FREQUENCY SELECTION FOR PARAMETER IDENTIFICATION IN BIOIMPEDANCE SPECTROSCOPY

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The paper deals with a new method for the selection of test frequencies for parameter identification of Cole model in bioimpedance spectroscopy. The evaluation of the sensitivity functions versus frequency for the unknown parameters is employed. The sensitivity magnitude is used as a criterion for the test frequency selection.

1. INTRODUCTION

The body impedance analysis method being simple, inexpensive, accurate and noninvasive has become largely used to predict the fluid body distribution in different compartments of the body [1–6]: intracellular water (ICW), extracellular water (ECW) and total body water (TBW). There were reported several variants of the body impedance analysis method: single-frequency and dual-frequency bioimpedance analysis, methods also called bioimpedance analysis (BIA) and multi-frequency bioimpedance analysis called also bioimpedance spectroscopy (BIS). Intracellular water (ICW) can be used to estimate body cell mass (BCM) which is an important indicator of nutrition status. The evaluation of extracellular water (ECW) is also important to predict changes in fluid distribution for people with wasting, obese people and people receiving dialysis [6]. The trend in body impedance analysis is to improve the method by increasing the level of accuracy. The present paper deals with a new method for the selection of test frequencies for parameter identification of Cole model in bioimpedance spectroscopy.

2. BIOIMPEDANCE SPECTROSCOPY METHOD

BIS method is based on the different behaviour of the organic tissue for electrical current flow of low (LF) and high (HF) frequencies. In the low frequency
(LF) radio range (1 kHz to 100 MHz), the capacitive reactance produced by the capacitance of the cell membrane has high values, the conduction through the cells is small and the electric current flows mainly through ECW, as illustrated in Fig. 1a. As the frequency increases, the capacitive impedance decreases and the current that flows through ICW increases. At higher frequencies (HF) the capacitive reactance decreases to very small values and the current flows both through ECW and ICW proportionally with their relative conductivities and volumes, as illustrated in Fig. 1b.

The behaviour of the organic tissue for electrical current flow can be modelled with an equivalent electrical circuit known as Cole model [2, 3, and 4], presented in Fig. 2a, where $R_1$ represents the resistance of the intracellular fluid, $C_1$ the capacitance of the cellular membrane and $R_2$ represents the resistance of the extracellular fluid.
When the frequency of the electrical current rises from low to high values (1Hz–1200 kHz), the impedance $Z$ produces in complex plan a semicircular locus with a depressed center that represents the relationship between $X$ and $R$ as shown in Fig. 2b. The characteristic frequency $f_c$ corresponds to the maximum dependence of $Z$ on the $C_1$ capacitance. The intersections of the impedance locus with resistance axe, determine the values of $R_o$, which represents the resistance of ECW and $R_{INF}$, which represents the equivalent resistance of ECW and ICW resistances in parallel connection. The BIS method described in papers [3, 5], proposes formulas to predict total extracellular fluid volume $V_{ECW}$, the ratio between the TBW and ICW volumes, intracellular fluid volume $V_{ICW}$. The experiments [3] use also for comparison reference methods to determine the volume of fluids in the different cavities of human body: total body potassium method (TBK) to predict ICW, bromide dilution method (NaBr) to predict ECW and deuterium oxide dilution method ($D_2O$) to predict TBW. The constants in the formulas are determined [3] by cross validation against the reference methods.

