The use of the formalism of the complex electrical module in the monitoring of oncological diseases

Zh A Salnikova¹ and R A Castro

Physics Department, Herzen State Pedagogical University of Russia, 48 Moika emb., Saint Petersburg, 191186, Russian Federation

¹e-mail: jannete90@mail.ru

Abstract. The article discusses the use of the formalism of a complex electrical module to determine the relaxation parameters $\alpha$, $\beta$, $\tau$ of blood serum. Approximating formulas for the real and imaginary components of the electrical modulus, obtained from the Havrilyak-Negami equation, are given. The assumption is made that for healthy organisms the parameters $\alpha$, $\beta$, $\tau$ are constant (or change insignificantly), and for cancer patients they change, and the more the disease develops, the more these parameters change. It is also assumed that the activation energies $E_a$ of macromolecules in the composition of blood serum are different for healthy and diseased organisms. Thus, the study of the dynamics of changes in the parameters $\alpha$, $\beta$, $\tau$, $E_a$ can be used in the monitoring of oncological diseases.

1. Introduction

In recent years, the method of dielectric spectroscopy has been widely used to study blood [1-4]. In oncological diseases, the conformations of the molecules that form the blood serum [5-7] change, which changes their dielectric spectrum. Consequently, by examining the dielectric spectrum of blood serum, one can obtain information about the development of cancer. The aim of this work is to establish a relationship between the course of cancer and dielectric parameters ($\alpha$, $\beta$, $\tau$, $E_a$) of blood serum.

2. Relaxation equations

Within the framework of the method of dielectric spectroscopy, to analyze the relaxation properties of dielectrics, the concept of a complex dielectric constant $\varepsilon^*(f)$ is used:

$$\varepsilon^*(f) = \varepsilon'(f) - i\varepsilon''(f)$$

(1)

where $f$ is the frequency of the applied electric field, $i = (-1)^{1/2}$ is the imaginary unit, $\varepsilon'(f)$ is the dielectric permittivity, $\varepsilon''(f)$ is the dielectric loss factor. The values of $\varepsilon'(f)$ and $\varepsilon''(f)$ are determined experimentally.

The equation describing the frequency dispersion of the complex dielectric constant $\varepsilon^*(f)$ in the general case is the Havriliak-Negami (H-N) equation [8]:

$$\varepsilon^*(\omega) = \varepsilon_\infty + \frac{\varepsilon_s - \varepsilon_\infty}{(1 + i\omega\tau)^{1-\alpha}}$$

(2)
where \( \omega = 2\pi f \) is the cyclic frequency of the electric field, \( \varepsilon _{s} \) and \( \varepsilon _{\infty} \) are the values of \( \varepsilon ' \) as \( \omega \to 0 \) and \( \omega \to \infty \) respectively, \( \tau \) is the most probable relaxation time of the sample molecules, \( \alpha \) is the width of the dielectric spectrum \((0 \leq \alpha < 1)\), \( \beta \) is the degree of its symmetry \((0 < \beta \leq 1)\). The larger \( \alpha \), the wider the relaxation spectrum; the smaller \( \beta \), the greater the degree of its asymmetry.

Parameters \( \alpha, \beta, \tau \) are the main relaxation parameters of the research object. They are determined if there are relaxation peaks on the experimentally measured dependence \( \varepsilon '(f) \). If these peaks cannot be detected, then the determination of these parameters by this method becomes impossible. Blood serum has increased electrical conductivity, which does not allow the detection of relaxation peaks by this method.

In our work, we used the formalism of a complex electrical module to define them. We have previously used this method for polyamides [9], for albumin solution [10], for blood serum in cancer – chronic lymphocytic leukemia [11,12].

3. Formalism of the complex electrical module

The complex electrical modulus \( M^*(\omega) \) is the inverse complex dielectric constant [13]:

\[
M^*(\omega) = \frac{1}{\varepsilon ' (\omega)} = M' (\omega) + i M'' (\omega)
\]

\[
M' (\omega) = \frac{\varepsilon ' (\omega)}{\varepsilon ' ^2 (\omega) + \varepsilon '' ^2 (\omega)}
\]

\[
M'' (\omega) = \frac{\varepsilon '' (\omega)}{\varepsilon ' ^2 (\omega) + \varepsilon '' ^2 (\omega)}
\]

