Simulation studies of statistical distributions of cell membrane capacities and an ellipse model to assess the frequency behaviour of biological tissues

Willard Gerritsen¹, Robin van den Berg¹, Jan Mulder², Rudolf M. Verdaasdonk¹ and Jan H. Meijer¹

¹ Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, the Netherlands
² Physical Practica & Didactics, VU University, Amsterdam, the Netherlands
jh.meijer@vumc.nl

Abstract. The frequency behaviour of biological tissues is commonly described by a Cole model reflecting a single-cell bio-impedance model extended with an exponent α. However, for this parameter α there is no physical or biological substrate, which impedes an interpretation. The present study confirms by computer simulations of tissue models that the factual frequency behaviour can be explained by assuming a distribution of the electrical impedance properties of cells and of the capacitive coupling between cells. This behaviour is modelled mathematically by an ellipse. A mathematical procedure is presented to estimate this ellipse from experimental data by a least square method. A model parameter β is introduced, representing the ratio of the axes of the ellipse. A higher value of β means a larger variation in cell properties, which makes a patho-physiological interpretation of changes possible.

1. Introduction
A frequently used single-cell bio-impedance model consists of a unit of two resistors and one capacitor (see figure 1). The model is used to describe the frequency behaviour of biological tissues in the middle frequencies, called beta-dispersion. In this model $R_e$ represents the extra-cellular resistance, $R_i$ the intra-cellular resistance and C the capacity of the cell membrane. The complex impedance of this model is given by:

$$Z_{tot} = \frac{R_0 + j\omega \tau R_e}{1 + j\omega \tau}$$

In which $\omega$ is the angular frequency: $\omega = 2\pi f$. The time constant $\tau = R_iC$. $R_0$ is the impedance at the low frequency limit, $R_0 = R_e$, and $R_\infty$ is the impedance at the high frequency limit and is given by:

$$R_\infty = \frac{R_e R_i}{R_e + R_i}$$

A graphical representation of the frequency behaviour of this simple model in the complex plane results in a semi-circle.
In practice, however, the shape of the graph in the complex plane of tissue impedance differs from this simple model behaviour. The factual shape is more “flattened”. A commonly used mathematical model of the factual frequency behaviour of the impedance of biological tissues is the Cole model [1]. In this model an adjusting parameter $\alpha$ enhances the agreement with the experimental data. This mathematical formulation of Cole model is:

$$Z_{\text{tot}} = \frac{R_0 + (j\omega\tau)^\alpha \cdot R_{\infty}}{1 + (j\omega\tau)^\alpha}$$

(3)

The parameter $\alpha$ takes care of the problem of “flattening” of the semi-circle by shifting the centre of the semi-circle below the real axis, as is shown in figure 2. However, this model poses a new problem, since there is no physical or biological substrate for the mathematical parameter $\alpha$. This means that no interpretation is possible when $\alpha$ changes in the tissue under study, for instance in healthcare, or differs from similar tissues.

In 1953 Herman Schwan presented an interpretation of the observed frequency behaviour in the beta-dispersion region[2, 3]. A combination of multiple cell units with distributed time constants $\tau$ is understood to be responsible for this behaviour. This interpretation was investigated in the present study by computer simulations in which two or more cell units, up to thousands, were coupled in series and parallel. Further, in the present study a semi-ellipse is proposed to fit the frequency behaviour in order to bypass the problem of the interpretation of the parameter $\alpha$. In the relevant range of frequencies both models are expected to differ little in numerical value. A parameter $\beta$ is introduced that describes the variation in cell properties and that can be interpreted (patho-)physiologically.

2. Experimental method

Computer simulations were programmed in Wolfram’s Mathematica. This allowed unlimited elements in series and/or parallel to be chosen. The values of $R_\infty$, $R_i$ and $C$ were all standard set on 1, unless the parameter was selected to vary. Simulations were performed using specifically chosen values for a specific variable. Also randomized values from one or more Gaussian distributions were used.

To study the effect of varying respectively $R_\infty$, $R_i$ and $C$, simulations with a two cell-unit model were done. The values of cell elements were varied respectively. Subsequently the model was extended to tens, hundreds and thousands of cell units in series and into models with cell units in series and parallel.

3. Results

3.1 Computer simulation of the frequency behaviour of biological tissues

Simulations with two cell units model with two different values for the elements resulted in a “flattening” of the complex impedance graph (see figure 3). It was found that especially variation of $C$ resulted a flattening of the curve. If the chosen C’s were very different, the curve indented in the middle.
Figure 3. The computed impedance behaviour of a biological tissue model with two cell units. The plot of 5 values of the ratio of the first to the second capacitor is shown: C2/C1 = 1 (purple, dotted line), 0.5 (black), 0.1 (blue), 0.01 (brown), 0.001 (red, striped).

