Cervical cancer detection by electrical impedance in a Colombian setting

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Abstract. Electrical properties of normal and neoplastic cervical tissues in a heterogeneous group of 56 Colombian women were studied by electrical impedance spectroscopy and a model based on the Generalized Effective Medium Theory of Induced Polarization (GEMTIP). Differences between the electrical bioimpedance spectra were correlated with cellular and tissue parameters. The analysis performed by the proposed model suggest that the number of different types of cellular layers that form the biological tissue, the intracellular and extracellular conductivity could be used to explain the differences between electrical bioimpedance spectra in normal and neoplastic tissues.

1. Introduction
Cancer is a disease associated to a high morbidity and mortality that causes about 12.5% of all deaths worldwide [1]. Cervical cancer is a public health problem in Colombia and the first cause of death by cancer in women [2]. The Colombian government promotes the Papanicolau test as a screening tool for early detection of cervical cancer. However, the incidence and prevalence of cervical cancer in Colombian women are high because the quality of the diagnostic and monitoring programs is not good enough [3]. Electrical characterization of cervical tissue has been proposed as a tool to improve the sensibility and specificity of cervical cancer screening [4, 5, 6].

Electrical characterization usually is performed by electrical impedance spectroscopy (EIS), which allows the study of electrical properties of tissue at different frequencies. Experimental data have been analysed by empirical or theoretical models as Cole–Cole [7], the three-element RC [8] and physiological models [9,10]. The Cole – Cole relaxation model is the most widely used for data analysis of electrical characterization techniques [5, 6, 11, 12], as it is useful to identify tissue changes and has simple mathematics behind it. However, it is not easy to quantitatively associate all Cole–Cole parameters to structural tissue properties [10].

Recently, Michael Zhdanov developed a physical – mathematical model of heterogeneous conductive media based on the Generalize Effective – Medium Theory of Induce Polarization (GEMTIP) to study the heterogeneity, multiphase structure and polarization in rocks [13]. After a rigorous mathematical work, Zhdanov [14] obtained the following equation to describe the effective resistivity of a composite model formed by a homogeneous host medium with resistivity \( \rho_0 \) and volume fraction \( f_0 \) filled with \( N \) types of spherical inclusions of radius \( a_l \) (see eq5), volume fraction of inclusion \( f_l \) and resistivity \( \rho_l \):
Here $k_i$ is a surface polarizability factor that usually takes the form of $k_i = a_i (i \omega)^{-C_l}$. Then,

$$\rho = \rho_0 \left(1 + 3 \sum_{l=1}^{N} \frac{f_i \rho_0 - \rho_l}{2\rho_0 + \rho_l + 2k_i a_i^{-1}}\right)^{-1}$$  \hspace{1cm} (1)$$

Where, $M_l = 3f_i \rho_0 \frac{\rho_0 - \rho_l}{\rho_0 + 2\rho_l}$; $f_i$ is the volume fraction of cell of $l$th type; $\tau_l$, a relaxation time and $C_l$, a relaxation parameter.

The Cole–Cole equation for resistivity can be derived from GEMTIP data, under the assumption that all spheres have the same ratio and the same resistivity. From this, we hypothesize that the behaviour of biological tissues can be described in an analogue way as Zhdanov did to describe rocks inclusions in an electrolytic media. We assume that cells are spheres with resistivity $\rho_l$ immersed in the extracellular medium of resistivity, $\rho_0$. In this paper we analyse some experimental data using GEMTIP with above assumptions.

2. Methods and Materials

Electrical impedance spectra (EIS) of human cervical tissues were measured at seven different frequencies between 9.6 KHz and 614 KHz using the MARK-III bioimpedanciometer [4] and a tetrapolar probe. EIS were collected into 56 Colombian women. From EIS experimental spectra one spectrum per classification group was selected: normal (NO), low grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) and carcinoma (CA). Abnormal tissue type was determined histopathologically. Experimental data were fitted to the GEMTIP model by mean of a genetic algorithm to obtain the parameter for each layer, $l$: Resistivity of extracellular medium, $\rho_0$; $M_l$: relaxation time, $\tau_l$ and relaxation parameter, $C_l$.

