Electrical properties with relaxation through human blood

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The present work aims to study the effects of the blood-microstructure on the electrical conduction from two different but correlated properties: Electrical and mechanical (viscosity), and to derive useful parameters for the evaluation of electrical conduction as a function of the blood viscosity. ac-conductivity and dielectric constant of normal and diabetic blood are measured in the frequency range 10 kHz–1 MHz at the room temperature. An empirical relation relating the resistivity and viscosity of the blood has been presented. The results show that a microfluidic device is a viable and simple solution for determination of electrical and rheological behaviors of blood samples. © *2010 American Institute of Physics.* [doi:10.1063/1.3458908]

I. INTRODUCTION

In recent years the measurement of blood impedance through an alternating current has been suggested as a noninvasive approach to determine some blood disorders.[1] Human blood has non-Newtonian fluid dynamic characteristics, the most important of which is the correlation between its microstructure and the electrical and mechanical properties. The intrinsic and extrinsic microcells, molecules, bacteria, protein, hormones, glucose, chemicals, vitamins, and antibodies affect drastically the chemical and physical characters of the viable fluid. For example, Zhou *et al.*[2] showed that deformability of erythrocyte is found to alter the wetting dynamics of red blood cell (RBC) suspensions during their invasion into capillaries. This effect shows the importance of the RBC deformability on microvascular perfusion by directly measuring the flow of blood through a microchannel network with realistic dimensions and architecture similar to real microcirculation.[3] This prevents eventually the congenital dyserythropoietic anemia.[4] Moreover, Zhou and Chang[5] found that blood suspension fails to penetrate a capillary with radius less than 50 μm even if the capillary is perfectly wet table. This is of great significance and consequences in evaluating blood flow occlusion after selective pulmonary artery perfusion.[6] Moreover, Basuray and Chang[7] demonstrated that the characteristic relaxation frequency of induced nanodipoles by dielectrophoresis is inversely proportional to the charging and discharging time of the diffuse-layer capacitance in microfluids, which affects both the electrical and mechanical properties of the blood.

In general, the electrical properties of human blood have received much of interest some decades ago for many reasons.[8–10] First, they determine the pathways of current flow through the body and, thus, are very important in the analysis of a wide range of biomedical applications, such as functional electrical stimulation and the diagnosis and treatment of various physiological conditions with weak electric currents, radio-frequency hyperthermia, body composition, and electrocardiography.

Second, on a more fundamental level, knowledge of these electrical properties can lead to an understanding of the underlying basic biological processes either on macroscopic level or microscopic one and to correlate between the two extents. Third, biological impedance studies have long

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been important in electrophysiology and biophysics; one of the first demonstrations of the existence of the cell membrane is based on dielectric studies on cell suspensions.[11] To analyze the response of the human blood to electric stimulation, one needs data on the specific conductivities and relative permittivities of the microbodies or micro-organs within that blood. A microscopic description of the response is complicated by the variety of cell shapes, their distribution inside the cytosol, as well as the various properties of the different components of blood. Therefore, a macroscopic approach is always a net result of several microscopic phenomena and is most often used to characterize field distributions not only in blood but also in biological systems as general. In the present work, it will be shown that the macroscopic electric and dielectric measurements of blood properties are due to several microscopic factors: Blood-inhomogeneity (intrinsic internal structure), physiological state of the blood, and the microbody starvation age[12] that could play a role for the dielectrophoretic crossover frequency[13] (cof) and the cof of the microbodies. It will be seen, in the present work, that this last frequency is correlated with the apparent, macroscopically measured, relaxation time of all the micro particles in the blood.

Moreover, any changes in blood physiology should produce changes in the blood electrical properties.[14] This principle has been used to identify or monitor the presence of various illnesses or conditions such as body fluid shift, blood flow, cardiac output, and muscular dystrophy[15] by various impedance diagnostic techniques, such as impedance thoracic impedance cardiograph, plethysmography, and rheoencephalography. For a detailed discussion of the applications of bio-impedance methods in medicine and biotechnology, one can see, for example, the work of Morucci et al.[16] and Riu et al.[17] If the blood flow is interrupted, both micro- and macroeffects will be manifested: Metabolism continues, but in an anaerobic way (macrophenomenon), while on the microlevel osmosis will cause cell swelling and finally tissue damage. As a consequence, the extracellular pathways narrow, which typically leads to an increase in the low frequency impedance (<10 kHz). The time of occurrence of these phenomena is different for different types of blood. Decreased blood flow also accounts for changes in its resistivity.[18] In all cases, the conductivity increases with time and changes in the frequency range above 100 Hz are lower and take a longer time to occur. For these reasons, considerable caution must be taken in the interpretation of electrical measurements that are performed on excised blood. The electrical properties of blood also depend on its temperature. The mobility of the ions that transport the current increases with the temperature as the viscosity of the extracellular fluid decreases. A general increase of about 2% occurs in the conductivity of blood[19] in the frequency range below 1 GHz up to a temperature of about 40 °C. Above that point, the cell membrane begins to deteriorate and allows the cytosol to leak into the extracellular space. The rapid increase of conductivity with temperature was suggested to be used to monitor the progress of hyperthermia treatment.[20]

In addition, electrical properties can also depend on the blood components not only the red and white cells but also, with the same importance, the different chemical compounds and biomaterials *in vivo* or *in vitro* those present in the blood and affect drastically the electrical properties. For example, plasma contains thousands of different substances, such as proteins, glucose, salts, vitamins, hormones, and antibodies. These substances are not as massive as the RBCs (and white blood cells) but they are, considerably, lighter. Moreover, the presence of some additional and permanent chemical substances in the blood alters the blood properties. Glucose, for example (the diabetes mellitus disorder), affects drastically the electric and dielectric properties of the blood.[21] Accordingly, caution must be used in both the design of the measurement procedure and the interpretation of the experimental data.

Moreover, even on a macroscopic level, the electrical properties of blood are complicated. They can depend on the frequency of the applied field (the blood is neither a perfect dielectric nor a perfect conductor), or they can be time- and space-dependent (e.g., changes in blood conductivity during the process of electropermeability). For these reasons, the present contribution aims to give a first step to investigate a microscopic description of the electrical properties of blood by relating both macromeasurements (complex permittivity) with a microphenomenon (dielectrophoretic crossover frequencies) via the relaxation times of the different bodies in the blood. In this

work, the term blood means human blood in the standard (normal) conditions without any malady-disorder, and the symbols n and D symbolize the normal and diabetic bloods, respectively. Also, the word sample stands for the blood sample.

