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Measurements of electrical impedance of biomedical objects

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Some basic problems related to measurements of electrical impedance of biological objects (bioimpedance) have been presented in this paper. Particularly problems arising from impedance occurring at the sensor–tissue interface (interfacial impedances) in contact measuring methods have been discussed. The influence of finite values of impedances of the current source and voltage measuring device has also been taken into consideration. A model of the impedance sensor for the four-electrode measurement method containing the interfacial, source and measuring device impedances has been given and its frequency characteristics obtained by the computer simulation have been presented. The influence of these impedances on the shape of frequency characteristic of the sensor model has been discussed. Measurements of bioimpedance of healthy and anomalous soft tissues have been described. Some experimental results, particularly the frequency characteristics of bioimpedance, have been shown. The presented results of measurement show that bioimpedance can be a valuable source of information about the tissues, so measurement of bioimpedance can be a useful supplement to other medical diagnostic methods.

Key words: *bioimpedance, bioimpedance spectroscopy, frequency characteristics*

1. Introduction

Measurements of electrical impedance of biological tissue (bioimpedance) have been widely used in medicine because of the relative simplicity of their technical realisation and potentially great possibilities for monitoring the state of tissues and organs [5], [10], both *in vitro* and *in vivo*. There can be distinguished an examination on a whole body scale, as fat-free mass (FFM), total body water (TBW), intracellular water (ICW), extracellular water (ECW) and body cell mass (BCM) or the body bigger parts (e.g., rheography and plethysmography [8]), examination of particular organs, glands or parts of the body (e.g., heart, liver, larynx, prostate, breast, blood, etc., [6], examination of some selected fragments (e.g., skin changes in dermatology [1]), and also examinations performed on a small scale (e.g., impedance measurements of a single cell).

The variation of bioimpedance as a function of frequency can be a valuable source of information about the state of an examined tissue – that leads to the electrical impedance spectroscopy method (EIS) [4], [9], [14], [15], [18]. This is a reason for increasing popularity of bioimpedance spectroscopy measurements at present. There are numerous descriptions of various bioimpedance spectroscopy systems available in literature [2], [19], [20].

Biological tissues belong to media that conduct the electric current [4], [7], [14], [15], [18]. Intercellular space and cell interior are ionic conductors and hence in general they are presented as resistive elements, whereas cell membranes, because of their structure, are presented as capacitive elements. Therefore, biological tissues are generally considered as objects of impeditive nature. The bioimpedance (as any impedance denoted usually by Z) can be described by two components: either as the real part, $\mathrm{Re}\{Z\}$ and

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the imaginary one, Im{Z}, or as the impedance modulus $|Z|$ and impedance phase angle φ.

The impeditive character of biological tissue causes electric current to be spread through tissues in a manner that is frequency dependent. It is commonly accepted that low frequency currents (of the order of kHz and below) flow mainly through the intercellular spaces whereas high frequency currents (hundreds of kHz, MHz) flow also through the cell membranes [7], [17]. Therefore, EIS can deliver information on the properties of various regions passed by currents of a given frequency. Diversification of the regions of different current flow provided by EIS makes it possible to evaluate the structure of the tissues being examined, e.g., the proportion between the intercellular space and the cell area (the state of cell membrane, etc.). In the case of many types of tumour with their growth of neoplasmic cells, degeneration of cell membranes occurs. This leads to changes of intercellular spaces which are the main flow paths for the low frequency currents – represented as a change of resistance and changes the higher frequency current flow path – this is related to the change of the cell membrane capacitance.

In the paper, results of bioimpedance measurements of selected healthy and abnormal tissues are presented. Samples of images of normal and anomalous tissue are shown in the next section.

