2021 43rd Annual International Conference of the
IEEE Engineering in Medicine & Biology Society (EMBC)
Oct 31 - Nov 4, 2021. Virtual Conference

Special Session Title:

Bioimpedance

Special Session Organizer:
Prof. César Antonio González Díaz
Instituto Politécnico Nacional - México

Special Session Speaker 1:

Antonio DellOsa
Universidad Nacional de Tierra de Fuego - Argentina

Special Session Speaker 2:

Gerardo Ames Lastra
Universidad Autónoma Metropolitana -México

Special Session Speaker 3:

Itsi Ariana Castillo Salazar
Instituto Tecnológico de Hermosillo – México

Special Session Speaker 4:

Angelica Nava Hernández
Universidad Politécnica Gómez Palacio – México

Special Session Speaker 5:

Daniela García Arias
Universidad de Caldas – Colombia

Special Session Speaker 6:

Nataly Patricia López Saquisili
Universidad Yachay Tech - Ecuador

Theme:

Biomedical Sensors and Wearable Systems

Special Session Synopsis— Max 2000 Characters

Special Session on Bioimpedance is structured as a platform for presenting recent scientific achievements and developments in the area of electrical bioimpedance. It represents an international foro for scients, academic, undergraduate and graduate students in the field of bioengineering to best understand breakdown bioimpedance applications in the biomedical field. Invited speakers are a well-organized international team of professors and students to present their most relevant scientific findings. Main applications are focus on the biosensors design for molecular markers and DNA, bioinstrumentation, mathematical modelling, tissue and biological fluids characterization as well as user-interfaces programing. In addition the session is an open room, thus contributions in the bioimpedance field in order to feedback and academic network establishment are welcome.

Iterative method to obtain semi-circle variables from bioimpedance measurements for Cole's Modeling

Tomás Villanueva Jousset, Alberto Concu and Antonio H. Dell'Osa

***Abstract*— Cole model and frequency sweep are common use models and measurements used to characterize a biological system. Cole model parameters may be obtained by fitting the measured bioimpedance data into a semicircle. This work proposes an iterative method to approximate a bioimpedance data set using only three points. This method was verified with commercial software and validated with other research publications. It obtained the best efficiency and the lowest mean error compared to other methods. Its advantages: is user and device independent.**

***Clinical Relevance*— Proposes an efficient iterative method for the obtainment of semi-circle variables to apply the Cole Model, facilitating the qualification of measurements by nontechnical users.**

I. Introduction

Bioimpedance is a physical parameter that quantifies the degree of opposition to the flow of an alternating current in a biological system. In the biomedical field, it is applied to diagnose in a wide variety of systems such as respiratory, cardiac, metabolic, among others [1]. Cole model [2] and frequency sweep are common use models and measurements used to characterize a biological system. One way of obtaining the Cole model parameters (R0, R∞, α, τ) is to approximate or fit the measured bioimpedance data into a semicircle. The present work proposes an iterative algorithm that takes bioimpedance measurements resulting from a frequency sweep as input and returns the characteristic Cole Cole parameters of the processed measurements, by the means of generating a semicircle that represents the measurements with the lowest error.

II. Methods

Iterative method: it was developed entirely in Python; in summary the algorithm is as follows: (I) parsing data set from file, (II) selection of all possible combinations of three points without repetition, (III) generate a circumference for each three points (IV) calculation of the normal error of all points form the data set in relation with the generated semicircle (V) select the best circumference and (VI) calculation of the Cole model parameters. *Verification test:* It consisted in inputting the Gonzalez-Correa [3] data set points in our own iterative algorithm and Wolfram Alpha©'s with the intention of comparing the traceability of the center coordinates and radius obtained. *Efficiency test:* It consisted in comparing models proposed by González-Correa and the iterative algorithm to determine the efficiency of each one using their respective normal error, 128 bioimpedance measurements data sets were considered.

T. Villanueva Jousset is with the IDEI, Universidad Nacional de Tierra del Fuego (UNTDF),Ushuaia, Arg. (tomasino-@hotmail.com).