II. EXPERIMENTAL METHODS

At room temperature, the electrical conductivity, σ, and the dielectric constant, ε_r', are measured in the frequency range from 10 kHz up to 5 MHz, as it was described by Desouky.[21] The samples of heparinized venous blood are collected from 20 patients with diabetes mellitus. The patients are previously diagnosed and are under the supervision of medical professionals. Blood from ten healthy individuals were used as a normal control for this study.[21]

III. MODEL AND ANALYSIS

A. Inhomogeneities of blood

From the electrical point of view, blood is a very inhomogeneous material. The cells, for example, RBCs, themselves are comprised of an insulating membrane enclosing a conductive cytosol. A suspension of cells can be regarded at low frequencies simply as insulating inclusions in a conducting fluid. The insulation is provided by the cell membrane. At higher frequencies in the megahertz range, capacitive coupling across this membrane becomes more important. Beginning in this range, the dispersive properties of the membrane and ultimately the cytosol must also be considered. In blood, the cells are surrounded by an extracellular matrix of different ions, which can be extensive, as in the case of some diseases, for example, diabetes mellitus.[21]

Interestingly, blood does not contain cells of a single size and function which affects the electrical properties. For example, red cells and white ones have neither the same surface area nor the same mobility in the cytosol and are embedded in a conductive viscous fluid (plasma). The cells are perfused with the cytosol and affected by the external applied electric field on the same time as the conductive cytosol. It is thus difficult to extrapolate from the dielectric properties of a conductive viscous fluid to those of membrane. Moreover, a large discrepancy exists between various data on electrical properties of biological materials found in literature. Why is there such a wide range of values obtained by different researchers? Excised samples carry along with them various amounts of body fluids, and the lack of standardization of measurement techniques presents its own difficulties and probably widens the range of resistivity values. In addition, there are seasonal, aged, and disease-linked changes as well as those that accompany the physiological function of various biologic materials.[17]

As it is well known,[22] blood consists of many components. These include plasma (55%) and components (45%). Of these components, 99% are erythrocytes (red blood cells) and 1% is leucocytes [white blood cells (WBCs)] and thrombocytes (blood platelets). Plasma contains thousands of different substances, such as proteins, glucose, salts, vitamins, hormones, and antibodies.[22] These substances are by far lighter than the relatively massive RBCs and WBCs and their inertia at low frequency is negligible, which affects the conduction by linear transport rather than the oscillation motion. However, the presence of these light materials should not be neglected when studying the electrical properties of the blood because they lead to an important drift-scattered motion alongside E. Therefore, in the present work, the blood is considered as insulated cells suspended in a conducting fluid. The cells are classified according to their masses. Let the number of total bodies in the blood be n. These microgerms are arranged so that $mass_1 > mass_2 > mass_3 \cdots > (mass)_n$. So, under an external ac-electric field E and at the same environmental conditions, one should expect that the relaxation times of these masses are arranged as $\tau_1 > \tau_2 > \tau_3 \cdots > \tau_n$. At a certain applied frequency, $f_{app} = \omega_{app}/2\pi$, where ω_{app} is the applied angular frequency, only certain number of the microbodies having relaxation time $\tau = 1/2\pi f_{app}$ will respond to the electric field and will form a flux of charges which moves carrying the electric energy alongside E, whereas the other part of bodies either having $\tau > 1/2\pi f_{app}$ or $\tau < 1/2\pi f_{app}$ will not match with the applied frequency and will have weak response to the applied electric field. So, they cannot carry the electric energy.

Moreover, these micromasses form electric dipoles, under the application of E, whose inertias are arranged as $I_1 > I_2 > I_3 > \cdots I_n$. The heavy cells form freely rotated dipoles in the cytosol and, thus, have rotational motion under the application of external field besides minor linear motion, while the lighter cells are considered to have higher drift velocity in a linear motion besides minor rotational motion under the application of E. We will see in the next section that the rotational motion (which is more manifested for m_1, m_2 rather than m_{n-1}, m_n) leads to displacement current while the scattering-drift motion (which is more manifested for m_{n-1}, m_n rather than m_1, m_2) leads to conduction current.

B. Electrical properties of blood: Mathematical approach

In polar materials, such as blood, the positive and negative charge centers in the molecules do not coincide. An electric dipole moment is said to exist. Owing to the intensity of the electric fields required to move submicrometer particles, the Joule heating can be a problem, often giving rise to electrical forces induced by the variation in the conductivity and permittivity of the suspending medium [electrothermal forces (ETFs)], thus it is necessary that the amplitude of the applied electric field should be kept minimum during the measurements to avoid this ETF. Under this condition, an applied field tends to orient the dipole(s) which produces an opposing field. Moreover, all microbodies respond to the field in different manners: The light substances move abruptly with a certain scattering-drift motion that is nearly linear motion, with scattering on the different ions and charges that exist in their path. Due to their light masses, these particles have small rotational inertia at low frequencies and thus their rotational (oscillation) motion is so feeble that it is neglected in the low frequency range. However, at high frequencies, the high inertia leads to a macroscopic quantity called the infinite value of the dielectric constant, ε'_∞. Under the application of an ac-field, the electric energy is carried by all the particles but not in the same manner.

The linear motion of all the charged particles (dipoles) leads to a constant flux of charges which is referred to as conduction (Ohmic) current, I_c; whereas the rotational motion of the particles occurs with oscillations in order to follow the electric field and leads to a displacement current, I_d (instantaneous energy storage within the particle). Thus, the net charge flux (macroscopic total electric current) flowing through the blood is the sum of the all the microcurrents: Both the conduction and the displacement currents. It is worth noting that these two currents are 90° apart in phase because of the difference in the trigonometric functions. This phase difference can be expressed conveniently by writing the time dependence of the applied voltage: $V(t) = V_0 e^{j\omega t}$, where $j = \sqrt{-1}$. The flux of the total charge carriers (or simply, current I in coulomb/s A) is the sum of the conduction current, I_c, and the displacement current, I_d, respectively, $I = I_c + I_d$,

$$I_c(t) = \frac{V_0}{R_c} e^{j\omega t} \quad \text{and} \quad I_d(t) = \frac{V_0}{R_d} e^{j\omega t}. \tag{1}$$

Here R_c and R_d are the electric resistance of the conduction and displacement current, respectively. One can write

$$I(t) = \sum_{i=1}^{n} (I_{ci} + I_{di}). \tag{2}$$

Here I_{ci} and I_{di} are the conduction and displacement currents that carried by any particle (i), respectively.