2. Material and methods

2.1. Object of measurement

Investigation on bioimpedance has been made in the frequency domain for normal and metastatic lymph nodes and for normal and malignant epithelium tissue. The measurements have been carried out by means of Solartron 1253 analyzer and HP 34401A using the needle electrodes arranged in a tetragon (four-electrode method). It has also been analysed how measurements of bioimpedance are influenced by electrochemical interfacial phenomena (manifesting themselves in additional interfacial impedances occurring at the sensor–tissue interface for the typical electrocardiographic (ECG) electrodes) and by the parameters of measurement system. The corresponding measurements have been made using the Solartron 1253 analyzer applying a two-electrode measuring method.

Photographs showing examples of the differences between normal and pathological states of a tissue are presented in Fig. 1a, b [3]. An anomalous number of cells and a decrease in intercellular spaces (pathological tissue states) can be seen in Fig. 1b. These morphological changes result in changing values of related real and imaginary components of the tissue impedance. The changes of bioimpedance components, in turn, shape its frequency characteristics.

In general, information about the state of tissue can be extracted from the frequency characteristics using both bioimpedance components, only one of them (often the real part) or the magnitude of bioimpedance.

2.2. Method of measurement of bioimpedance

The simplest electrical scheme of a single cell, including the intercellular space, is shown in Fig. 2. Similarly clusters of cells (tissues, organs) are mod-

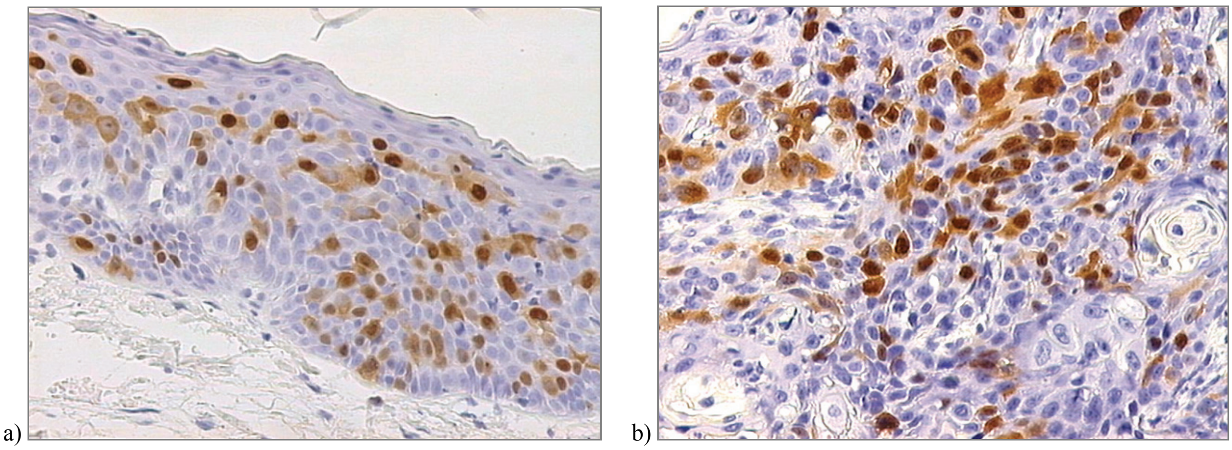

Fig. 1. Cells of the larynx epithelium in normal (a) and pathological (b) states (Photo M. Frączek)

elled [6], [7]. In more complex models of single cells and tissues a resistance representing ionic channels in the cell membrane is also taken into account.

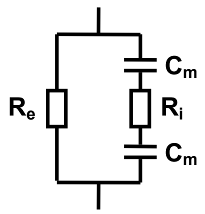

Fig. 2. Model of cell represented by its electrical components, where: C_m – capacitance of cell membrane (dielectric), R_i – intracellular resistance, R_e – extracellular resistance

In practice, measurements of bioimpedance are usually performed by means of contact methods, i.e., those with measuring electrodes being in a direct electrical contact with tissue. The current sources are often employed in the measurements.

Phenomena occurring at the contact surface of electrodes and tissue introduce the interfacial impedances to the measurement circuit. This means that the interfacial impedances (Z_c in Fig. 3b) are unavoidable in the measurement circuit.