A. Concu is with 2C Technologies, Cagliari, It. (aconcu44@gmail.com).

A. H. Dell'Osa is with IDEI, UNTDF, Fuegia Basket 251, Ushuaia, 9410, Argentina (phone: +54 9 115821 1921 e-mail: aahdellosa@untdf.edu.ar).

III. Results

For the verification test the Bland Altman graphic analysis is applied, all the parameters calculated by both methods fall within the 95% confidence interval. From the efficiency test it was obtained that in 87.5% of the cases the proposed iterative method has the lowest associated normal error and the lowest average error value (0.022 ± 0.027). Figure 1 shows different data set plots with their respective semi-circle. Measurements have different bioimpedance magnitudes.

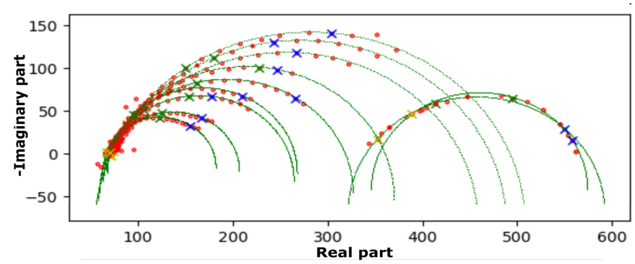

Figure 1. Cross represents selected points for iterative method in each case for different data sets.

IV. Discussion & Conclusion

Criteria of the point selection proposed by Gonzales-Correa for generating the 9 exposed models is biased by their experience in the bioimpedance area, his quickness in the analysis and in the range of frequencies in which they operate the frequency sweep in their equipment. The iterative method can be implemented easily by inexperienced users and is independent of the frequency sweep of any equipment. In addition, the iterative method possesses the best performance and reaches the lowest error in 112 of said sets (87.5% of the cases) and having the lowest average normal error with less dispersion. It adapts to any bioimpedance data set no matter the frequency sweep range used by the measuring device owing to the fact that it takes points in the complex plane.

References

[1] F. Simini and P. Bertemes-Filho, "Bioimpedance in Bioimedical Applications and Research", 1st ed., Springer, Ed. Switzerland.

[2] K. S. Cole "Permeability and impermeability of cell membranes for ions" Cold Spring Harb. Symp. Quant. Biol., vol. 8, 1940, pp. 110-122.

[3] C. A. Gonzalez-Correa, "Simplified geometrical adjustment of bioimpedance measured data to the complex plane with just three parameters", in Proc. 3rd Latin-Am Conf. Bioimpedance, Manizales, 2018, Paper: 012018.

DNA Biosensor by Means of Bioimpedance Measurements: *an instrumentation proposal*

Gerardo Ames-Lastra, Universidad Autónoma Metropolitana-CI3M, México.

***Abstract*— In this work, we propose the instrumentation of a gene biosensor by the integration of a bioimpedance relative changes measurement system. Initial validation of the system was developed by comparison of electrical properties on Mili-Q water and Saline solution samples.**

V. Introduction

Polymerase Chain Reaction became a common and important method of DNA detection and it's been widely used by medicine to diagnose viral and bacterial infections, genetic diseases, several types of cancer and other diseases [1]. Motivated by the limitations of conventional and quantitative PCR, electrochemical DNA biosensors have been of great interest in the last decades [2]. In this work, we propose the instrumentation of a gene biosensor by the integration of a bioimpedance measurements system, for initial validation relative changes of the electrical properties on Mili-Q water and Saline solution samples were compared.

VI. Methods and Materials

The genosensor proposal consists of 4 main modules: 1) Thermal cycler: based on thermoelectric cooling modules 2) Function generator: for injecting a sinusoidal signal to the sample; 3) Gain and phase detector: for bioimpedance measurement of the PCR sample compared to the voltage drop across a reference resistor; and, 4) Control: this module concentrates the general control of the system. Relative measurements of bioimpedance changes were developed in 25 microliters of Mili-Q and Saline Solution in a wide frequency range.