The quantities \( M'(\omega), M''(\omega) \) are called, respectively, the real and imaginary components of the complex electrical module. From the H-N equation, one can derive equations for \( M'(\omega), M''(\omega) \) [14]:

\[
M' (\omega) = \frac{M_{m0} M_{s} A \beta [A \beta M_{s} + (M_{m0} - M_{s}) \cos \beta \phi]}{A^2 \beta M_{s}^2 + 2 A \beta (M_{m0} - M_{s}) M_{s} \cos \beta \phi + (M_{m0} - M_{s})^2}
\]

\[
M'' (\omega) = \frac{M_{m0} M_{s} A \beta (M_{m0} - M_{s}) \sin \beta \phi}{A^2 \beta M_{s}^2 + 2 A \beta (M_{m0} - M_{s}) M_{s} \cos \beta \phi + (M_{m0} - M_{s})^2}
\]

where

\[
M_{s} = \frac{1}{\varepsilon _{s}}; \quad M_{m0} = \frac{1}{\varepsilon _{m0}};
\]

\[
A = \left[ 1 + 2 (\omega \tau _{0})^{1-\alpha} \sin \left( \frac{\pi \alpha}{2} \right) + (\omega \tau _{0})^{2(1-\alpha)} \right]^{-\frac{1}{2}}
\]

\[
\phi = \arctg \left[ \frac{\omega \tau _{0}^{1-\alpha} \cos \left( \frac{\pi \alpha}{2} \right)}{1 + (\omega \tau _{0})^{1-\alpha} \sin \left( \frac{\pi \alpha}{2} \right)} \right]
\]

In this case, the parameters \( \alpha, \beta, \tau _{0} \) have the same physical meaning as in equation (2).

4. Possibilities of use in oncology

The quantities \( \varepsilon '(f) \) and \( \varepsilon ''(f) \) are measured experimentally. Then, using formulas (4,5), the values of \( M'(\omega), M''(\omega) \) are determined. As an example, Fig. 1 and Fig. 2 show the results for \( M'(f), M''(f) \) taken from [11] \((T = 20 ^{0}C)\).
Further, $M'(\omega)$, $M''(\omega)$ are approximated by curves according to the formulas (6,7). Relaxation parameters $\alpha$, $\beta$, $\tau$ are determined empirically from the principle of the best approximation at the same time $M'(\omega)$ and $M''(\omega)$. Each organism will have its own values of $\alpha$, $\beta$, $\tau$. We assume that for healthy organisms they will not change over time (or change insignificantly), but for cancer patients there will be changes, and the more the disease develops, the more the values of these parameters will change. The $M''(M')$ graph (Cole-Cole diagram for the electrical module) can clearly demonstrate the difference in the spectra of healthy people from sick people. As an example, Fig. 3 show the results for $M''(M')$ taken from [12] ($T = 20^\circ C$).
Figure 3. Cole-Cole diagram of the electrical modulus \( M''(M') \) for donors and patients. 1-4 – donors, I-VI – patients \((T = 20^\circ C)\) \[12\].

Probably, the differences in parameters \( \alpha, \beta, \tau \) for healthy and cancer patients will become larger at higher measurement temperatures. This assumption is confirmed by the results of studies of a solution of one of the most important serum proteins, human albumin at various temperatures \[10\]. As an example, we give the graph \( M''(f) \) taken from this work at different temperatures. The relaxation peaks in Fig. 4 shift to higher frequencies with increasing temperature, which confirms the relaxation type of the sample polarization process. For human albumin parameters \( \alpha, \beta, \tau \) change with increasing temperature.

Figure 4. Frequency dependence of the imaginary part of the electrical module \( M''(f) \) at different temperatures: 1 – 33 °C, 2 – 35 °C, 3 – 37 °C, 4 – 39 °C, 5 – 41 °C, 6 – 42 °C \[10\].

The graphs \( M''(f) \) presented in Fig. 2 and Fig. 4 show that for proteins in the blood serum by the method of a complex electrical module, it is possible to detect 3 relaxation peaks in the frequency ranges \( 10^0 - 10^9 \) Hz. Having carried out measurements at different temperatures \( T_i \) and calculated the relaxation times \( \tau_i \) for them, it is possible, by plotting the dependence of \( \ln(\tau_i) \) on \( 1/T_i \) (Arrhenius dependence), to determine the activation energy of macromolecules \( E_a \). Since this parameter is dependent on the conformation of macromolecules, it can also be a parameter that can be used to
monitor cancer. In this work, we considered the relationship between changes in the relaxation parameters $\alpha$, $\beta$, $\tau$, $E_a$ of blood serum only for oncological diseases. For other diseases, these parameters are likely to change as well. The study of the dynamics of changes in these parameters with the development of a specific disease is a topic for further research.

5. **Conclusion**

Thus, observation of the dynamics of changes in the parameters $\alpha$, $\beta$, $\tau$, $E_a$ of blood serum in cancer patients is likely to be a method for monitoring cancer.

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