In the two-electrode measurement they are added to the tissue impedance Z_x, hence the result Z_{meas} of such a measurement is a sum of impedances

$$Z_{meas} = \frac{V}{I} = 2Z_c + Z_x \tag{1}$$

where V, I, Z_c, Z_x – as shown in Fig. 3.

From equation (1) it follows that the two-electrode method essentially precludes measurement of tissue impedance Z_x alone.

It is possible to minimise the influence of interfacial impedances when a four-electrode method of measurement is applied – Fig. 4 [12], and the measuring circuit is excited by a current source. Here, two separate pairs of electrodes are used: a pair of current electrodes – for supplying measuring current and a pair of potential electrodes (voltage electrodes) – for detecting the voltage drop produced by current flowing across the tissue impedance. The interfacial impedances are formed on the measuring electrodes at their contact with the object under test (Z_v in Fig. 4b) similarly as for current electrodes (Z_c in Fig. 4b). However, the effect of these impedances on the measurement is usually minimized, because they are in series with a high input impedance of the measuring device. Similarly, the interfacial impedances of the contact of current electrodes and tissue, do not affect the value of the measured current because they are in series with a high impedance of the current source. Hence, in this method the tissue impedance Z_x is measured because the interfacial impedances Z_c and Z_v are omitted

$$Z_x = \frac{V}{I}. \tag{2}$$

It should be noted that relationship (2) is strictly valid provided that some idealised conditions are fulfilled, apart from the infinitely high impedances of the voltage measuring device and of the current source also a negligible influence of the potential electrodes

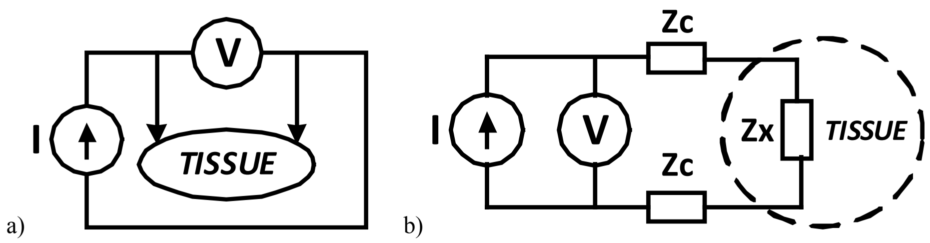

Fig. 3. Principle of two-electrode method of measurement (a), and its equivalent circuit (b). Notation: Z_x – measured impedance of tissue, Z_c – interfacial impedance of current electrodes, I – current, V – voltage

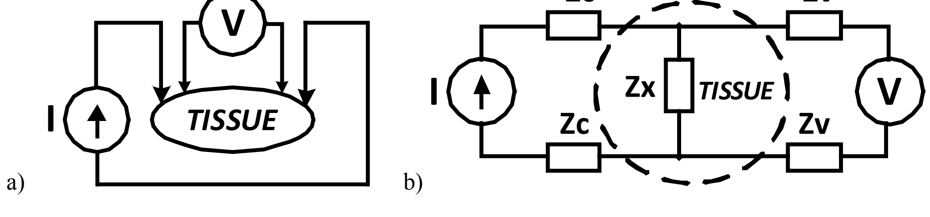

Fig. 4. Principle of four-electrode method of measurement (a) and their equivalent circuit (b). Notation: Z_v – interfacial impedance of potential (voltage) electrodes, Z_x, Z_c, I, V – as shown in Fig. 3

is demanded (deformation of the original electric field in the object of measurement is negligible). In real measurement systems, because of the existing interfacial impendances Z_c, Z_v and finite impedances of the current source and voltage measuring device, advantages resulting from applying the four-electrode method are attainable only within some limited frequency band [2]. In practice, it is possible (to some extent) to determine appropriately the frequency band of measurements by careful design of the current source and voltage measuring device and by minimising the interfacial impedances. These last ones can be considerably limited choosing electrodes made up of a proper material, of large contact surface with the tissue and good quality of this contact, improved, e.g., by covering the electrode surface with a gel.