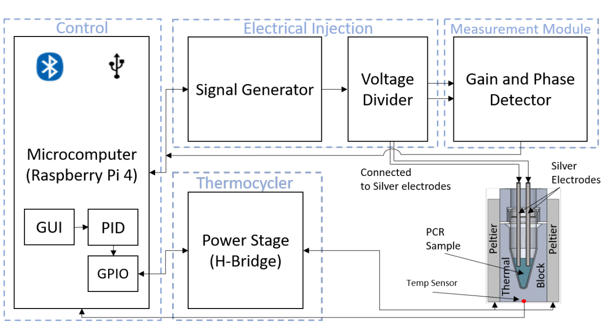

Figure 1. Block diagram of the DNA Biosensor on the basis of bioimpedance Measurmentes.

VII. Results

Fig. 1 shows the magnitude and phase of the two samples at 72 °C. We observe that our system has a considerable range to measure electrolytic sample (as PCR samples).

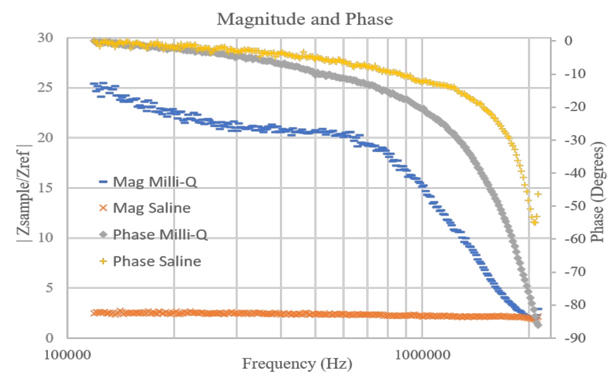

Figure 2. Magnitude and Phase of Milli-Q water and Saline Solution.

VIII. Discussion & Conclusion

Fig. 2 shows a coherent magnitude and phase bioimpedance relative changes for Mili-Q and saline samples, values are in dynamic ranges theoretically expected. Experiments with actual PCR samples are needed to confirm observations and viability of the system to detect DNA, but those are out of the scope of the present work.

References

[1] D. Jiang, G. Xiang, J. Wu, C. Liu, F. Liu, and X. Pu, "A real-time resistance measurement for DNA amplification and detection," *Int. J. Electrochem. Sci.*, vol. 7, no. 6, pp. 5273–5285, 2012.

[2] A. S. Patterson, K. Hsieh, H. T. Soh, and K. W. Plaxco, "Electrochemical real-time nucleic acid amplification: Towards point-of-care quantification of pathogens," *Trends Biotechnol.*, vol. 31, no. 12, pp. 704–712, 2013, doi: 10.1016/j.tibtech.2013.09.005.

[3] V. Sailaja, R. Datla, K. N. Raju, and M. L. Prasad, "Design and Development of Embedded System Based PCR Thermal Cycler," vol. 14, no. 3, pp. 45–53, 2019, doi: 10.9790/1676-1403034553.

Correlation Analysis of DNA Concentration *vs.* Electrical Bioimpedance.

Angélica Hernández, Universidad Politécnica de Gómez Palacio-Durango, México.

***Abstract*— In this work, the relationship between different Deoxyribonucleic Acid (DNA) concentrations and their electrical properties associated with electrical bioimpedance (EBI) was studied. Functions that characterize the correlation DNA *vs. EBI* were estimated through the least-squares regression method. The results indicate that through a linear function it is feasible to determine DNA concentration from EBI measurements at specific frequency.**

IX. Introduction

Recent advances in the development of sensitive and specific biosensor have opened up new opportunities for technologies based on nucleic acid recognition, due to their potential for use in the identification and genetic characterization of diseases such as Salmonella, human papilloma or breast cancer [1-2]. Also, electrical impedance-based biosensors have significant potential for use as simple and inexpensive detection devices, due to their size, speed and label-free operation [3].

