

# Determination of intracellular electrical parameters in bioelectrical impedance analysis

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**Abstract.** Creating a frequency characteristic curve for bioelectrical impedance analysis involves analyzing electrical resistance (impedance) values at different frequencies. This curve is used to evaluate the electrical properties of biological tissues or fluids. In the article, the impedance of the intracellular environment was evaluated and frequency dependence was established based on the electrical circuit model of the biological system.  $X_c = f(f)$ ,  $Z = f(f)$ ,  $\varphi = f(f)$ ,  $tg\delta = f(f)$  dependencies were created for different frequency values of the intracellular environment in the Matlab program through a series-connected RC circuit. Regression and general statistical analyzes were performed. The most appropriate frequency range was determined to evaluate the impedance of the intracellular environment. The correlation relationship of electrical and dielectric parameters of the intracellular environment was also taken into account. Purpose: The main goal of the research is the selection of the optimal frequency range for bioimpedance analysis. In particular, the selection of the most optimal frequency was carried out in the assessment of intracellular electrical activity. The frequency range is determined depending on the electrical and dielectric parameters of the cell. Materials and Methods: Using the Matlab program, the equivalent circuit model of the cell was assembled. Frequency dependence of electrical and dielectric parameters characterizing intracellular processes was performed by model-based measurements. Conclusion: According to the obtained value, regression and general statistical analyzes were performed for the dependencies  $X_c=f(f)$ ,  $Z=f(f)$ ,  $\varphi=f(f)$ ,  $tg\delta=f(f)$ . Based on analysis of variance (Analysis of Variance-ANOVA) of the output variables, statistical parameters were determined for each dependency.

## 1 Introduction

Bioelectrical impedance analysis (BIA) is a non-invasive research method used to evaluate body segments. The level of interest in this research method is associated with certain advantages: it is non-invasive, inexpensive, portable [1]. Alternating current is applied to the tissues at different frequencies through electrodes. The "impedance" parameter is used to characterize the voltage drop. Liquids rich in electrolytes are more resistant to electric

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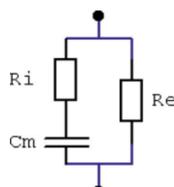
current than minerals in fat and bone tissue [2]. While high frequency currents up to 50 kHz pass through cell membranes and determine the amount of water in the whole body, currents up to 1 kHz cannot pass through the cell membrane and only allow the determination of the amount of extracellular fluid. Body components such as body fat percentage, body fat content, lean body percentage, lean body mass, body water percentage, body water content, and body mass index are calculated by substituting the resulting impedance changes into constant equations. As mentioned, pathological changes in the body can be usefully predicted based on bioelectrical impedance analysis.

As a result, we can say that the BIA method can provide a reliable, safe and effective way to examine body composition as well as other parameters resulting from the distribution of water in the body. It can be used in body composition examination in both cases: in healthy and chronic patients, with particular emphasis on metabolism-related diseases. The results of BIA research are affected by factors related to the correct selection of the BIA option used and the operation of the device, as well as the correct preparation of the subject [2].

### 1.1 Statement of the problem

The main structural element of the biological system is the cell, consisting of the cytoplasm and the membrane surrounding it. The cell membrane acts as a barrier between intracellular fluid and extracellular fluid. From a technical perspective, it can be said that the electrical resistance of the biological system varies depending on the cell structure, that is, the physical-chemical exchange between the internal environment and the external environment of the cell. Depending on the research methodology (determination of body mass index, fat ratio, dry muscle ratio on the bioimpedance analyzer) the resistance of the elements of the biological system is determined. Apparently, electrical resistance is a carrier of diagnostic information for a biological system [1, 3].

As we mentioned, depending on the research methodology (measurement of the electrical conductivity of the biological system), both constant and alternating current can be used as a stable source in the measurement circuit. Each form of current will produce unique biophysical effects in the biological system [4]. It is appropriate to use these biophysical effects in investigating the properties of the biological system. It is preferable to use an alternating current source as a stable source, especially considering the phenomenon of polarization. When applied from a low-frequency alternating current source, the probe current does not penetrate the cell membrane and flows through the circuit in proportion to the resistance of the extracellular fluid. When a high-frequency current source is used, probe current will flow through the circuit depending on the resistance of the cell membrane and extracellular fluid. Electrical modeling is used to calculate the probe current and electrical conductivity of the seed according to the structure of the biological system. When a low-frequency current flows through the tissue, this process is modeled by a resistance, when a high-frequency current flows, the cell membrane is modeled by capacitance, and intracellular and extracellular fluid is modeled by resistances (Figure 1) [5].