So, the current, I could be written as

$$I(t) = \sum_{i=1}^{n} (G_{ci} + G_{di})V, \tag{3}$$

where G is the conductance and it equals the inverse of its resistance, R,

$$G = 1/R.$$

The displacement current I_d which arises from the rotational motion of all the particles through the cytosol is given by

$$I_d = \sum_{i=1}^{n} C_i \frac{dV_0 e^{j\omega t}}{dt}. \tag{4}$$

Thus, the total current that passes through the blood can be represented as

$$I(t) = \sum_{i=1}^{n} \left[(G_{ci}V + G_{di}V) + \left(C_{di}V \frac{dV}{dt} + C_{di}V \frac{dV}{dt} \right) \right] = \sum_{i=1}^{n} \left[(\sigma_{ci} + \sigma_{di}) + i\omega(\varepsilon_{ci} + \varepsilon_{di}) \right] V \frac{A}{d}, \tag{5}$$

where ω is the angular frequency: $\omega = 2\pi f$, f is the frequency of the applied electric field σ_{ci} and σ_{di} stand for the electrical conduction-conductivity and displacement-conductivity, respectively, of any particle in the blood. Similarly, ε_{ci} and ε_{di} represent the conduction-dielectric constant and displacement-dielectric constant, respectively, of any particle i, A and d are the effective area and the effective length, respectively, of the sample between the two electrodes, and ε_0 is the reference dielectric constant $\varepsilon_0 = 8.855 \times 10^{-12}$ F/m.

The blood, then, can be characterized as having complex admittance, Y^*, given by

$$Y^* = \sum_{i=1}^{n} \left[(G_{ci} + G_{di}) + j\omega(C_{ci} + C_{di}) \right] = \sum_{i=1}^{n} \left[(\sigma_{ci} + \sigma_{di}) + j\omega(\varepsilon_{ci} + \varepsilon_{di}) \right] \frac{A}{d}, \tag{6}$$

where * indicates a complex-valued quantity. In terms of material properties, one can write a corresponding, complex conductivity,

$$\sigma^* = \sum_{i=1}^{n} \left[(\sigma_{ci} + \sigma_{di}) + j\omega(\varepsilon_{ci} + \varepsilon_{di}) \right]. \tag{7}$$

Describing the blood in terms of its admittance emphasizes its ability to transport current. Alternatively, we could emphasize its ability to restrict the flow of current by considering its impedance, $Z^* = 1/Y^*$. Factoring $j\omega\varepsilon_0$ in Eq. (5) yields

$$I = \sum_{i=1}^{n} \left[(\varepsilon_{ci} + \varepsilon_{di}) - i \frac{(\sigma_{ci} + \sigma_{di})}{\omega\varepsilon_s} \right] j\omega\varepsilon_0 \frac{A}{d} \tag{8}$$

One can write a complex-valued, relative permittivity as

$$\varepsilon^* = \sum_{i=1}^{n} (\varepsilon_{ci} + \varepsilon_{di}) - j \frac{(\sigma_{ci} + \sigma_{di})}{\omega\varepsilon_s} = \varepsilon_r' - i\varepsilon_r'',$$

$$\varepsilon^* = \left(\varepsilon_r - j \frac{\sigma}{\omega\varepsilon_s} \right) = \varepsilon_r' - j\varepsilon_r'', \tag{9}$$

with

$$\varepsilon_r' = \sum_{i=1}^{n} \varepsilon_{ci} + \varepsilon_{di} \quad \text{and} \quad \varepsilon_r'' = \sum_{i=1}^{n} \frac{\sigma_{ci} + \sigma_{di}}{\omega\varepsilon_0}.$$

This mathematical approach shows that as a dielectric dispersion is traversed by changing the frequency of measurement, the change in conductivity is directly proportional to the change in permittivity. This follows from the fact that the total energy in the field is constant (for a given

voltage) and must either be stored [as reflected in $\varepsilon'(\omega)$] or dissipated [as reflected in $\varepsilon''(\omega)$] by the system with which it interacts. This allows an additional check upon the validity of the experimental data.

It is also true that the application of the Debye processes cannot be distinguished from a small distribution of relaxation times.[23] We may therefore characterize any dielectric dispersion observed in biological materials in terms of two parameters only: The dielectric increment ε_r' and the relaxation time (τ_c) or characteristic frequency $f_c : f_c = 1/(2\pi\tau_c)$.[23] At this frequency, on a microscopic level, knowledge of the net force on the particle (dielectrophoretic) can lead to an understanding of the underlying basic biological processes: The particles (microdipoles) orient their position in order to get the lowest energy position, i.e., they direct themselves in order to have the minimum strength of the dielectrophoretic force. Following the pioneer study of Pohl[24] on the subject, dielectrophoresis (DEP) is the net force experienced by a dielectric object in a nonuniform electric field (there is no net force in a homogeneous electric field). This effect exists because the dipole charges $\pm q$ induced at characteristic locations are subject to different values of the electric field. The DEP force can produce directed motion of electrically polarizable particles in the convergent field direction to neutralize the external field on the dipole moment and finally the dipoles relax with a relaxation time τ_c. The vector sum of the net DEP forces results in a net electric force on the charge carriers $F = qNJ/\sigma$, where N is the density of charge carriers at any time t, J is the current density, q is the electronic charge, and σ is the electric conductivity. This force F is a macroscopic quantity.

To get the current density, J, one should consider the conservation of charge law (Kirchhoff's law): It shows that the charge per second at any condition should be conserved, i.e., the charge per time at very low frequency should equal the charge per time at very high frequency and, also, should equal the charge per time at any time; thus one can write

$$\frac{qN_0}{\tau_0} = \frac{qN}{j\left(\dfrac{f}{f_c}\right)\tau} = \frac{qN_\infty}{\tau_\infty}, \tag{10}$$

where N_0, N_∞, and N are the density of charges at very low, very high frequency and at any frequency f, respectively. τ_0, τ_∞, and τ are the relaxation time of the particles at very low, very high, and at any frequency, respectively. The complex factor j is necessary because N is out of phase with respect to both N_0 and N_∞. Equation (6) leads to

$$\frac{N_0}{\tau_0} + \frac{N_\infty}{\tau_\infty} = 2\frac{N}{i\left(\dfrac{f}{f_c}\right)\tau}. \tag{11}$$

Considering that there is no charge leakage, from the boundaries, through the blood flow $N_0 \approx N \approx N_\infty$, then Eq. (11) gives

$$\frac{1}{\tau_0} - \frac{1}{i\left(\dfrac{f}{f_c}\right)\tau} = \frac{1}{i\left(\dfrac{f}{f_c}\right)\tau} - \frac{1}{\tau_\infty}, \tag{12}$$

which leads to

$$\tau^* = \tau_\infty + \frac{(\tau_0 - \tau_\infty)}{1 + i\left(\dfrac{f}{f_c}\right)} \tag{13}$$

and

$$\tau^* = \tau_\infty + \frac{(\tau_0 - \tau_\infty)\left\{1 - i\left(\frac{f}{f_c}\right)\right\}}{1 + \left(\frac{f}{f_c}\right)^2}. \tag{14}$$