The BIS method presented in [3, 5] is affected by important sources of errors. The relationship between $R$ and body water is nonlinear. The influence of mixture effects [3] on resistivity of skeletal muscle tissue is greater at low frequencies. The apparent conductivity of a conductive medium depends on the concentration of nonconductive material in suspension [3]. At LF the conductive medium is the ECW while at HF the conductive medium is formed by the combination of both ECW and ICW. The resistivity of conductive fluid is increased at LF because the current flow is restricted by the nonconductive cells. At high frequencies, over 500 kHz [3] and especially around 1MHz, the measurements are affected because of time delay $T_d$ effects. The delay caused by the finite speed of electrical signal through the conductor cannot be neglected and a model with distributed parameters could be more accurate. So, the errors of the measured data increase from 500-600 kHz. In this conditions, the accurately calculus of the ICW resistance become difficult. All in all, the measurements at LF and HF may have great uncertainties. The most important data are the measurements at frequencies surrounding the characteristic frequency $f_c$, because these data are more accurate. The ECW volume is predicted directly from the model term $R_o$, being strongly dependent of LF measurements. The ICW volume is determined indirectly from the ratio between TBW and ECW where TBW is estimated using the values $R_o$ and $R_{INF}$. The accuracy of prediction is poor, because the method, measure and calculus errors are cumulating in ICW volume determination. So, it is reasonably right to presume, that a direct determination of ICW and ECW volumes from the
measurements made in the mid-part of frequency range [1–1,248 kHz], could raise the accuracy of the method.

3. TEST FREQUENCY SELECTION IN BIOIMPEDANCE SPECTROSCOPY

The problem to be solved is to find a range of frequency where the three parameters of Cole model are not influenced by both mixture effects and \( T_d \) effects and small enough to consider the Cole model parameters constant. In this hypothesis there are necessary three equations to determine the Cole model parameters. The three equations could be generated evaluating the impedance function (1) of the electrical circuit corresponding to Cole model (fig. 2.a.), for three different frequencies.

\[
Z = \frac{R_R + \sigma C_i^2 R_R (R_R + R_2)}{1 + \sigma C_i^2 R_R (R_R + R_2)^2} + j \frac{\sigma C_i R_R - \sigma C_i R_2 (R_R + R_2)}{1 + \sigma C_i^2 R_R (R_R + R_2)^2}.
\]  (1)

The equation system has to fulfil the conditions of existence and unicity of solution. In order to determine the ranges of permitted frequencies, the sensitivity method was employed [7–8]. The sensitivity analysis for identifying the zones where the optimal frequencies have to be chosen has been made on the basis of two criteria: the sensitivity values must be high and the difference between sensitivities (measured at the same frequency) must be also high. The higher the sensitivity, the more significantly influenced is the function value by an unknown parameter which is thus easier to compute. The higher the difference between sensitivity characteristics, the more distinguishable is the influence of a certain parameter and thus, easier to identify. So, the frequencies ranges where the sensitivities characteristics vs. frequency have the same values or have the same shape must be avoided.

In the first case the module of impedance from (1) is used to generate the equations for parameter identification. The sensitivity functions are:

\[
S_{M1}^R = (\partial M)/(\partial R_1), \quad S_{M2}^R = (\partial M)/(\partial R_2) \quad \text{and} \quad S_{M1}^C = (\partial M)/(\partial C_1).
\]

The sensitivity dependence on frequency considering the nominal values of the parameters \( R_1 \), \( R_2 \) and \( C_1 \) are presented in Fig. 3. The nominal values of Cole model parameters were considered the mean values determined in paper [3]: \( R_1 = 1110 \Omega \), \( R_2 = 580 \Omega \), \( C_1 = 2.32 \text{nF} \). In the range 1 Hz–50 kHz, the sensitivities \( S_{M1}^R \), \( S_{M2}^R \) and \( S_{M1}^C \) shows different signatures. In the range 1Hz–40 kHz the sensitivities \( S_{M1}^R \) and \( S_{M1}^C \) are linear and parallel. Between \( S_{M1}^R \) and
there are more than ten orders of magnitude. In the range 50 kHz–1,000 kHz the sensitivities $S_M^{R_1}$, $S_M^{R_2}$ and $S_M^{C_1}$ shows different signatures. In the range 500 kHz–1,000 kHz the sensitivities $S_M^{R_1}$ and $S_M^{R_2}$ are linear and parallel. In conclusion, the range 70 kHz–300 kHz seems to be the most appropriate for test frequencies choosing. The conclusion was verified by simulation.

The nonlinear system of equations generated by the chosen test frequencies was solved employing Newton-Raphson (N-R) algorithm. For any set of test frequencies that contains the first frequency in the range 70–100 kHz and the other two in the range 100–300 kHz the N-R algorithm is convergent. For any set of frequencies in the range 100–300 kHz the N-R algorithm is convergent.