X. Methods

Total DNA extracted from bacterium was prepared in a typical master mix Polymerase Chain Reaction (PCR). Four DNA concentration samples were considered, and one additional sample without DNA was included as negative control. Every sample was content in a final volume of 25 ul. EBI measurements in a wide bandwidth were developed, and correlation analysis regarding DNA concentration *vs*. EBI measurement at every explored frequency was carried out.

XI. Results

A. Bioimpedance findings.

Evident Z increments and phase decrements follow coherently DNA concentrations in specific bandwidths. Significative correlations ($p<0.01$) were found below 5MHz and above 300KHz for magnitude and phase respectively, as marked in graphs. As a first approach for linear regression analysis, bioimpedance data at the frequency of 1MHz were selected to show significative correlation for both Z and phase parameters.

*Research supported by "Instituto Politécnico Nacional-México" by grant number SIP-20210684. A.H. is with "Universidad Politécnica de Gómez Palacio-Durango, México.

B. Linear regression

Functions that characterize the correlation DNA *vs* EBI, obtained from linear regression, corresponds to:

$$\text{Z;} \qquad y_Z = -0.036x + 43.252 \qquad (5)$$

$$\text{Phase;} \qquad y_{Phase} = 2.255x + 32.441 \qquad (6)$$

XII. Discussion

The biophysical foundation of our proposal is on the hypothesis that induced currents at frequencies centered in the lower part of the gamma dispersion band promote the dipole relaxation effect of the water molecule and interact with the electronegative charge of the DNA molecule, such interaction is a function of DNA concentration and might correlates with changes in volumetric bioimpedance for DNA detection.

Considering the results of Equations 5 and 6, there is a statistically significant correlation between DNA concentration data and sample EBI parameters centered at 1 MHz. This means that linear electrochemical DNA interactions and biophysical effects are observed in the specific bandwidth of Z and Phase, so EBI can be used to estimate the concentration of DNA present in the sample.

XIII. Conclusion

The present work demonstrated that through a linear function it is feasible to determine different DNA concentrations, based on measurements of its electrical properties associated with multifrequency bioimpedance.

Acknowledgment

AH is grateful for the patience, time and dedication of Dr. César Antonio González Díaz for his support in the preparation and writing of this work. And to the Academia Mexicana de Ciencias for the support received to carry out this research project as scholarship holders of the "XXX Verano de la Investigación Científica" program.

References

[4] V. Kavita. "DNA biosensors-a review". *J. Bioeng. Biomed. Sci*, vol 7, pp. 222, Jan. 2017.

[5] D. Zhang, Y. Yan, Q. Li, T. Yu, W. Cheng, L. Wang, S. Ding, "Label-free and high-sensitive detection of Salmonella using a surface plasmon resonance DNA-based biosensor", *J. Biotechnol*, vol 160, pp. 123-128, Aug. 2012.

[6] K. Kivirand, M. Min, T. Rinken, "Challenges and Applications of Impedance-Based Biosensors in Water Analysis in Biosensors for Environmental Monitoring" in: *IntechOpen*, pp. 2-4, Oct 2019.

Graphical Interface User-Biosensor for interpretation of the relation DNA-Bioimpedance

Itsi A. Castillo, Instituto Tecnológico de Hermosillo, Sonora-México

***Abstract*— This work reports the design and programming of a graphical user interface (GUI) for the control of a Deoxyribunucleic Acids (DNA) biosensor based on Electrical Bioimpedance (EBI) measurements. A linear function algorithm was programmed into the system to correlate concentrations of DNA *vs.* EBI. The design is based on structured programming and is implemented in Python V3.0. Results are displayed as graphical windows of the biosensor control and detected DNA concentration.**

XIV. INTRODUCTION

In the last two decades, some research groups seems converge in the view that DNA could works as an electronegative charge carrier and give it electrical properties associated to conductivity [1], such properties might are a function of volumetric bioimpedance.