The real part of the relaxation time is given by

$$\tau_{\text{real}} = \tau_\infty + \frac{(\tau_0 - \tau_\infty)}{1 + \left(\frac{f}{f_c}\right)^2}, \tag{15}$$

while the imaginary relaxation time as

$$\tau_{\text{imaginary}} = \tau_\infty - i\left(\frac{f}{f_c}\right)\frac{(\tau_0 - \tau_\infty)}{1 + \left(\frac{f}{f_c}\right)^2}. \tag{16}$$

Equation (16) matches exactly with the Debye model despite the present work starts from energy conservation (Kirchhoff's) law rather than dipole relaxation (Debye model). Moreover, Eq. (16) means that the relaxation time τ is the time necessary for a set of particles having relaxation times in the range $\tau \approx \tau_c \pm \Delta\tau = 1/2\pi f_c \pm 1/2\pi\Delta f_c$ to respond with the electric field (to try to orient themselves alongside with the applied field). One will see later in Sec. IV C that $\Delta\tau$ is correlated with the width of a Gaussian distribution of relaxation times. The difference between the crossover frequency and the relaxation time is that the former describes the dipole relaxation time reaction under an applied ac-field on microscopic level whereas the latter depict the same time necessary to try to orient the particles alongside with the applied field for a set of dipoles (macroscopic level). This means that under the application of an ac-electric field with very low frequency, the heavy particles (that have high inertia and high relaxation time) will curiously respond faster than the light particles whereas the very high frequency field will stimulate only the light particles.

Thus, our previously mentioned physical model considers the dipoles to be spheres whose rotation in response to the field is opposed by frictional interaction with the surrounding viscous medium. The relevant relaxation time for the orientation of such a sphere is given by[25]

$$\tau = \frac{X}{2kT}, \tag{17}$$

where X is a molecular friction coefficient which relates the torque exerted on the dipolar molecule by the applied electric field to the molecule's angular velocity, k is Boltzmann's constant, and T is the absolute temperature. Assuming the dipole to be equivalent to a rigid sphere of radius R turning in a hydrodynamic fluid of viscosity coefficient η, the Stokes–Einstein relation gives $X = (8\pi\eta R^3)$ so that the relaxation time could be given as

$$\tau = \frac{4\pi R^3}{kT}\eta. \tag{18}$$

Now, one applies Eq. (18) for the case of water molecules rotating in bulk water. At 293 K, the distance between adjacent oxygen molecules is 0.28 nm, i.e., $R = 0.14$ nm. The viscosity of water is 10^{-3} kg m^{-1} s^{-1} (i.e., 1 m/Pa s) so that the value for the relaxation time of water molecules at this temperature that one would derive from Eq. (18) is 8.5 ps, in excellent agreement with the experimentally observed value of 9.3 ps.[26] Thus, one will fairly use this model in the next paragraph to interpret the electrical data of normal and diabetic blood.
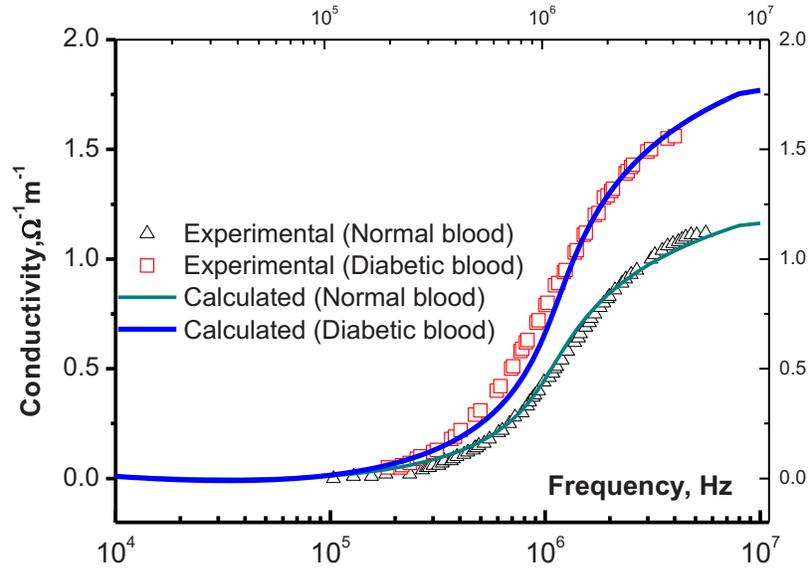
FIG. 1. The electrical conductivity of normal and diabetic blood as a function of the applied frequency. Solid lines represent calculated values after Eq. (19) and triangles and squares are experimental data for normal and diabetic bloods, respectively.

IV. RESULTS AND DISCUSSION

A. Electrical conductivity of normal and diabetic blood

The behavior of the electrical conductivity of both the normal and diabetic bloods is illustrated in Fig. 1. Depending on the frequency, it is clear that the diabetic blood is (13%–43%) more conductive than the normal one. Now, we apply the previously described model to elucidate the experimental data.

First, we consider that n dipoles are suspended inside the cytoplasm, relax under the action of an external ac-field, and obey the Debye model.[27] Applying this model on the present data, the conductivity, σ, is given as a function of the applied angular frequency, ω, as

$$\sigma = \sum_{i=1}^{n}\left[\sigma_{ci} + \frac{(\varepsilon_{di} - \varepsilon_{ci})}{1 + \omega^2\tau_i^2}\omega^2\tau_i\right]. \tag{19}$$

The exact number of particles n is not easy to be defined; however, one can consider the following average quantities: σ_0 is the average conductivity of the particles that move linearly leading to drift (dc) conductivity,

$$\sigma_0 = \sum_{i=1}^{n}\sigma_{ci}. \tag{20}$$

Similarly, the part of conductivity which is due to the rotational motion of the particles could be given as σ_{ac},

$$\sigma_{ac} = \sum_{i=1}^{n}\frac{(\varepsilon_s - \varepsilon_\infty)}{1 + \omega^2\tau_i^2}\omega^2\tau_i. \tag{21}$$