**Fig. 1.** RC circuit model in determining the electrical resistance of a biological system.

Here  $R_e$  is the resistance of the extracellular fluid,  $R_i$  is the resistance of the intracellular fluid,  $C_m$  is the membrane capacitance and  $z$  is the complex resistance [6].

As it is known, the impedance of biological tissue changes depending on the probe current at different frequencies. The law of variation of voltage with angular frequency and small amplitude is as follows [5].

$$\Delta V = V_m \sin \omega t = V_m \sin(2\pi f t) \quad (1)$$

Under the influence of the voltage, current will flow through the circuit with a certain phase shift. The law of variation of probing current will be as follows.

$$\Delta I = I_m \sin(2\pi f t - \theta) \quad (2)$$

Equations (1) and (2) can be used to determine the complex resistance expression of a biological object.

$$Z = V_m / I_m e^{j\theta} \quad (3)$$

Equation (4) can be obtained using Euler's equations in equation (3):

$$Z = \frac{V_m e^{j\omega t}}{I_m e^{j(\omega t - \theta)}} = e^{j\omega t - j(\omega t - \theta)} = e^{j\theta} = \cos\theta + i\sin\theta \quad (4)$$

$z_0 = V_m / I_m$  if we accept, we can write as follows.

$$z(\omega) = z_0 \cos\theta + i\sin\theta \quad (5)$$

If we look at the model in Figure 1, we can see that the complex resistance can be calculated by determining the voltages  $V_z$  and  $V_a$  and the ratio of the current passing through the circuit. Let's assume that the current passing through  $Z_x$  and  $R_a$  are equal ( $I_x = I_a$ ). We can then determine the ratio of voltages  $V_z$  and  $V_a$  with the following expression.

$$\frac{V_z}{V_a} = \frac{IZ_x}{IR_a} = \frac{Z_x}{R_a} \quad (6)$$

Based on expression (6), the following expression can be determined.

$$Z_x = R_a \frac{V_z}{V_a} = R_a \frac{|V_z| \angle \varphi_1}{|V_a| \angle \varphi_2} = R_a \frac{V_z}{V_a} \angle \theta \quad (7)$$

With the help of this equation, the bioimpedance of biological tissue can be determined [7-8].

As you can see, the electrical properties of the body can be approximated by an RC circuit. The parallel circuit shown in Figure 1 is a more accurate representation of the body's electrical circuit; where  $R_e$  and  $R_i$  represent the resistance of the extra- and intracellular fluid of the body, respectively, and the capacitance C characterizes the capacitance of the cell membrane.

Let's replace the two resistors connected in parallel with an equivalent resistor.

$$Req = (R_1^{-1} + R_2^{-1})^{-1} \quad (8)$$

The expressions for effective resistance and effective capacitance for the circuit in Figure 1 are determined as follows ( $R_e$  for extracellular and  $R_i$  for intracellular resistance):

$$R_{eff} = \frac{R_e R_i (R_e + R_i) + R_e X_i^2}{(R_e + R_i)^2 + X_i^2} \quad (9)$$

$$X_{C,eff} = \frac{R_e^2 X_i}{(R_e + R_i)^2 + X_i^2} \quad (10)$$

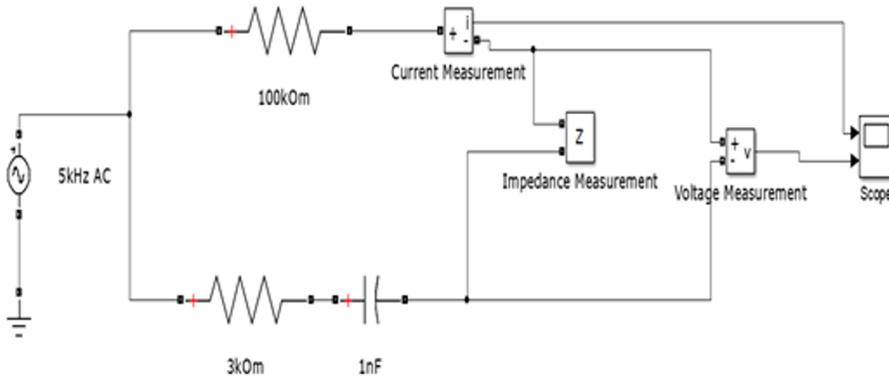
The model created in Figure 1 is also called the Cole-Cole model. The Cole-Cole model is a model used to characterize electrical conductivity and dielectric properties. This model is used to describe the complex impedance spectrum and is particularly used to describe the electrical behavior of polymers, biomaterials and other complex systems. The Cole-Cole model allows the electrical behavior of a biological system to be evaluated numerically based on these properties. Thanks to this model, it is possible to predict the intracellular and extracellular environment by determining electrical and dielectric parameters.