2.3. Four-terminal model of impedance sensor

The model of the impedance sensor for the four-electrode measurement method is shown in Fig. 5. In this model, the following elements have been taken into account: the current source impedance (R_i, C_i), impedances of measuring device (R_d, C_d, R_{v1}, R_{v2}) and interfacial impedances of current (R_c, C_c) and voltage (R_v, C_v) electrodes. Parameters R_e, R_r and C_r represent the electrical properties of the object studied – the tissue. The frequency characteristics (the Bode plots) of the above sensor model obtained by the computer simulation are shown in Fig. 6. The characteristics in the high frequency region are limited mainly by the finite values of impedances of the current source and the measuring device. In the low frequency range the value of interfacial impedances of voltage electrodes is the limiting factor. In the mid-band the frequency characteristics can be shaped by the values of impedance of the object investigated. For example, some changes in the frequency characteristics due to various impedances of the object are shown in Fig. 6 (a – change of the R_r, b – change of the C_r). This implies that the shape of the

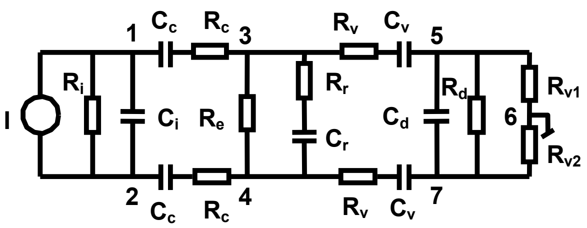

Fig. 5. The four-terminal model of impedance sensor used in simulation, where: I = 1 mA, R_i =200 kOhm, C_i = 100 pF, $C_c = C_v$ = 1 μF, $R_c = R_v$ = 100 Ohm, R_e = 5 Ohm, R_r = 5–20 Ohm, C_r = 2–10 μF, C_d = 10 pF, R_d = 100 MOhm, $R_{v1} = R_{v2} = 10^{10}$ Ohm

frequency characteristics can be an important source of information about the object.

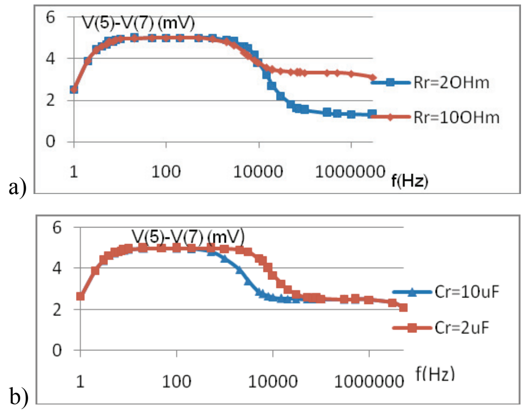

Fig. 6. The frequency characteristics of the model of impedance sensor (Fig. 5). The influence of R_r (a) and C_r (b) is shown

3. Results

3.1. Electrical impedance of soft tissues

In Figs. 7–9, the results of examination of healthy and pathological tissue obtained by the EIS method (four-electrode method of measurement) using the needle electrodes are presented [3].

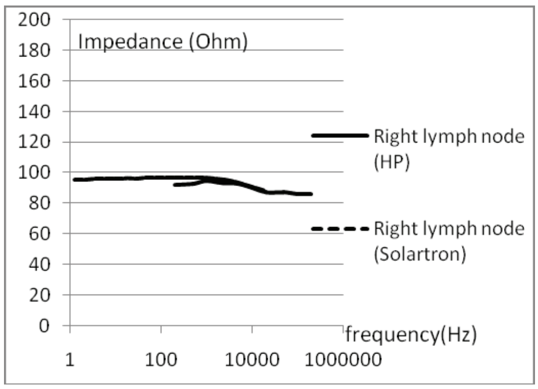

Fig. 7. Impedance spectrogram for normal lymph node. Superposition of the results obtained by Solartron 1253 Analyzer (1 Hz–20 kHz) and HP 34401A (100 Hz–300 kHz) is presented

It can be possible to carry out the EIS of soft tissues by a non-invasive method, applying the typical electrocardiographic (ECG) electrodes. Their large surfaces and a good skin–electrode contact minimise interfacial impedances. The authors performed a series of experiments in investigation aimed at determination of the tissue and interfacial impedance values occurring when applying such electrodes. In the measurements the ECG electrodes were stuck directly to the skin surface – Fig. 10. As a result, the frequency band of minimal influence of the electrode impedance and the input impedance of the measurement system on the results of the measurements have been determined.