In recent study, we have proposed the use of Electrical Bioimpedance (EBI) measurements to detect the dipole effect of the water molecule, and its interaction with the electronegative charge of the DNA molecule, such interaction is a function of DNA concentration and correlates with changes in volumetric electrical properties and bioimpedance of DNA [2, 3].

In this work, we present a general sketch of a graphical user-biosensor interface with the ability to host a DNA *vs* bioimpedance correlation algorithm in a friendly environment with the possible end-user.

XV. METHODS

The design of the graphical user interface (GUI) is oriented to host the DNA vs electrical bioimpedance correlation algorithm and in turn synchronize the biosensor system, in such a way that the electrical bioimpedance measurements are shown to the end-user as their equivalent concentration of DNA present in the sample.

The operating principle of the GUI is ilustrate in the flowchart in Fig. 1. The implementation of the graphical interface was programmed in Python language version 3.8.3 with the support of the Visual Studio Code IDE, using Windows 10 as the operating system.

*Research supported by “Instituto Politécnico Nacional-México” by grant number SIP-20210684. Itsi. A. Castillo is with the Instituto Tecnológico de Hermosillo, Sonora-México; e-mail: itsicst@gmail.com.

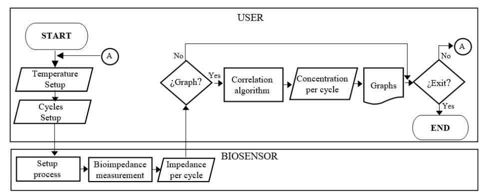

Figure 3. Flowchart representing the operating principle of the GUI.

XVI. RESULTS

The result is shown in Fig. 2, where presents the graphic window that interprets the bioimpedance measurements of the biosensor with their corresponding DNA concentrations.

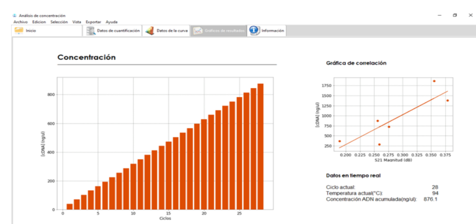

Figure 4. Graphical window of the interface that displays the results obtained by the correlation algorithm between DNA and EBI.

XVII. DISCUSSION & CONCLUSION

The design of the GUI allows host the DNA *vs* EBI correlation function, creating a friendly communication between the user and the biosensor, as well as presenting the results in an attractive way for the user.

ACKNOWLEDGMENT

IAC thanks Dr. César A. González Diaz for his mentorship in the preparation and writing of this work.

REFERENCES

[7] Dekker C and Ratner MA, ‘’Electronic properties of DNA’’, Phys World, pp. 29-33, August 2001.

[8] Gnaim R., Sheviryov J, Golberg A., Ames G, Oziel M. and González CA. ‘’Label-Free cDNA Detection Based on Radiofrequency Scattering Parameters: A New Approach for an Inexpensive Gene Sensor’’, J Med Device, vol.14, no.1, 2020.

[9] Ames G., R. Gnaim, J. Sheviryov, A. Goldberg, M. Oziel. E. Sacristán, and César Antonio González, ‘’Impedance Measurements Sensitive to Complementary DNA Concentrations’’, Springer Nat Singapore Pte Ltd, vol.72, pp. 1-4, 2020.

Dynamic of Cell Disintegration Index in ex-vivo tissues estimated by Multifrequency Bioimpedance

Daniela García, Universidad de Caldas-Manizales, Colombia.

