Sensibility analysis of the electrical impedance parameters by the Monte Carlo method

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Abstract. Electrical properties of biological tissues are used to analyze its state in different practical applications, e.g., assessing the risk of cancer. The modeling of electrical properties usually is performed by circuital models or semiempirical models as Cole-Cole. Still, another option is available, the application of the generalized effective medium theory of induced polarization. In the framework of the effective medium theory, we proposed a model for biological tissues which we called MOPET. This model links physiological parameters of tissues with their electrical properties. However, it has a higher number of parameters than the Cole-Cole and circuital models. This large number of parameters is a limitation for the use of effective medium theory to describe the electrical properties of tissue and also suggests that some of these parameters have negligible effects. We used a Monte Carlo simulation to study the effect of each MOPET parameter on the electrical impedance spectra, where uniform random variables were used to simulate the variability of the parameters of this model. We found that the heterogeneity coefficient is the most sensible parameter, i.e., a variation above 1% in this parameter alters enormously the impedance spectra.

1. Introduction
The electrical impedance spectroscopy is usually used to study the electrical properties of tissues [1] and to predict diseases like cancer [2–4]. The use of models with some parameters is common in the electrical impedance spectroscopy studies. The most common models to describe the experimental results are Cole-Cole [5] and circuital models [6]. In 2013, Miranda, et al. [7] proposed a model to apply the generalized effective-medium theory of induced polarization (GEMTIP), i.e., the MOPET model, to analyze the electrical properties of tissues. GEMTIP was developed to explaining the phenomenon of the induced polarization in rocks exposed to an external electrical field [8]. As its name suggests, GEMTIP is a generalization of the theory of the effective medium that allows us to represent a heterogeneous medium as a homogeneous one using the induced polarization present in each of the inclusions of the heterogeneous medium.

An advantage of using GEMTIP in the study of the electrical properties of biological tissue is the relation between the physiology of the tissue and the parameters that model its electrical behavior, as we describe below. Spite of the advantage of GEMTIP to construct models to describe the electrical properties of biological tissues, its number of parameters is higher than the used in Cole-Cole or circuital models [7]. It would be useful to determine what of these parameters can be omitted or approximated to reduce the number of effective parameters needed to model the electrical properties of biological tissues. The question is how to identify what parameters are relevant in the model.
A possible way to address the relevance of each parameter is to perform several simulation of the model, with different values for the parameters. By comparing the simulation results, the effect of each parameter on the electrical properties studied can be determined. In this paper, we treated each MOPET parameter as a random variable, under a uniform distribution that offers the same probability of output for each of the variables presented. The Monte Carlo theory [9] was selected to simulate the model and to analyze the sensibility of the MOPET’s parameters.

2. The MOPET model
The GEMTIP can be applied to describe electrical properties of biological tissues, in particular, the cervical tissues can be modeled as organized structures with $N$ different cell types, with internal resistivity ($\rho_l$), radio ($a_l$), surface polarizability coefficient ($\alpha_l$), immersed into a homogeneous medium (extracellular medium) with resistivity ($\rho_0$) where the subscript ($l$) means the cell type, i.e., the MOPET model [7]. In this way, the GEMTIP theory can be used to analyze biological tissues [7] as follow. Equation (1) defines the admittance ($Q_l$) of the $l$th type of cells, this means, how easily the cell will allows the current flow:

$$Q_l = \frac{a_l}{\alpha_l} (2\rho_0 - \rho_l).$$

(1)

The effective medium electrical resistivity can be expressed as Equation (2), which contains the real and imaginary parts of the electrical impedance spectrum.

$$\rho_e = \rho_0 \left[ 1 + \sum_{l=1}^{N} M_l \left[ \frac{1}{1 + Q_l(j\omega)_{cl}} \right] \right]^{-1}.$$  

(2)

In Equation (2), ($c_l$), is a heterogeneity parameter, ($M_l$), the weighted polarizability presented in the Equation (3), a quantity related to the cell volume fraction ($f_l$), extracellular medium resistivity ($\rho_0$) and resistivity ($\rho_l$) of each of the spherical inclusions (cells). Where $M_l$ is defined by Equation (3).