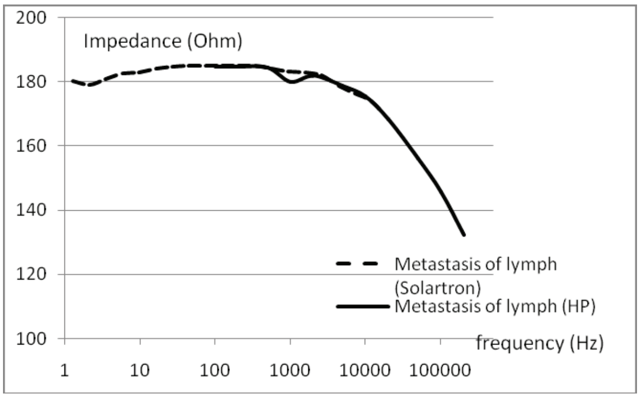

Fig. 8. Impedance spectrogram for metastatic lymph node. Superposition of the results obtained by Solartron 1253 Analyzer (1 Hz–20 kHz) and HP 34401A (100 Hz–300 kHz) is presented

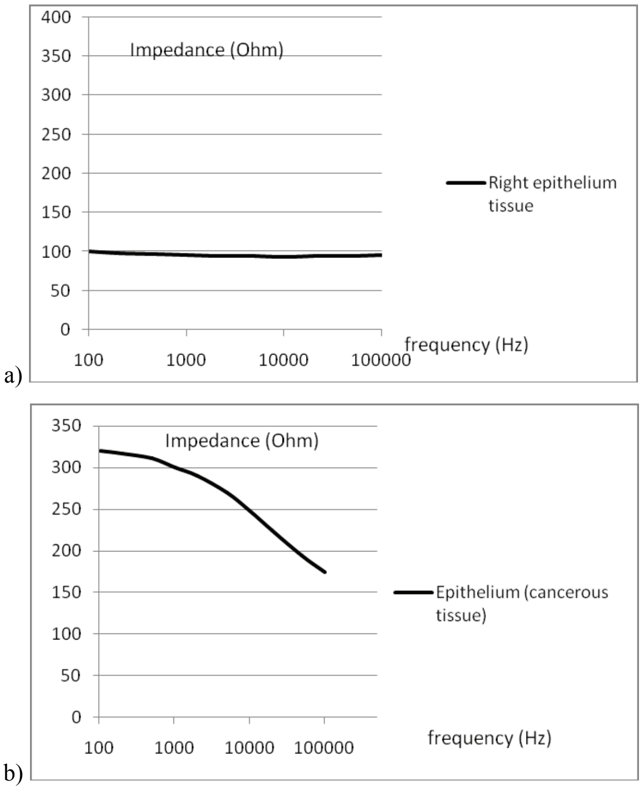

Fig. 9. Impedance spectrogram for normal (a) and malignant (b) epithelium tissue

An example of using the ECG electrodes in bioimpedance measurement (investigations of the effects of muscle injury) is presented in [13].