Abstract— **Electrical Bioimpedance (EBI) measurements has been widely used to evaluate and characterize the integrity of different tissues and organs, as well as to detect tissue structural alterations. The influence of the anisotropy of the tissue structure and its intrinsic metabolism on the tissue degradation dynamic has not been completely understood. In this work the temporal course of the cell disintegration index in *ex vivo* skeletal muscle, skin and white adipose tissues was evaluated by the use of EBI measurements. The results indicate a non-lineal degradation progress in the three evaluated tissues, and such non-linearities might be associated to different capacities of adaptation to anaerobic metabolism, energy production and water content under stress conditions.**

Clinical Relevance— **Characterization of the tissue degradation dynamic in different tissues might be of interest to practicing clinicians to best understand tissue viability after stress conditions, for instance tissue and organs transplantations.**

INTRODUCTION

The cell is a complex structure formed by a membrane that has a semipermeable behavior, it is composed of a double layer of lipids with proteins. [1], biological tissues conduct electrical current according to their composition, to a greater or lesser extent [2]. Electrical impedance is a property of materials and tissues, which allows a physical and physiological characterization of cells and tissue [3]. The cell disintegration index has been described by the measurement of changes in the conductivity of the cellular electrical complex exhibit by intact and permeabilized tissue. The value of this index varies between 0, for the intact tissue, and 1, for the fully permeabilized tissue [4, 5]. In this work the temporal course of the cell disintegration index of three different *ex vivo* tissues were evaluated by the use of EBI measurements.

METHODOLOGY

An observational study in which *ex-vivo* tissue from two pigs obtained in a local abattoir. Tissue samples were obtained from the genitourinary area and part of the abdomen, divided into four quadrants and in each quadrant a portion of the muscle, adipose tissue (fat) and skin were selected. EBI measurements were made at three times (t=0h, t=5h and t=10h), where t=0 is immediately after dissecting the tissue, t=5h and t=10h at 5 and 10 hours respectively, after dissecting the tissue. The study used the Mark 3 bioimpedance spectrum analyzer which uses the following frequency spectrum 1, 2, 5, 10, 20, 50, 100 and 200 kHz, with a current of 50µA.

* D. García is with "Universidad de Caldas-Manizales, Colombia".

CELL DISINTEGRATION INDEX

RESULTS

Tissue	time	Index
Muscle	t=5h	0.477
Muscle	t=10h	0.855
Fat	t=5h	0.577
Fat	t=10h	0.695
Skin	t=5h	0.910
Skin	t=10h	0.858

DISCUSSION

The tolerance of tissues to ischemic events depends on the nature of the tissue and also changes with time. Another point that influences the aforementioned disparity is the anisotropy structure that appears in tissues such as skin, skeletal muscle and white adipose since they have electrical routes preferred by the movement of ions.

Skin measurements do not seem to have a change in the cellular disintegration index, this occurs because the stratum corneum, the superficial layer of the epidermis is made of dead cells, therefore it represents very different characteristics from living tissue [2, 5]. The skeletal muscle is the tissue that is most vulnerable to ischemia, this occurs because in the absence of oxygen the muscle uses the lactic anaerobic pathway as a method for obtaining energy. So, lactate accumulates in the cell, decreasing pH, this is correlated closely with worsening muscle necrosis.

CONCLUSION

Cell disintegration index follows a non-lineal progress in the three evaluated tissues, a preliminary theoretical analysis suggests that such non-linearities might be associated to different capacities of the tissue for adaptation to anaerobic metabolism, energy production and water content under stress conditions.

REFERENCES

[1] M.E. Moncada, M.P. Saldarriaga, A.F. Bravo and C.R. Pinedo, "Medición de impedancia eléctrica en tejido biológico–revisión" Tecnologicas, vol. 25, pp. 51-76, Dec. 2010.

[2] S. Gómez, "Estudio de las propiedades dieléctricas de los tejidos: una aproximación mediante modelado computacional y experimentación (Thesis or Dissertation style),", Dept. Sys. Eng., Univ. de Sevilla., Sevilla, España, 2017.

[4] D. Miklavčič, N. Pavšelj and F.X. Hart, "Electric properties of tissues," Wiley encyclopedia of biomedical engineering, April, 2006.

[5] R. Bobinaite, G. Pataro, N. Lamanauskas, S. Šatkauskas, P. Viškelis and G. Ferrari, "Application of pulsed electric field in the production of juice and extraction of bioactive compounds from blueberry fruits and their by-products," J Food Sci Technol vol. 52, pp. 5898-5905, Nov 2014.

