely rotating ions around the electrodes, rotating about themselves, will be well characterized in the plot of α and width of D_τ. This analysis may also be applicable to a comparison of different types of bio-organs, e.g., tissue *in vivo*.

In our previous paper [7], we studied the distribution D_τ of the MPs from dielectric measurements using the Gaussian distribution (GD) method. In the present work, the dependence of α on distribution of different RBCs, WBCs and MLPs is investigated using the proposed GD distribution technique.

2. Experimental methods

We use the experimental data published by Gabriel et al. [15] in this work to confirm the validity of the presented model.

3. Model and simulations

Permanent (and/or induced) dipoles are always present in human blood due to the permanent presence of MPs; for example, RBCs are negatively charged with about -15 mV [16]. Several authors have demonstrated that the negative charges on the red cell surface can be completely attributed to the carboxylic group of neuraminic acid [16–18]. n-Acethyl neuraminic acid is also found to be the major component in the reaction of the negatively charged red cell surface with positively charged poly-L-lysine [19,20].

In the current study, we consider blood to be composed of three main types of MPs suspended in serum: WBCs, RBCs, and MLPs, arranged in descending order with respect to their masses. These MLPs include proteins, hormones, glucose, salts, macro molecules, etc. Under application of an external electric field, polarization occurs and all the present MPs form "induced" dipoles. Due to their different masses, MPs in the blood have different values of inertia and will thus have different relaxation rate distributions. In fact, the polarization due to orientation of MPs in the blood plays a major role in the dielectric properties of blood and in biomaterials in general. The distribution D_τ could be assessed from another point of view. The behavior of polar particles (dipoles) suspended in serum is similar to those of substances with ellipsoidal form in a viscous fluid. If these micro-substances in the fluid are not all similar in physical properties (e.g. size and mass) then their orientations will necessarily include more than one relaxation times. In reality, since particles are not spherically shaped, the coefficients of friction along the three spatial axes are different; therefore, three different D_τ curves may exist. The D_τ of blood may depend on several parameters, the clearest being homogeneity. It is likely that not all dipoles in the blood are subject to the same conditions; some are likely to rotate more freely than others. Consider an extreme case of a single particle whose the dipole may find certain orientations more favorable than others depending on factors such as surrounding charges and the fact that certain transitions between orientations are more probable than others. The extensive rate of variation in such local transitions affects the variation in activation energy for dipole orientation and hence affects D_τ, τ, and the α parameter in Eq. (1). In polarized fluids such as blood, the molecules are complex; the orientation of the polar group related to the link segment along a certain direction may involve many relaxation times. For example, in amino acids, the degree of rotation of the polar groups about the C–C axis depends on position and angle of the section of C–C links [21]. If a system has more than one types of dipole, the relaxation times will be distributed [21].

To estimate the mathematical shape of D_τ, let n be the number of dipoles of one type per unit volume; then we can write for the three types of micro-particles in blood

$$n = (n_0)_{WBC} f(\tau)_{WBC} + (n_0)_{RBC} f(\tau)_{RBC} + (n_0)_{MLP} f(\tau)_{MLP} \quad (2)$$

Here n_0 is the total number of dipoles of all three different types per unit volume and $f(\tau)$ is the distribution function of the relaxation time τ or the probability density of τ. Thus, $f(\tau)d\tau$ represents the probability density of $f(\tau)$ in the interval between τ and $\tau+d\tau$. So, we can write

$$\int_0^\infty [(n_0)_{WBC} f(\tau)_{WBC} + (n_0)_{RBC} f(\tau)_{RBC} + (n_0)_{MLP} f(\tau)_{MLP}] d\tau = 1 \quad (3)$$

Distribution of the three MPs will be the subject of another work; however, the proposed distribution function in the present work will consider only RBCs, which constitute 99% of blood. Thus, one can approximate Eq. (3) to

$$\int_0^\infty (n_0)_{RBC} f(\tau)_{RBC} d\tau = 1$$

Taking into consideration the distribution of D_τ of RBCs, the Debye equation becomes

$$\varepsilon^* = \varepsilon_\infty + (\varepsilon_{DC}-\varepsilon_\infty) \int_0^\infty \frac{f(\tau)d\tau}{1+(j\omega\tau)} \quad (4)$$

Separating the real and imaginary parts, this last equation can lead to the dielectric constant ε' (real part) and the dielectric losses ε'' (imaginary part) as

$$\varepsilon' = \varepsilon_\infty + (\varepsilon_{DC}-\varepsilon_\infty) \int_0^\infty \frac{f(\tau)d\tau}{1+(\omega\tau)^2} \quad (5)$$

and

$$\varepsilon = (\varepsilon_{DC}-\varepsilon_\infty) \int_0^\infty \frac{\omega\tau f(\tau)d\tau}{1+(\omega\tau)^2} \quad (6)$$

If we consider $f(\tau)$ as having a Gaussian distribution (GD), then for one type of MPs we can write

$$f(\tau) = \frac{\tau}{\sqrt{2\pi(T_S)^2}} \exp\left[\frac{-(\tau-\tau_c)^2}{2{T_S}^2}\right] \quad (7)$$

where T_S is the standard deviation of probability density (sometimes called variance or width of the bell curve) and τ_c is the most probable relaxation time within the distribution, which corresponds to the maximum probability. We can then consider that GD of D_τ is the most probable relaxation time τ_c surrounded homogeneously by different relaxation times. Here we denote $(\tau_c)_{WBCs}$ to be the most probable relaxation time for WBCs, $(\tau_c)_{RBCs}$ to be the most probable relaxation time for RBCs, and $(\tau_c)_{MLPs}$ to be the most probable relaxation time for MLPs. Thus, one can write