Intracellular resistivity $\rho_l$ of $l$th layer, was calculated by:

$$\rho_l = \frac{3-\eta_l}{3+2\eta_l} \rho_0$$  \hspace{1cm} (3)$$

and $$\eta_l = \frac{M_l}{f_l}$$  \hspace{1cm} (4)$$

Where, $f_1 \leq 1$ and $f_0 + \Sigma f_i = 1$ were selected according to the tissue structure.

The radius of $l$th cell, was calculated as:

$$a_l = \frac{2\alpha_l \tau_l C_l \rho_0}{\rho_0 + 2\rho_l}$$  \hspace{1cm} (5)$$

Where $\alpha_l$ is the surface-polarizability coefficient. The values for surface-polarizability coefficient were selected to obtain cellular radius between 10 ~ 23 μm considering that typical eukaryotic cell sizes range from ~10 to ~100 μm [15]:

3. Results and Discussion

Figure 1 shows the real and the imaginary part of the electrical impedance spectrum for selected EIS readings from samples classified as NO, LSIL, HSIL and CA. The imaginary part was obtained by fitting from the GEMTIP model. This figure shows clear differences in the spectra due to tissue condition.
Numerical values of the model parameters are shown in table 1. These values evidence the relations between abnormalities and GEMTIP parameters as, for instance: $\rho_0$ tend to decreases as abnormality in tissue increase. The intracellular resistivity in NO tissue data shows a resistivity below to the extracellular resistivity. Otherwise, intracellular resistivities in LSIL exhibit two different situation: two cell types have a similar behavior than NO and one have a intracellular resistivity near to extracellular resistivity value. The behavior of LSIL data suggests an electrical differentiation in the intracellular compartment that, we theorize, could be associated with cancer field effect [16]. This hypothesis could explain the high difficulties to analyze experimental data of LSIL cervical tissue [17] using computational models, where a similar resistivity is assumed to the intracellular compartment of all cells. In HSIL and CA data, the differentiation in the resistivity of cells decreases related to LSIL. However, HSIL data show two intracellular resistivities which, we theorize could be associated with the cancer field effect present in an advanced lesion. CA data only show one type of behavior. This could be associated with a homogeneous distribution of cellular sizes and electrical properties in the tissue.

| Tissue state | $a_1$ [m] | $\tau_1$ [s] | $c_1$ | $M_1$ | $\rho_1$ [\Omega m] |
|--------------|-----------|-------------|-------|-------|------------------|
| NO $\rho_0$ = 8.40 [\Omega m] | 10.6 | 1.18E-06 | 0.999 | 0.289 | 0.05 |
| | 15.7 | 1.40E-06 | 1.000 | 1.400 | 0.08 |
| | 20.9 | 1.50E-06 | 1.000 | 1.094 | 0.11 |
| LSIL $\rho_0$ = 5.08 [\Omega m] | 10.8 | 2.63E-06 | 0.999 | 1.094 | 0.03 |
| | 15.4 | 3.29E-06 | 0.999 | 1.400 | 0.01 |
| | 22.7 | 0.671036 | 0.998 | 0.001 | 4.84 |
| HSIL $\rho_0$ = 3.49 [\Omega m] | 13.5 | 2.01E-06 | 0.834 | 1.247 | 0.22 |
| | 24.2 | 3.46E-05 | 0.269 | 0.119 | 2.33 |
| CA $\rho_0$ = 2.28 [\Omega m] | 26.0 | 2.63E-07 | 0.548 | 0.430 | 1.38 |

Table 1. Numerical values of the model parameters.

GEMTIP model allows us to understand the meaning of the differences between the resistivity in the intra- and the extra-cellular medium as an induced polarization effect due to charge re-distribution [13,14]. This effect could be associated with a potential difference in the cell membrane. Note that the differences in the resistivity of inner and outer cellular compartment change with the neoplastic state of the tissue.
4. Conclusions
Electrical impedance spectra were collected from a heterogeneous Colombian population. In order to understand the relation between physiological parameters of tissue and electrical properties, four experimental data were selected to be analyzed in the framework of the GEMTIP model. Differences between structure and electrical properties of NO, LSIL, HSIL and CA cervical tissue were observed in the numerical values of the model parameters. We theorize that the different numerical values of the intracellular resistivity for each cell type could be associated with the cancer field effect.

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