$$M_l = 3f_l \frac{\rho_0 - \rho_l}{\rho_0 + 2\rho_l}.$$  

(3)

Note that the sum of all volume fraction is given by Equation (4).

$$f_0 + \sum_{l=1}^{N} f_l = 1,$$  

(4)

where ($f_0$) represents the volume fraction of the extracellular medium and the ($f_l$) is a weighted fraction of the volumes associated with each type of the spherical cells, where the sum of both should be the complete tissue. The fraction of volumes that are associated with each cell type can be obtained by the Equation (5) depending on the radius of these ($a_l$).

$$f_l = (1 - f_0) a_l^3 / \sum_{l=1}^{N} a_l^3.$$  

(5)

3. Methods and materials
From Equation (1) to Equation (5), we built a MOPET model to describe healthy cervical tissue with three types of cells ($l = 1, 2, 3$). We used the parameters of healthy cervical tissue reported by Miranda, et al. [7]. These three types of cells involve the use of a MOPET model with 14 parameters: ($f_0$), ($\rho_0$) and three per each ($\rho_l$), ($a_l$), ($\alpha_l$), and ($c_l$). We select a uniform
distribution to model the uncertainty in each parameter of the model, i.e., a uniform random variable was defined to each MOPET parameter. The mean value of each variable is given in Table 1. Each uniform random variable was constructed using uncertainties ($\Delta f_0$), ($\Delta \rho_0$), ($\Delta \rho_l$), ($\Delta a_l$), ($\Delta \alpha_l$), and ($\Delta c_l$); these uncertainties were variate to analyze its effects in the electrical impedance spectra. For each mean values, and uncertainties, a Monte Carlo simulation with 250 iterations were performed.

| l | $\rho_l$ [Ωm] | $a_l$ [µm] | $c_l$ | $\alpha_l$ [Ωm$^2$/s$^{c_l}$] |
|---|---|---|---|---|
| 1 | 0.05 | 10.60 | 0.99 | 148.42 |
| 2 | 0.08 | 15.70 | 1.00 | 187.50 |
| 3 | 0.11 | 20.90 | 1.00 | 232.54 |

**4. Results and discussion**

Several Monte Carlo simulations were performed with different uncertainties in the MOPET parameters. The simulations were implemented with Python in a Jupyter Notebook. Figure 1 shows the electrical impedance spectra without uncertainty in the parameters, and the lower uncertainty we observed is in Figure 2. The electrical impedance spectra are plotted as real part (blue) and minus the imaginary part (red) as a function of the frequency. In the electrical impedance spectra plotting the frequency is on a logarithmic scale and the impedance on a linear scale. In the following sections, we describe and discuss the two more important results we obtained with the Monte Carlo simulations.

**Figure 1.** Electric impedance spectra of a healthy cervical tissue modeled with the parameters of Table 1.

**Figure 2.** Best model obtained by Monte Carlo simulation of the electric impedance spectrum presented in Figure 1, real part in blue and imaginary part in red. ($\Delta f_0 = 10\%$), ($\Delta \rho_0 = 0.7\%$), ($\Delta \rho_l = 10\%$), ($\Delta a = 3\%$), ($\Delta \alpha = 2\%$), ($\Delta c = 0.1\%$).

**4.1. The parameter with the lower uncertainty**

There are two concepts associated with the effect of parameters variability into the electrical impedance spectra, one is the uncertainty and other is the sensibility, as illustrated in the Equation (6). The uncertainty is given by the width ($\Delta x$) of the statistical uniform distribution ($u_x$).
where \((\bar{x})\) is the mean value of a given \((x)\) parameter. The sensibility is associated with the minimum amount of \((\Delta x)\) associated to a high variation of the electrical impedance spectra. High sensitivity for a parameter \((x)\) means this parameter affects the electrical impedance spectra with lower changes on the uncertainty \((\Delta x)\). According to Figure 2, Figure 3 and Figure 4, the parameter with greater sensitivity is \((c_l)\), this means that the range of uncertainty of this parameter must be small to obtain a reliable model of the electrical properties of tissue. Into the model, this parameter \((c_l)\) is related to the relaxation times distribution of the cells, i.e., the distribution of the times that each cell needs to return to its initial state after being submitted to an external field that induces a polarization.