Here, τ_i is the relaxation time of any particle under the application of an ac-field; the sum over ε_{di} gives the dielectric constant at low frequency ($f \to 0$), which gives ε_s the static dielectric constant; while the sum over ε_{ci} gives the dielectric constant at high frequency ($f \to \infty$), which leads to ε_∞ the dielectric constant at very high frequency,
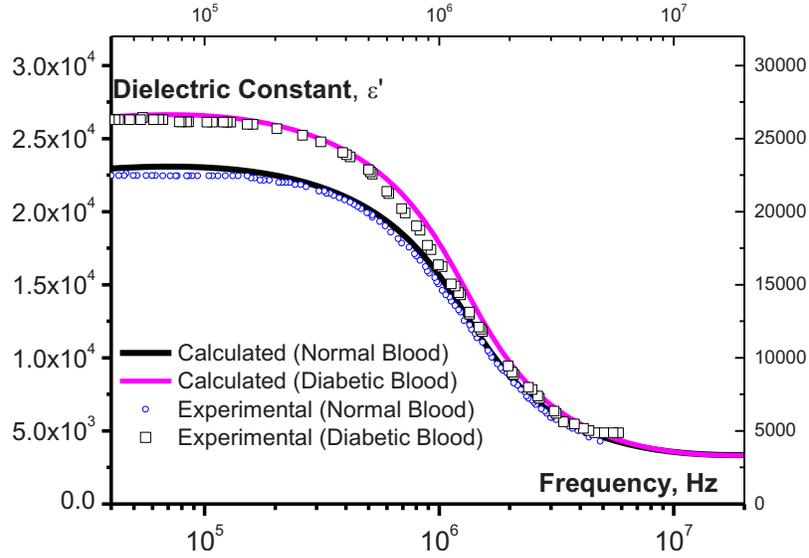
FIG. 2. The dielectric constant of normal and diabetic blood as a function of frequency. Solid lines represent calculated values after Eq. (25) and symbols are experimental data for normal and diabetic bloods, respectively.

$$\varepsilon_s = \lim_{\omega \to 0} \left\{ \sum_{i=1}^{n} \frac{\varepsilon_{di} - \varepsilon_{ci}}{1 + \omega^2 \tau_i^2} \omega^2 \tau_i \right\} \tag{22}$$

and similarly,

$$\varepsilon_\infty = \lim_{\omega \to \infty} \left\{ \sum_{i=1}^{n} \frac{\varepsilon_{di} - \varepsilon_{ci}}{1 + \omega^2 \tau_i^2} \omega^2 \tau_i \right\} \tag{23}$$

and

$$\tau = \sum_{i=1}^{n} \tau_i. \tag{24}$$

Considering these averages, Eq. (19) fits well the experimental data in Fig. 1 with the fitting parameters: First, the normal blood: $\sigma_0 = 1.09 \times 10^{-2}$ Ω^{-1} cm^{-1}, $\sigma_{ac} = 0.91 \times 10^{-2}$ Ω^{-1} cm^{-1}, $\varepsilon_s = 22\,983 \varepsilon_0$ F/m, with $\varepsilon_0 = 8.855 \times 10^{-12}$ F/m, $\varepsilon_\infty = 3279.3 \varepsilon_0$ F/m, and $\tau = 1.27 \times 10^{-7}$ s. Second, for the diabetic blood: $\sigma_0 = 1.23 \times 10^{-2}$ Ω^{-1} cm^{-1}, $\sigma_{ac} = 1.11 \times 10^{-2}$ Ω^{-1} cm^{-1}, $\varepsilon_s = 28\,115 \varepsilon_0$ F/m, $\varepsilon_\infty, = 1179.3 \varepsilon_0$ F/m, and $\tau = 1.47 \times 10^{-7}$ s. These parameters are not too far from the obtained experimental values and coincide with the published data of Desouky.[21]

B. Dielectric constant of normal and diabetic bloods

Similar to the conductivity, we have considered that the dielectric constant of both the normal and diabetic bloods is due to the relaxation of the dipoles with a Debye type. The dielectric constant ε_r' at any frequency is given as a function of ω as[27]

$$\varepsilon_r' = \sum_{i=1}^{n} \varepsilon_{ci} + \frac{(\varepsilon_{di} - \varepsilon_{ci})}{1 + \omega^2 \tau_i^2}. \tag{25}$$

Here, one follows the same steps which have been done for the conductivity, i.e., the calculated values (solid line) after Eq. (25) fit well the experimental values (open symbols) as it is shown in Fig. 2. With the mean values given by Eq. (24) and the dielectric mean value ε_r',

$$\varepsilon'_r = \sum_{i=1}^{n} \varepsilon'_i. \tag{25'}$$

In Ref. 28 the authors gave evidence that glucose stimulates the formation of free radicals in diabetes by several bio-oxidation processes.[28] So, the increase of free radicals in the diabetic blood augments the density of dipoles and consequently increases the dielectric constant.

C. Probability of the distribution of relaxation times in the blood

A key feature of the present study is the time elapsed to orient a dipole alongside with an applied ac-electric field. As it is mentioned in Sec. III A, the blood is considered to be composed of n particles suspended in the plasma. Each of these particles has its own mass $m_1, m_2, m_3, \ldots, m_n$. If one considers that $m_1 > m_2 > m_3 \cdots > m_n$, thus, one should expect that under the application of an ac-electric field, the corresponding times necessary to orient the particles alongside with the field are $\tau_1 > \tau_2 > \cdots > \tau_n$, i.e., each particle has its intrinsic relaxation time. These times are considered to be widely distributed through the plasma in a Gaussian manner so that any particle could have a relaxation time under the probability $P(\tau)$,[29]

$$P(\tau) = \frac{1}{T_s\sqrt{2\pi}} \exp - \frac{(\tau - \tau_c)^2}{2T_s^2}, \tag{26}$$

where the normalization of the probability function is given as

$$\int_{-\infty}^{\infty} P(\tau)d\tau = \int_{-\infty}^{\infty} \frac{1}{T_s\sqrt{2\pi}} \exp - \frac{(\tau - \tau_c)^2}{2T_s^2} = 1.$$

T_s are the standard deviation of the probability which specifies the "width" of the bell curve. One can also consider that T_s encounters the most relaxation times within a narrower width. τ_c is the most probable relaxation time within the distribution.

Macroscopically, the measured relaxation time τ_{mes} is the summation all over the relaxation times, between τ_0 (when $f \rightarrow 0$) and τ_∞ (when $f \rightarrow \infty$), of each particle weighted by its probability, as follows:

$$\tau_{\mathrm{mes}} = \int_{\tau_\infty}^{\tau_0} \tau P(\tau)d\tau = \int_{\tau_\infty}^{\tau_0} \frac{\tau}{T_s\sqrt{2\pi}} \exp - \frac{(\tau - \tau_c)^2}{2T_s^2} d\tau. \tag{27}$$

Generally, the Gaussian distribution (GD) is widely applied in biosystems in recent times.[30] Even so, we have successfully used this distribution in fitting experimental ac-conductivity with a proposed model in semi-insulating materials.[31,32] The interesting application of this distribution is that it significantly correlates the micro- and macroproperties of a biosystem through a comprehensive phenomenon. For example, earlier, Pohl[24] defined the cof as follows: It is the frequency at which the induced dipole of a particle exactly vanishes, which is microscopic property. One can correlate this macroscopically; with the most probable relaxation time τ_c for a set of particles at which the applied electric field is exactly neutralized. Thus, the cof exists if there is only one particle in the GD. In this particular case the GD will turn into a δ-function. Unfortunately, the application of the GD requires definite information about the number of conductive sets which is out the scope of this study. However, one can overcome this problem as follows: If the possible relaxation times are distributed within the range 1.0×10^{-9} s $< \tau < 1.0 \times 10^{-3}$ s.