In the second part of the chapter, the phase of the bio-impedance function from (1) was used to generate the equations for parameter identification. The sensitivity functions are:

$S_{\phi}^{R_1} = (\partial \phi)/\partial R_1$, $S_{\phi}^{R_2} = (\partial \phi)/\partial R_2$, $S_{\phi}^{C_1} = (\partial \phi)/\partial C_1$.

The sensitivity functions versus frequency considering the values of the unknown parameters equal with their nominal values are presented in Fig. 4. In the range 1 Hz–50 kHz, the sensitivities $S_{\phi}^{R_2}$ and $S_{\phi}^{C_1}$ are linear and parallel and between $S_{\phi}^{C_1}$ and the others two there are more than ten orders of magnitude. In the range...
50 kHz–1 MHz, the sensitivities $S_{\phi}^R$ and $S_{\phi}^R$ have almost the same signature and between $S_{\phi}^C$ and the others two there are almost ten orders of magnitude. The influences of the sensitivities $S_{\phi}^R$ and $S_{\phi}^R$ are almost null all over the range of frequency 1Hz–1MHz, regarding to the phase function of the impedance.

That means that only the capacitance can be determined from the phase of the bioimpedance function with the condition that the values of the other two variables are known.

4. EXPERIMENTAL VALIDATION

The method presented in the third chapter of the paper needs an experimental validation. The most important thing to prove is that for the range of frequency 70–300 kHz, the values of the ICW and ECW resistances are slow variables, and according to the presumed hypothesis the method can be applied. There are employed, for this purpose, the measured results for bioimpedance multifrequency analysis of impedance module $M$ and phase $\phi$ for 21 frequencies, from paper [3].
The dependence between the reactance $X = \text{Im}[Z] = M \cdot \sin \varphi$ and the resistance $R = \text{Re}[Z] = M \cdot \cos \varphi$ is presented in Fig. 5. In the range 74–248 kHz there were chosen sets of three successive frequencies. The ratios between the values of two successive frequencies were chosen in the range 1.15–1.35 kHz. It results that the frequencies of a test set are spread in a range of almost 50 kHz.

The equations were generated evaluating the module of the bioimpedance function of Cole model (1) for the chosen set of frequencies. The system of nonlinear equations was solved employing N-R method. The results are presented in Fig. 6a. The variations of the three variables, between the biggest and the smallest values, are 4.35 % for $R_1$, 6.08 % for $R_2$ and 45.22 % for $C_1$. The average values for the three variables in the range 74–248 kHz are $R_1 = 2114.55 \, \Omega$, $R_2 = 442.62 \, \Omega$, and $C_1 = 535 \, \text{pF}$. The variations of the three variables, between the biggest values, the smallest values and the average values, are $+2.52$ % and $−1.87$ % for $R_1$, $+3.5$ % and $−2.65$ % for $R_2$ and $+27.3$ % and $−24.63$ % for $C_1$. If the difference between two frequencies is lower than 10 %, the generated equation is not distinct enough and the system has no solution, or if the solution can be obtained, it has a large level of error. E.g. the set 100–148–160 kHz for which the solutions of the equations, $R_1 = 1944.9 \, \Omega$, $R_2 = 47276 \, \Omega$ and $C_1 = 841.9 \, \text{pF}$, compared with the maximum values in the range [74…248] kHz, have higher errors (9.91%, 7.14% and 49.6 % respectively) than the values presented in Fig. 6a. In conclusion, with a variation under 5 %, the resistances $R_1$ and $R_2$ are slow variables in the range 74–248 kHz. That proves that the presumed
hypothesis is quite right. The values of $C_1$ are decreasing while the frequency increases in the range [74–248 kHz], from 736.1 pF to 403.2 pF that represents a variation of 45.22 %. The variation of capacity $C_1$ is produced in a range of frequency where its influence over the resistances $R_1$ and $R_2$ is small. The range of frequencies 25–60 kHz, where the influence of $C_1$ over the resistances $R_1$ and $R_2$ is maximum, has to be avoided.