Time Characterization of *ex-vivo* tissues by Multifrequency Bioimpedance

Nataly P. López , Universidad Yachay Tech-Imbabura, Ecuador.

***Abstract*— The behavior of biological tissue when it is subjected to different frequencies of excitation is modeled thanks to its dielectric properties. In this work, the factors that cause the differences that occur between the magnitude and phase of the evaluated tissues were evaluated. The results indicate that these could be related to the flow and frequency of the electric current and the relaxation phenomena, as well as to the structure, composition and state of the tissue.**

XVIII. Introduction

The cell is comprised of a membrane formed by a lipid bilayer, where several proteins act as ion exchange channels (1). The components of the cell membrane allow it to act as a dielectric interface by assimilating the two plates of a capacitor.

The main dielectric properties are permittivity and electrical conductivity, which model the behavior of the material when subjected to different frequencies of excitation. These properties are related to the flow of electric current and the magnitude of the polarization effects (1).

When the tissue is under the action of an electric field, the charged ions move and displacement currents occur. The response of a biological tissue to the action of an electric field depends on the characteristics of its structures, composition, dipoles and capacity for formation and orientation (2).

XIX. Methodology

Ex vivo tissues from two pigs were analyzed by Electrical Bioimpedance measurements. Muscle, adipose tissue and skin samples were taken from the genitourinary area and part of the abdomen. IBE measurements were performed at three times (t = 0h, t = 5h and t = 10h), where t = 0 is immediately after dissecting the tissue. Subsequently, the data of each type of tissue were combined.

The Mark 3 bioimpedance spectrum analyzer was used, which has a frequency spectrum that varies between 1-200 kHz, with a current of 50μA, In addition, a probe with 5.5 mm diameter in the shape of a pencil with 4 electrodes was used. 1mm diameter gold beads, placed on the tip of the probe.

*N.P. López is with "Universidad Yachay Tech-Imbabura, Ecuador.

XX. Results

Impedance spectra in magnitude (Z) and Phase were observed for muscle, fat and skin evaluated at three times ex vivo after tissue dissection. As a reference, the graphs have been placed in the same dynamic range in order to facilitate comparison and detection of changes in the values obtained.

XXI. Discussion

Each tissue has particular electrical properties that depend on its constitution, state, and extracellular fluid content. This electrical behavior reveals a dependence of the dielectric parameters with the frequency of the currents due to different relaxation phenomena that occur when the currents pass through the tissue (3). The relaxation or scattering factors related to the tissue response to current and frequency can be alpha scattering (α), beta scattering (β) and gamma scattering (γ), which depends on the tissue-water ratio. (4).

XXII. Conclusion

The differences that occur between the magnitude and the phase as a function of time of the three tissues studied could be associated with the flow and frequency of the electric current, the polarization effects, the relaxation phenomena, as well as with the structure, composition, state and content of extracellular fluid of the tissue.

Acknowledgment

NPL thanks Dr. César A. González Diaz for his mentorship in the preparation and writing of this work.

References

[1] B. Rigaud, J. P. Morucci, N. Chauveau, "Bioelectrical impedance techniques in medicine." In Bioimpedance measurement, section: Impedance spectrometry, 2nd ed. Vol. 24. 1996, pp. 257-351.
[2] M. E. Moncada, M. D. P. Saldarriaga, A. F. Bravo, & C. R. Pinedo, "Medición de impedancia eléctrica en tejido biológico" in revisión. TecnoLógicas, 2010, pp. 51-76.
[3] K. R. Foster, H.P. Schwan, "Dielectric properties of tissues" in Handbook of Biological Effects of Electromagnetic Fields. C. Polk and E. Postow, Ed. CRC Press Inc., Boca Raton, FL, 1996, pp. 25–102.
[4] S. Grimnes, and O. G. Martinsen, "Bioimpedance and Bioelectricity Basics". Academic Pres, 2000.