Although this model helps understand the electrical behavior of complex systems, it is not possible to accurately predict biophysical processes based on the electrical properties of the biological tissue under study. Therefore, the Cole-Cole model is used only as a tool for analyzing the electrical properties of biological tissue. Dielectric parameters of biological tissue can also be determined according to the Cole-Cole model. Considering that dielectric parameters are also a diagnostic indicator, it can be said that the use of this model in the evaluation of biological systems is widespread. During the literature review, it was determined that the model created to investigate the dielectric behavior of biological tissue as a function of frequency took different forms with subsequent research and was named Cole-Cole to express the dielectric properties of biological tissues. Based on this model, the following mathematical expression is obtained, which determines the dielectric constant [9].

$$\varepsilon(\omega) = \varepsilon_\infty + \frac{\varepsilon_S - \varepsilon_\infty}{1 + (j\omega\tau)^{(1-\alpha)}} + \frac{\sigma_i}{j\omega\varepsilon_0} \quad (11)$$

## 2 Materials and methods

In the multi-frequency and multi-segment human body bioimpedance determination study by Xiue Gao and Jia Tang, 2.7 GHz Ad8302 amplitude and phase adjustable from 0 V to 1.8 V were used in the measurement circuit. Referring to [6], the maximum value of the voltage in the simulation is taken as 1.8 V. In the research conducted by Kayu Chinen et al., numerical values of electrical resistance and capacitance for the right and left parts were determined. Based on the research [6],  $R_e = 100 \text{ K}\Omega$ ,  $R_i = 3 \text{ K}\Omega$  and  $C_m = 1 \text{ nF}$  were taken and the equivalent circuit model of the biological object was created in the Matlab program. Using the capabilities of the model, complex resistance that changes as a result of biophysical and biochemical processes occurring in the internal environment of biological tissue was measured.



**Fig. 2.** Electric circuit model of biological tissue in Matlab/Simulink.

### 2.1 Solution to the problem.

An RC series circuit was used to determine internal resistance and internal fluid capacity from an electrical circuit model of biological tissue in Matlab/Simulink. Figure 3 shows the electrical circuit model of the cell's internal environment. According to the circuit model, the impedance of the cell internal environment is determined according to the following expression [10].

$$Z_{RC} = R + jX_C = R + \frac{1}{j\omega C} \quad (12)$$

In this circuit we can also mathematically determine the electrical circuit parameters as a diagnostic indicator. First, let's adjust the  $X_C$  resistor.

$$X_C = \frac{1}{\omega C} = \frac{1}{2\pi f C} \quad (13)$$

By considering expression (12) in expression (11), we can obtain the mathematical expression that determines the frequency dependence of the complex intracellular resistance.

$$|Z_{RC}| = \sqrt{R^2 + \frac{1}{(\omega C)^2}} = \sqrt{R^2 + \frac{1}{(2\pi f C)^2}} \quad (14)$$

In some technical literature, angle is studied as a diagnostic indicator. There are basic studies on the use of phase angle as a clinical indicator in predicting various diseases. Phase angle has been found to be used in the prediction of diseases such as hemodialysis, cancer, immunodeficiency syndrome and liver disease [11]. For this purpose, the mathematical expression of the phase angle of the circuit has been defined.

$$\phi = \tan^{-1} \left( -\frac{1}{\omega C R} \right) = \arctan \left( -\frac{1}{\omega C R} \right) = \arctan \left( \frac{1}{2\pi f C R} \right) \quad (15)$$

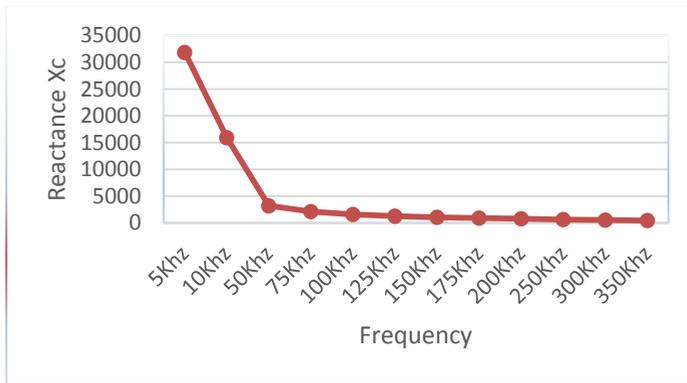
Electrical circuit parameters were directly measured for the intracellular environment for the circuit  $R_i = 3 \text{ K}\Omega$  and  $C_m = 1 \text{ nF}$  using current and impedance sensors in the