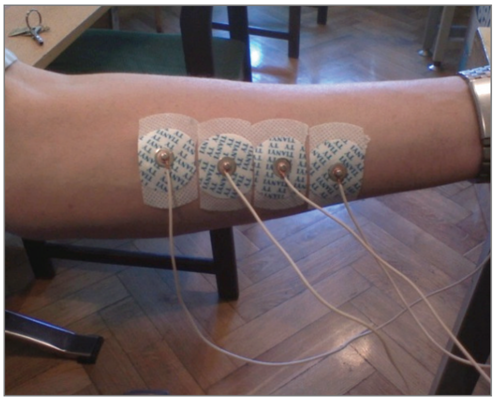

Fig. 10. Location of the electrodes during the impedance measurements for forearm, standard ECG electrodes

In order to determine the interfacial impedance values, the measurements were carried out by the two-electrode method, in the frequency band 2 Hz–20 kHz. In Fig. 11, examples of the results of measurement of the forearm impedance (real part of impedance – Fig. 11a, imaginary part of impedance – Fig. 11b), performed using the Solartron 1253 impedance analyzer, are presented.

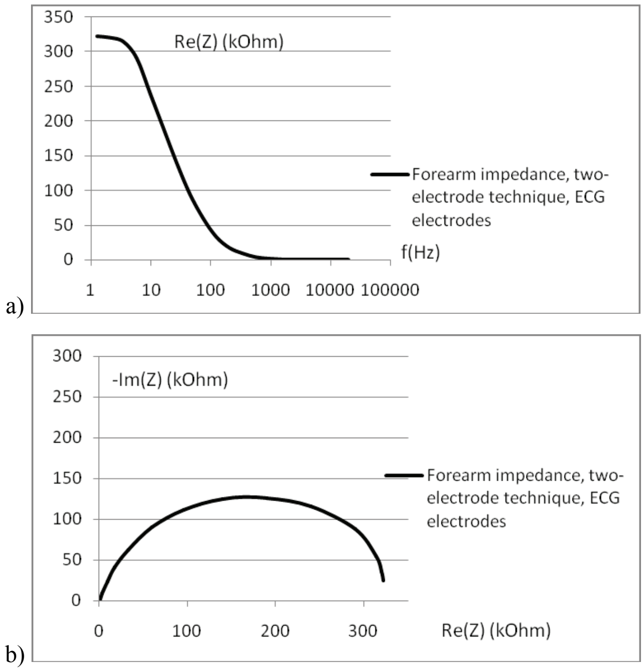

Fig. 11. Impedance spectrogram (Re Z – a, Im Z – b) for forearm

In Fig. 12, results of measurement of the real component of the forearm tissue, carried out by the four-electrode method, are presented. These results indicate that the tissue impedance is not large and is equal to about 38 Ω at the frequency band from hundreds of Hz to several kHz. Beyond this band the influences of the interfacial impedances and the measurement system impedances reveal themselves. It should be noted that value of measured impedance depends on the distance between potential electrodes – the higher the distance, the higher the value of measured impedance.

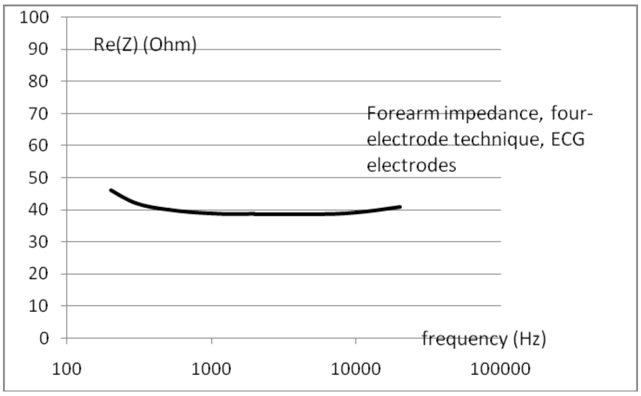

Fig. 12. Results of measurement of the real component of the forearm tissue impedance carried out by the four-electrode method using Solartron 1253 analyzer

4. Discussion

It results from the analysis of related literature sources that the impedance of each healthy tissue does not change significantly over a considerably wide range of frequency and only above a certain cutoff frequency it systematically decreases [4], [15], [18]. The largest change is characteristic of the dry skin – its impedance rapidly decreases in the frequency range 1 kHz–1 MHz. Other tissues tend to exhibit less dynamic changes of impedance as a function of frequency and the changes occur for much higher frequencies, e.g., muscle (along) – above 1 MHz, uterus – above 1 MHz [4]. The impedance of abnormal tissue, for example, the breast tissue, according to [15], [18], is lower than the impedance of healthy tissue and it also decreases above a certain cutoff frequency.