Any particle with its natural relaxation time τ will have a probability $\omega\tau$ to respond to the applied field if $\tau > 1/2\pi f$, where f is the applied frequency, there will be weak response; similarly, if $\tau < 1/2\pi f$, there will be weak response. Only when $\tau = 1/2\pi f$ there will be maximum response. Figure 3 shows the probability, $\omega\tau$, as a function of the applied frequency. One can notice that
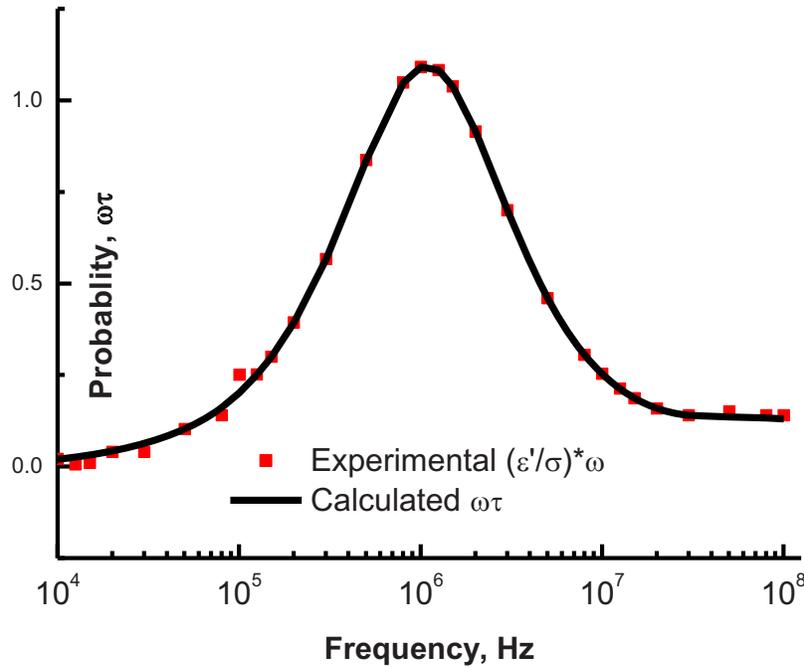
FIG. 3. Solid squares represent the experimental $\omega*(\varepsilon'/\sigma)$ which is $\omega\tau$, while the solid line represents the calculated probability after the product $\omega\tau$. Here τ varies in a logarithmic manner from 10^{-9} up to 10^{-3} s. The maximum probability occurs at $f_c = 1.25 \times 10^6$ Hz.

when the intrinsic relaxation time matches with the inverse of applied angular frequency ($2\pi*1.25 \times 10^6$ Hz), the probability will be a maximum which corresponds to maximum transfer of the electric energy.

The transfer of energy could be explained as follows: In physical terms, we can conceive the electrical conductivity of the blood as a measure of the ability of its internal charge to transfer the electrical energy from one electrode to another. Similarly, the blood permittivity is a measure of the ability of its dipoles or its charge to store the applied external energy.

As the transfer of energy occurs by oscillations of the particles, the transfer time of the electric energy is related to the conductivity σ and the dielectric constant ε' for the blood particles as

$$\tau = \frac{\varepsilon' \varepsilon_0}{\sigma}. \tag{28}$$

One can calculate τ from the experimental data of σ and ε'; then calculate the electric loss ε'' as a function of frequency as

$$\varepsilon'' = \frac{\sigma_{ac}}{\omega}. \tag{29}$$

As it is shown in Fig. 4, the frequency dependence of the electric dispersion of the normal and diabetic blood ε''_n and ε''_D, respectively, are reported. ε''_n pass by a maximum at a frequency $f_{max}(n) = 1.25$ MHz while ε''_D pass by a maximum at $f_{max}(D) = 1.12$ MHz.

The corresponding relaxation times of the sample in the normal and diabetic bloods, respectively, are $\tau_n = 1/2\pi f_{max}(n) = 1.27 \times 10^{-7}$ s and $\tau_D = 1/2\pi f_{max}(D) = 1.42 \times 10^{-7}$ s. It is worth noting that $\tau_n = 1/2\pi f_{max}(n)$ matches well with the maximum probability occurring at $f_c = 1.25 \times 10^6$ Hz (Fig. 3).

The electrical losses ε'' as a function of angular frequency has been derived after Eqs. (21) and (29) as follows:
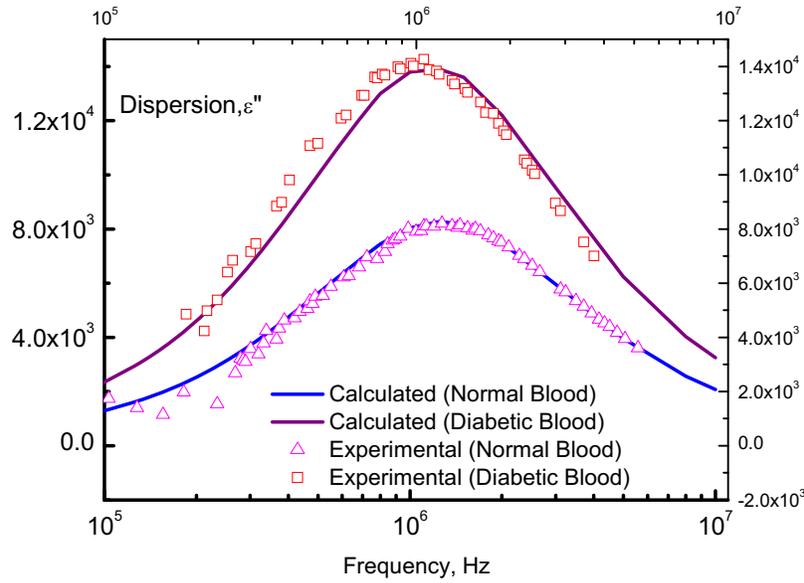
FIG. 4. The electric dispersion of normal and diabetic blood as a function of frequency. Solid lines represent calculated values after Eq. (30) and triangles and squares are experimental data for normal and diabetic bloods, respectively.

$$\varepsilon'' = \sum_{i=1}^{n} \frac{(\varepsilon_{di} - \varepsilon_{ci})}{1 + \omega^2 \tau_i^2} \omega \tau_i. \tag{30}$$