The electrical impedance spectra simulated with uncertainty range of the \((c_l)\) parameter between \((\Delta c_l = 0.1\%)\) and \((\Delta c_l = 10.1\%)\) are shown in Figure 3 and Figure 4, respectively. At low uncertainties \((\Delta c_l = 0.1\%)\) the simulations have similar spectrum shape and properties, but when \((c_l)\) is varied in a higher range, the spectrum changes from the spectrum with out uncertainties, Figure 1, reinforcing the observation of the high sensitivity of this parameter. The heterogeneity of the tissue could explain the sensibility of the parameter \((c_l)\), i.e., each cell type has a different relaxation time distribution.

4.2. The parameter with the higher uncertainty

High uncertainty in a parameter \((x)\) means the electrical impedance spectra obtained remain unchanged when the parameter changes in a high proportion. Then, a parameter with high uncertainty has a few effects on the electrical properties of the tissue and can be considered as a low sensible parameter. From the simulation, we observed the parameter with the higher uncertainty and the less alteration in the electrical impedance spectra was \((\rho_l)\), Figure 5, and Figure 6: this is an unexpected result due to this parameter is associated with the intracellular medium resistivity and biologically is an essential part of the tissue.

Note in Figure 6 the uncertainty of \((\rho_l)\) is 90\%, and in Figure 5, 0.1\%, however, the spectra appear equals. This low sensitivity in the parameter \((\rho_l)\) for a healthy tissue suggest the more important parameter in this tissues are the parameter \((\rho_0)\), the extracellular resistivity medium, as is suggested in previous works [2–4, 10]. A numerical analysis of Equation (3)
can explain this observation, because \((\rho_l)\) is introduced into the electrical properties of the tissues by the parameter \((M_l)\). The parameter \((M_l)\) depend upon intracellular resistivity \((\rho_l)\), extracellular resistivity \((\rho_0)\), and the fraction volume \((f_l)\). In epithelial tissue, the ratio of the volume occupied by the cells to the volume of extracellular medium is small, so the extracellular resistivity would \((\rho_0)\) should predominate over \((\rho_l)\) [11]. Due to the higher value of the extracellular resistivity \((\rho_0)\) respect to the intracellular resistivity \((\rho_l)\), a high variation on \((\rho_l)\) don’t affect the parameter \((M_l)\), instead, a change of \((\rho_0)\) has a significant effect; this means, the parameter \((\rho_l)\) have a low impact on the electrical properties of the healthy tissue.

**Figure 5.** Monte Carlo simulation to analyze the parameter with the higher uncertainty but few effects in the electrical impedance spectra. The model used to the simulations includes the uncertainties: \((\Delta f_0 = 20\%)\), \((\Delta \rho_0 = 1\%)\), \((\Delta \rho_L = 0.1\%)\), \((\Delta a = 5\%)\), \((\Delta \alpha = 5\%)\), \((\Delta c = 1\%)\).

**Figure 6.** Monte Carlo simulation to analyze the parameter with the higher uncertainty but few effects in the electrical impedance spectra. The model used to the simulations includes the uncertainties: \((\Delta f_0 = 20\%)\), \((\Delta \rho_0 = 1\%)\), \((\Delta \rho_L = 90.1\%)\), \((\Delta a = 5\%)\), \((\Delta \alpha = 5\%)\), \((\Delta c = 1\%)\).

5. Conclusions
The electrical properties of healthy cervical tissue were modeled by MOPET, a model based on the GEMTIP. The effect of the higher number of parameters of the model was analyzed by Monte Carlo simulations taking each parameter as a random uniform variable. Results showed, for healthy tissue, the intracellular resistivities \((\rho_l)\) have a few effects on the electrical impedance spectra and can be considered as a few sensible parameters in the model. This means the intracellular resistivities for healthy cellular tissues doesn’t contribute significantly to the electrical properties of the tissue. However, these results are valid only to healthy tissue where the values of the intracellular resistivity are much smaller than the extracellular resistivity. This implicates that in spite of the low sensitivity of the parameter \((\rho_l)\), the numerical values of them must be much lower than the \((\rho_0)\) for healthy tissue.

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