On the basis of the results of measurements it can be noted that the dynamics of impedance changes with frequency for the healthy and anomalous tissues is different. For the right lymph node (Fig. 7) there is a smaller decline in values of impedance for frequencies above 1 kHz than for metastatic lymph node (Fig. 8). For epithelium tissue (cancerous tissue) (Fig. 9b) there is a decrease of impedance at frequencies near 1 kHz, while for the right epithelium tissue (Fig. 9a) this change is not visible in the measuring frequency range (up to approx. 100 kHz). An assessment of the dynamics of changes of tissue impedance as a function of frequency and the frequency band in which these changes are visible can provide initial information about the state of tissue and may indicate the need for further medical examinations.

The results of impedance measurements of lymph (Fig. 7 and Fig. 8) show a good convergence of results obtained by two types of measuring apparatus (Solartron 1253 Analyzer and HP 34401A in some frequency range.

However, the comparison of the absolute values of impedances of healthy and anomalous tissues is at present difficult due to their incompatibility and different storage conditions for samples.

On the basis of the analysis, it can be concluded that the presented results illustrating the changes of impedance of healthy tissue well correspond with data of the tissue impedance as a function of frequency presented in the literature on the subject [4], [14]–[16], [18]. The results of measurement of impedance of an anomalous tissue show that the variations are consistent with reference data [18] – the impedance decreases with frequency.

A semi-circular shape of the frequency characteristic shown in Fig. 11 testifies to a capacitive character of the measured impedance and indicates a distinct domination of the interfacial impedances over the tissue impedance in the range of low and medium frequencies. The electrode impedances reach the values of the order of hundreds of kΩ at frequencies below 1 kHz. For frequencies above 1 kHz the influence of the electrode impedances decreases and the tissue impedance begins to dominate in the measured impedance.

In Fig. 12, a real part of the impedance of the forearm measured using the four-electrode method is shown – the tissue impedance is of the order of tens of Ω in the 100 Hz to several kHz frequency range. A slight increase in the value of the impedance in the higher frequencies can indicate the effect of the measuring system capacitances (capacitances of the sensor, connecting cables and measuring device).

Numerous simulation experiments (they are the subject of a separate study) made by the authors on the model of measuring system based on the four-terminal model of impedance sensor in which the capacitances of the sensor, connecting cables and measuring device have been additionally taken into account, show that for certain combinations of values of the capacitances this effect can occur at higher frequencies. This imposes corresponding requirements on the design of devices intended for such measurements, particularly for application in the frequency range up to hundreds kHz (e.g., investigation of state cellular membranes – β relaxation).

The obtained results confirm that the correct measurements of the tissue impedance itself (without the contributions of the electrode phenomena) require the four-electrode method of measurement. The expected range of the measured impedances (depending on the type of tissue and the sensor) can be estimated approximately as a few Ω to several kΩ, assuming appearance of the interfacial impedances even 100 times higher than the tissue impedance. It is desirable to perform the measurements in the frequency band from about 1 kHz (minimisation of the interfacial impedance) up to hundreds of kHz, because of investigation of state cellular membranes [7], [17].

5. Conclusions

The presented results of the bioimpedance measurements show the differences in shapes of frequency characteristics of healthy and anomalous tissues. This means that the results of the measurements of bioimpedance in some frequency band can be useful in studies of the state of the tissues. Therefore, the measurement of bioimpedance can be a valuable supplement to other medical diagnostic methods.

The standard ECG electrodes have been tested and successfully employed in the bioimpedance measurements. However, it has been shown that the interfacial impedances of the applied electrodes can be at some frequencies many times greater than the impedance of measured tissue. This effect can deteriorate the measuring accuracy and it has to be taken into consideration in the design and exploitation of bioimpedance measuring instrumentation.

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