Taking the average values given by Eqs. (20), (24), and (25′), one can calculate the dielectric losses for the normal blood, ε_n'', and for diabetic one, ε_D''. The solid lines, which are illustrated in Fig. 4, represent the calculated values after Eq. (30) while the experimental data are shown as open symbols. The best fits of the experimental relaxation times with the calculated values, after Eq. (30), in the normal and diabetic bloods are found to be $\tau_n = 1.258 \times 10^{-7}$ s and $\tau_D = 1.49 \times 10^{-7}$ s, respectively, whereas the net (apparent) values which are calculated from Eq. (28) are $\tau_n = 1.25 \times 10^{-7}$ s and $\tau_D = 1.40 \times 10^{-7}$ s. These values of τ_n and τ_D lie in the logic domain and match well with the experimental data of Sozou.[33]

The experimental relaxation time is estimated from dividing the experimental values of the dielectric constant, ε', by the experimental data of the ac-conductivity, i.e., $\tau_{expt} = \varepsilon'_{expt}/\sigma_{expt}$. Thus, the experimental values of τ_{expt} vary in the range of 2.35×10^{-5} s $> \tau_{expt} > 2.3 \times 10^{-8}$ s. Figure 5 shows the experimental values of the relaxation time (open squares) as a function of the frequency for both the normal and diabetic bloods (solid triangles).

These curves show that the distribution of the relaxation times extends over the up mentioned range of 2.35×10^{-5} s $> \tau_{expt} > 2.3 \times 10^{-8}$ s. The diabetic blood contains bodies with relaxation times higher than those of normal blood as the presence of glucose enhances the generation of free radicals,[28] which increases the number of free charges. This increase raises the values of the dielectric constant[34] and consequently, increases the relaxation time.

In the next paragraph, the correlation between the relaxation times of the dipoles in the blood and the viscosity coefficient η is presented. Then, the relation between η and the electrical conductivity σ will be derived.

The blood red cells (and the other relatively massive particles) are polarized when applying an external ac-electric field. So, these RBCs can carry the ac-electric current through the blood. Within the polarization procedure, the normal blood particles relax with a relaxation time τ_{BRC-n} and the diabetic ones relax with a relaxation time τ_{BRC-D}. These times depend on the internal energy of the particles, i.e., thermal energy, kT and mechanical one. In the absence of an electric field, the particles tend to attain the minimum position of energy which is given when kT equals the total internal (mechanical/oscillation) energy. On applying an external electric field, however,
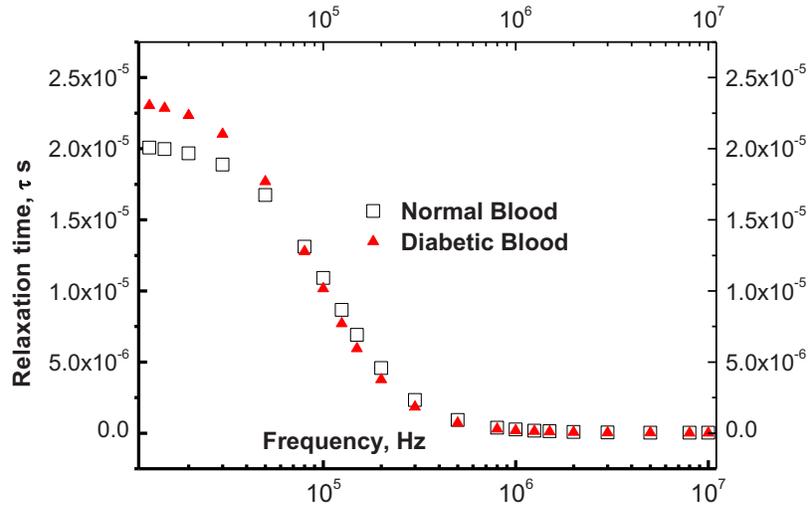
FIG. 5. The relaxation time, τ, of normal and diabetic bloods as a function of frequency. The calculated values after Eq. (30) coincide with the experimental values (squares and triangles are experimental data for normal and diabetic bloods, respectively); but these calculated values are omitted for more clarity.

the previously mentioned minimum (neutrality of energy) will be out of equilibrium and the RBCs are now forced to oscillate according to the new electric force with a certain relaxation time that depends on the applied frequency. Thus, the transfer of energy will maximum when the natural frequency of the RBCs, τ, coincides with the angular frequency of the applied electric field ω, i.e., when $\tau = 1/\omega$. The maximum of energy transfer is reflected as two maximum values on the ε''-ω curve (Fig. 4).

Figure 5 shows the experimental values (open symbols) of the relaxation time $\tau = \varepsilon'_r/\sigma$ as a function of the applied frequency. These experimental values are well fitted with Eq. (16) when $\tau_0 = 2.1 \times 10^{-5}$ s, $\tau_\infty = 1.26 \times 10^{-7}$ s, and f_c is 1.25×10^6 Hz. The calculated data are not represented in the figure for more clarity.

D. Blood viscosity as a function of the ac: Electrical conductivity for normal and diabetic bloods

It is well known[34] that the dielectric constant, ε, is a function of the number n of dipoles that relax under the effect of an ac-field. Also, the viscosity coefficient η is a function of n. This number will be divided into two sets of particles: The first contains light-mass particles such as proteins, hormones, micromolecules, free radicals, salts, ions, etc., and denoted L with an average radius R_L; the second set contains the relatively heavy mass particles such as erythrocytes, leukocytes, thrombocytes, etc., and denoted H with an average radius R_H. Moreover, one will consider that the viscosity coefficient at infinite frequency, η_∞, is corresponding to the relaxation time at infinite frequency τ_∞ and that the viscosity coefficient at low frequency, η_0, corresponds to τ_0. Moreover, τ_0 and τ_∞ are the maximum and minimum relaxation times in the Gaussian distribution. Physically, τ_0 represents the relaxation time of the heavy particles and τ_∞ stands for the light particles. The limits of the mentioned relaxation times could be given with the aid of Eq. (18) as

$$\tau_\infty = \frac{4\pi(R_L)^3}{kT}\eta_\infty \quad \text{and} \quad \tau_0 = \frac{4\pi(R_H)^3}{kT}\eta_0. \tag{31}$$