Matlab/Simulink software environment. Based on the obtained indicators, the reactive resistance, phase angle and loss angle were determined. Note that measurements are made in different frequency ranges. The minimum value of the frequency is 5 kHz. 5 kHz was chosen because there is a high correlation between the impedance of the intracellular and extracellular fluid at this frequency value [12]. In other studies, 50 kHz was sometimes chosen as the minimum limit value of the frequency [13].

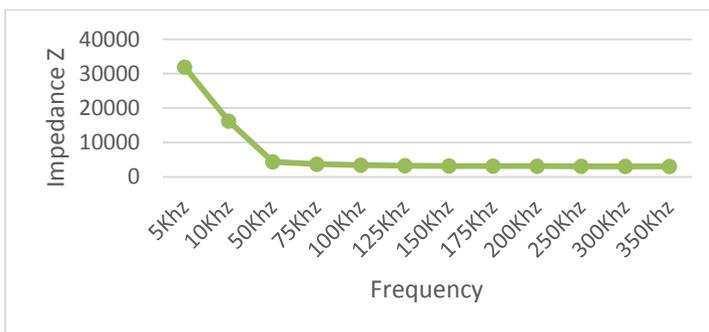
**Table 1.** Calculated parameters for cycle  $R_d C_m$  of biological tissue.

Frequency	Reactance $X_c$	Impedance $Z$	Phase angle $\phi$	Tanges $\delta$
5 kHz	31830	31970	84.62	64.76
10 kHz	15920	16200	79.33	46.69
50 kHz	3180	4370	46.7	11.95
75 kHz	2120	3670	35.27	8.05
100 kHz	1590	3400	27.95	6.05
125 kHz	1270	3260	23	4.85
150 kHz	1060	3180	19.48	4.04
175 kHz	909.46	3130	16.86	3.46
200 kHz	795.77	3100	14.86	3.03
250 kHz	636.62	3070	11.98	2.4
300 kHz	530.52	3050	10.03	2.02
350 kHz	454.73	3030	8.62	1.7

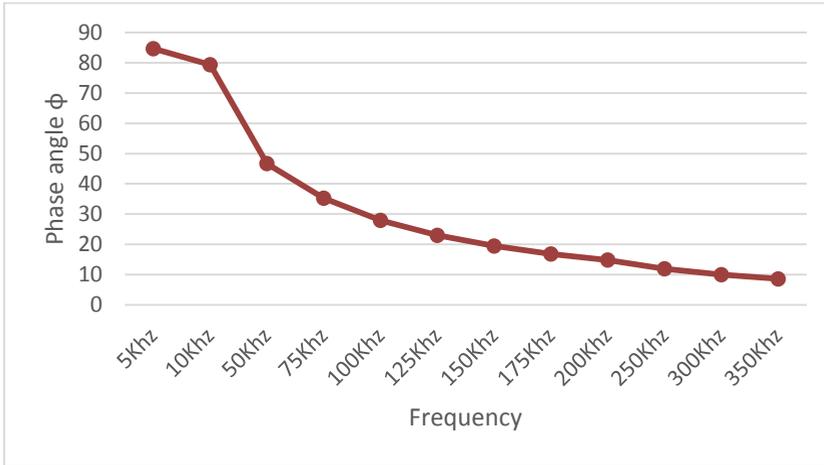
Based on the obtained parameters, frequency-reactive resistance, frequency-impedance, frequency-phase angle, frequency-tangent delta angle dependencies were established (Figures 3-6).