Figure 4. With increasing ranges of values of C the semi-circle flattens. The plotted values are: sd = 0 (purple, dotted line), 0.2 (black), 0.4 (brown), 0.6 (blue), 0.8 (purple), 1 (red), 2 (orange). Other parameter values Re = Ri = 1 (n = 1000 elements).

Simulations with larger numbers of cell units, using series of randomized numbers with a sufficient standard deviation, resulted in a “flattened” curve as well (see figure 4). If two series of randomized numbers with a different mean were combined, flattening was pronounced. Varying Re and/or Ri also resulted in flattening, however variation of C had the largest influence.

3.2 Method to find the best fitting ellipse for experimental data and establishing the ratio a/b.

From the simulations above it follows that the factual shape of the complex impedance curve deviates from a circle. In the present study it is assumed that the “flattened” form of the curve can be approximated by an ellipse.

The ellipse has two main axes, a real axis (long, a) and an imaginary axis (short, b). The ratio of the main axes a/b is considered to be a measure for the wideness of the distribution and is therefore physiologically interpretable. The ellipse can be fitted to measurement data by means of a least squares method, which results in a unique solution.

It is assumed that the centre of the ellipse is on the base line (real axis). Therefore the ellipse can be written as:

\[
\left(\frac{x-x_0}{a}\right)^2 + \left(\frac{y}{b}\right)^2 = 1
\]  

This is rewritten as:

\[
y^2 = b^2 - \left(\frac{b}{a}\right)^2 x_0^2 + 2\left(\frac{b}{a}\right) x_0 x - \left(\frac{b}{a}\right)^2 x^2
\]  

Three parameters are defined: \(\kappa = -\left(\frac{b}{a}\right)^2\), \(\lambda = 2\left(\frac{b}{a}\right) x_0\), \(\mu = b^2 - \left(\frac{b}{a}\right)^2 x_0^2\).

Finding the best fitting ellipse is reduced to finding the optimal solutions for \(\kappa x_i^2 + \lambda x_i + \mu = y_i^2\).
To solve this equations, two matrices are defined:

\[
A = \begin{bmatrix} x_1^2 & x_1 & 1 \\ x_2^2 & x_2 & 1 \\ \vdots & \vdots & \vdots \\ x_n^2 & x_n & 1 \end{bmatrix}, \quad B = \begin{bmatrix} y_1^2 \\ y_2^2 \\ \vdots \\ y_n^2 \end{bmatrix},
\]

in which \( n \) is the number of data sets. Using any mathematical program solutions can be calculated for \( AX = B \) using the least squares method in which

\[
X = \begin{bmatrix} \kappa \\ \lambda \\ \mu \end{bmatrix}.
\]

A new parameter \( \beta \) can be defined:

\[
\beta = \frac{a}{b} = \frac{1}{\sqrt{-\kappa}}
\]

to describe the frequency behaviour of biological tissues.

4. Discussion

The computer simulations confirmed the interpretation that the frequency behaviour of biological tissues originate from a distribution in the electrical impedance model parameters of tissue cells. A wider distribution corresponds to a “flatter” graph in the complex plane which resembles a lower \( \alpha \) in the Cole model, although the graph in the complex plane differs from a semi-circle. This distribution of tissue properties can be interpreted physiologically: Biological tissues usually consist of more than one type of cells. Differences in the properties of the cells, e.g. in cancer, may influence the variation in these impedance parameters. Even within one type of cells a distribution in age and therefore a distribution in stage of development and size will be present. Further, cells are not arranged within tissues with a mathematical regularity. This will result in a statistical distribution in capacitive coupling between the cells. For instance, the volume of interstitial fluid and/or inflammation may influence this coupling.

To bypass the problem of absence of a physiological substratum for the Cole parameter \( \alpha \) and the theoretical absence of an indication to fit a semi-circle, an ellipse model is designed to fit measured impedances and a procedure is presented extract to model parameters. A parameter \( \beta \) is introduced, that represents the ratio of the long axis to the short axis of the ellipse. The computer simulations show that tissues with a large variation in cell properties lead to a flatter ellipse, resulting in a higher value of \( \beta \). Thus a higher value of \( \beta \) means less uniformity. These considerations make patho-physiological interpretations of differences and variations in frequency behaviour possible. Therefore, this interpretation offers a variety of clinical applications. Future studies have to validate this ellipse model by comparing the quality of the fit with the Cole model in experimental data.

References

[1] Cole K S 1972 Membranes, Ions and Impulses 2nd printing (University of California Press, Berkeley and Los Angeles)
[2] H P Schwann and K Li 1953 Capacity and conductivity of body tissues at ultrahigh frequencies National Convention Record, i.e., Proc. Of I.R.E. 41 1735
[3] Grimnes S and Martinsen Ø G 2008 Bioimpedance and bioelectricity basics (2nd edition) Elsevier. Amsterdam, Boston, Heidelberg