If one considers the particles as capacitors of dielectric constant $\varepsilon'_r = \varepsilon\varepsilon_0$ and electric resistivity ρ due to the membrane, the time of charging/discharging of this capacitor equals to the relaxation time τ: It is related to the resistivity, ρ, and the dielectric constant, ε'_r, as
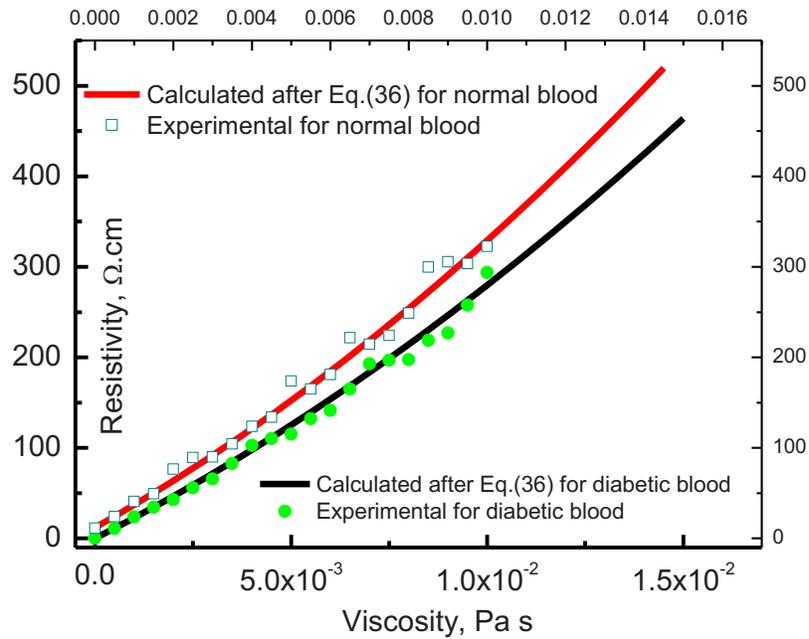
FIG. 6. Variation of blood electrical resistivity (ρ cm) with the viscosity in Pa s; the continuous lines are calculated after Eq. (36) while closed circles and open squares are experimental values of the conductivity after Popa *et al.* (Ref. 36).

$$\tau = \rho \varepsilon_r'. \tag{32}$$

The corresponding limit values of the resistivity at high and low frequencies could be given as

$$\rho_\infty = \frac{4\pi(R_L)^3 \eta_\infty}{\varepsilon_\infty kT} \quad \text{and} \quad \rho_s = \frac{4\pi(R_H)^3 \eta_0}{\varepsilon_s kT}. \tag{33}$$

ρ_∞ is the electric resistivity due to light particles which is rather manifested at higher frequencies and ρ_s is the electric resistivity due to heavy particles (predominant at low frequency).

Using Eqs. (26) and (33), one can write

$$\rho = \int_{\tau_\infty}^{\tau_0} \rho(\tau) P(\tau) d\tau = \int_{\tau_\infty}^{\tau_0} \frac{\rho(\tau)}{T_s \sqrt{2\pi}} \exp\left[-\frac{(\tau - \tau_c)^2}{2T_s^2} \right] d\tau, \tag{34}$$

where T_s is the standard deviation of the distribution,

$$\rho = \frac{4\pi}{kT\sqrt{2\pi}} \int_{\tau_\infty}^{\tau_0} \frac{R(\tau)}{\varepsilon(\tau) T_s} \exp\left[-\frac{(\tau - \tau_c)^2}{2T_s^2} \right] d\tau. \tag{35}$$

$R(\tau)$ is the radius of any particle inside the blood; the determination of the exact values of these radii is not an easy task and it will be the subject of another study. However, the average values of the resistivity ρ will be considered in this study as

$$\rho = \frac{4\pi}{kT} \left(\frac{(R_h)^3}{\varepsilon_s'} + \frac{(R_L)^3}{\varepsilon_\infty'} \right) \eta. \tag{36}$$

Figure 6 shows the blood resistivity ρ as a function of the normal and diabetic blood viscosity η calculated after Eq. (36) with $R_L = 2$ μm and $R_H = 11$ μm at T of 300 K, $(\varepsilon_s)_D = 28\,513\varepsilon_0$ F/m and $(\varepsilon_\infty)_D = 3211\varepsilon_0$ F/m and for the normal blood $(\varepsilon_s)_n = 22\,975\varepsilon_0$ F/m and $(\varepsilon_\infty)_n = 3099\varepsilon_0$ F/m. These fitting parameters are not too far from the data of Piet Aarts *et al.*[35] On the same figure, the viscosity-electrical conductivity experimental data of Popa *et al.*[36] is plotted as

open symbols. From this figure (Fig. 6), one remarks that the blood viscosity is about 7% higher in diabetic than in normal blood. This is in good agreement with the results of Donald McMillan[37] and Zingg *et al.*[38] To explain why the diabetic blood is more viscous, Obrosova *et al.*[28] reported that free radicals are produced in diabetes by glucose autoxidation, polyol pathway or/and nonenzymatic glycation of proteins. Consequently, the increase of free radical density in the diabetic blood increases the density of dipoles and consequently increases both the dielectric constant and the average relaxation time, which leads directly to an increase of the viscosity. Higher dielectric constant for diabetic blood with respect to normal one is reported in Fig. 2. In Fig. 5 one can notice that the relaxation time of diabetic blood, which can respond to the field, is a function of the frequency and is higher than the normal blood.

V. CONCLUSIONS

It is shown that bioimpedance measurements could provide an important method for the noninvasive investigation of blood internal structure and properties or for monitoring physiological change i.e., "static" or "dynamic" human organism properties. One of the main problems one encounters using bioimpedance measurements is still the reliability of the results. The scatter of the data for the electrical parameters of blood illustrates the problem of measurement reproducibility. This scatter makes it difficult to establish criteria of normality or reference value for particular measurement results. However, in spite of the large differences between reported data on dielectric properties of different samples of blood, we can still find some very useful applications based on the measurements of the differences or changes in the specific conductivity or relative permittivity. As a first step, the presents work shed a light on the importance of the study of the blood internal structure when assessing the blood from its electrical properties. It gives also an important chance to the early diagnosis of the tumor cells in blood.

More future studies are needed to investigate the role participated by each component of the blood in the electrical properties which may open a great chance for both early diagnosis and effective therapy and thus, a microfluidic device could be designed to investigate the electrical and rheological behaviors of blood flow. The electrical measurements under various stimulating frequencies show that the electrical properties of different blood components vary with the flow conditions, and can thus be used as a measure of the rheological behavior. To this extent, the correlation of the apparent viscosity of whole blood and its electrical resistance measured by the device could be performed.

Here, an attempt has been made to predict the role of microfluidic devices in biomedical research. In particular automated detection and automated fluid manipulations will both improve the overall usefulness of such devices. Moreover, automation may also play an important role in the development of creating better *in vitro* models of *in vivo* processes. If so, the role of microfluidic devices in laboratory settings will only grow more popular, especially in those areas where high-throughput determinations and biological assays are required.

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