![Graph](image)

Fig. 6 – $R_1$, $R_2$ and $C_1$ vs. set of test frequencies.

In the second example, all the possible sets of test frequencies in the range 100–200 kHz were used. The sets of frequencies containing the successive frequencies 148 and 160 kHz were avoided. The results are presented in Fig. 6b. The variations of the three variables, between the biggest and the smallest values, are 3.89 % for $R_1$, 3.55 % for $R_2$ and 29.7 % for $C_1$. The variations of the three variables, between the biggest values, the smallest values and the average values, are +2.73 % and −1.19 % for $R_1$, are +1.3 % and −2.28 % for $R_2$ and are +11.46 % and −20.58 % for $C_1$. It could be presumed that for a range of 50 kHz
representing the range of the test set of frequencies (e.g. 100-128-148 kHz), the variation of the three variables are not bigger than the values for a range of 100 kHz, so they are slow variables. As a conclusion the presented method can be applied to determine resistances $R_1$ and $R_2$.

The algorithm proposed in the paper to predict the fluid body distribution in different compartments of the body has the following steps:

1. There are preformed the measurements at several frequencies in the range [1-1200 kHz]; the range could be reduced at [20–300 kHz];
2. There are chosen at least three sets of test frequencies in the permitted range [70–300 kHz], e.g.: 100–128–148, 128–148–200, and 128–160–200 kHz;
3. The module of impedance from relation (1) is used to generate the equations for parameter identification for every set of test frequencies;
4. The equations are solved using N-R algorithm and the values of the three unknowns are determined for every set of test frequencies;
5. The resistances of ICW $R_I$ and ECW $R_E$ are determined as average values of $R_1$ and $R_2$;
6. Finally, in order to predict the fluid volumes of ICW and ECW, formulas based on the relation of proportionality between volume($V_I$ or $V_E$), height ($H_t$) and electrical resistance($R_I$ or $R_E$) [2, 3, 4, 5] could be used:

$$V_I = k_I \cdot W_I \cdot (H_t^2 / R_I),$$

$$V_E = k_E \cdot W_B \cdot (H_t^2 / R_E),$$

where $V_I$ is the intracellular fluid volume and $R_I$ is average value of $R_1$;

where $V_E$ is the extra cellular fluid volume and $R_E$ is average value of $R_2$. The coefficients of proportionality $k_I$ and $k_E$ could be determined by cross validation against the reference methods.

5. CONCLUSIONS

The paper proposes a new method for the selection of test frequencies for parameter identification of Cole model in bioimpedance spectroscopy. The evaluation of the sensitivity functions versus frequency for the unknown parameters is employed. The module of the bioimpedance function was used to generate the equations for parameter identification. For any set of test frequencies that contains the first frequency in the range 70–100 kHz and the other two in the range 100–300 kHz the proposed algorithm is convergent. For any set of frequencies in the range 100–300 kHz the proposed algorithm is convergent. The
ratios between the values of two successive frequencies have to be at least 1.15. In the determined range of permitted frequencies 70–300 kHz the values of the ICW and ECW resistances are slow variables. The range of permitted frequencies is rather far from \( f_c \), so the influence of the capacitance of the cellular membrane \( C_1 \) over ICW and ECW resistances is limited. An important advantage of the proposed method is that in the range of permitted frequencies the measurements are slightly influenced by both mixture effects and time delay \( T_d \) effects. Another important advantage is that ICW and ECW resistances are determined in the same conditions, using the same measured data at the same frequencies. In comparison with the method presented in [2, 4], in the proposed method the volumes of ICW and ECW can be determined directly from measurements with high level of accuracy. As a consequence the ICW and ECW volumes of fluid can be determined with a higher level of accuracy than other bioimpedance methods. Accurate information about fluid distribution in different compartments of the body is very important in drug dosage, drug and renal replacement therapy and nutritional support.

BIS is cheap, does not presume expansive laboratories, laboratory materials, high trained personnel. It is a friendly method and does not imply prelevation of fluids and has a huge prevention potential.

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