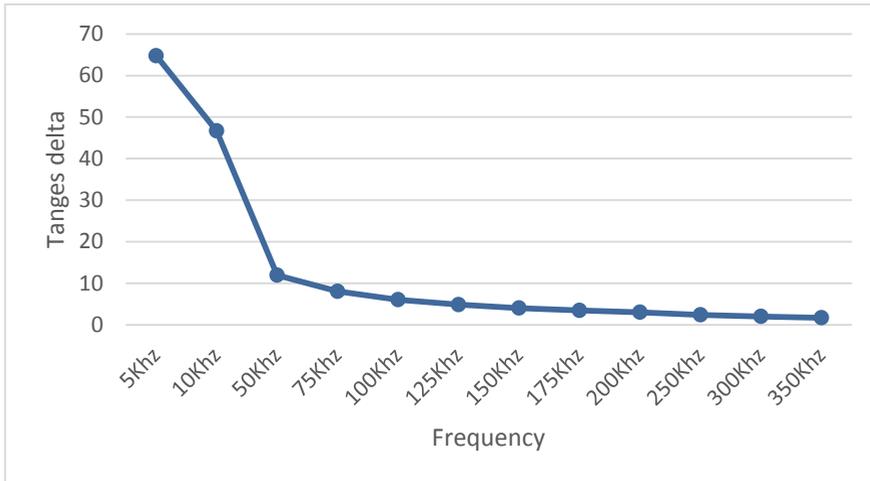
**Fig. 3.** Frequency-reactive resistance dependence in the frequency range of 5-350 kHz.



**Fig. 4.** Frequency-impedance dependence in the frequency range of 5-350 kHz.



**Fig. 5.** Frequency-phase angle dependence in the frequency range of 5-350 kHz.



**Fig. 6.** Frequency – tangent delta angle dependence in the frequency range of 5-350 kHz.

### 3 Results and Discussion

Bioelectrical impedance analysis is a diagnostic method performed by measuring the electrical resistance (impedance) of biological tissues. This method is used to evaluate the distribution of intrabody fluids, physiological properties of tissues and even some diseases. Frequency analysis can be used for this analysis. Frequency analysis in bioelectrical impedance analysis means examining the response of the tissue to electric current applied at different frequencies. Information about the properties of tissues is obtained by evaluating how signals applied at different frequencies behave in the tissue. This technique, specifically called bioelectrical impedance spectroscopy, can be used to detect diseases or fluid changes. Based on the mentioned ideas and the obtained indicators, the series-connected RC circuit model was used to evaluate the intracellular processes and cell membrane in the equivalent circuit model of the biological object, and effective frequency ranges were determined for analysis.

## 4 Conclusion

According to the obtained value, regression and general statistical analyzes were performed for the dependencies  $X_c = f(f)$ ,  $Z = f(f)$ ,  $\varphi = f(f)$ ,  $tg\delta = f(f)$ . Statistical parameters  $R = 0.9$ ,  $R^2 = 0.81$  and standard error  $SE = 2.51$  were set for dependence  $X_c = f(f)$ . For the dependence of  $Z = f(f)$ , statistical parameters  $R = 0.82$ ,  $R^2 = 0.67$  and standard error  $SE = 1.27$  were set. For the dependence  $\varphi = f(f)$ , statistical parameters were set  $R = 0.92$ ,  $R^2 = 0.85$ , and standard error  $SE = 0.9$ . For the dependence  $tg\delta = f(f)$ , statistical parameters were set  $R = 0.9$ ,  $R^2 = 0.81$ , and standard error  $SE = 0.9$ . Based on analysis of variance (Analysis of Variance-ANOVA) of the output variables, statistical parameters were determined for each dependency.

The statistics obtained allow us to say that dielectric parameters should also be examined in addition to electrical parameters when examining intracellular and cell membrane properties. Because the standard error rate in the dependencies  $\varphi = f(f)$  and  $tg\delta = f(f)$  is lower than the dependencies  $X_c = f(f)$  and  $Z = f(f)$ . Additionally, it was determined that the correlation coefficient regarding the dependencies  $X_c = f(f)$ ,  $Z = f(f)$ ,  $\varphi = f(f)$ ,  $tg\delta = f(f)$  was disrupted in the frequency range of 1 – 50 kHz. insignificantly. Particularly in the range of 30 – 50 kHz, the correlation coefficient obtained for the electrical circuit parameters for the intracellular and cell membrane was equal to  $R = 0.6$ . This means that there is no close relationship between these two parameters.

Frequency-reactive resistance, frequency-impedance, frequency-phase angle, frequency-tangent delta angle dependencies and the density and character of the connection in different frequency ranges are taken into account. For  $Z = f(f)$  dependence, it was determined that  $R = 0.99$  and  $SE = 3.8$  in the electrical circuit model for intracellular and cell membrane in the frequency range of 30 – 50 kHz. As we said before, more emphasis should be placed on the use of dielectric parameters in the evaluation of intracellular and cell membrane activity. In the same frequency range, the correction coefficient in the dependencies  $\varphi = f(f)$  and  $tg\delta = f(f)$  was high, i.e.  $R = 0.98$ . The standard error is lower here,  $SE = 05$ , due to electrical parameters and dependencies.

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