Prototype of a Wireless System for Electrical Impedance Spectroscopy: Demonstration of Real Time Measurements on Cells and Biological Medium

E. De Roux, M. Terosiet, F. Kölbl, A. Histace, O. Romain
Laboratoire ETIS, ENSEA, UMR8051
Université de Cergy-Pontoise
Cergy, France
{edwin.de-roux; terosiet; kolbl; histace; romain}@ensea.fr

M. Boissière, E. Pauthe
Laboratoire ERRMECe, EA1391,
Université de Cergy-Pontoise,
Neuville sur Oise, France
{mboissie; emmanuel.pauthe }@u-cergy.fr

J. Chrun, P.H. Aubert, P. Banet
Laboratoire de Physicochimie des Polymères et des Interfaces, EA2528,
Université de Cergy-Pontoise,
Neuville sur Oise, France
{chrun; philippe.banet; auber}@u-cergy.fr

***Abstract*—A wireless and portable system, consisting in an electronic board and a computer software graphical interface, is presented as a feasible way to do electrochemical impedance spectroscopy of cells and biological medium. It is designed to work inside a culture chamber performing impedance measurement in the frequency range of 64Hz to 200KHz. The board is equipped with a Bluetooth Low Energy (BLE) module allowing it to be wirelessly controlled. The software interface (also called ISMI) is coded with all required functionalities to manage the parameters of the board such as start frequency and sweep, measuring intervals, data acquisition and visualization and also a function to perform automatic measuring between desired time intervals during whole day for many days. A validation of the system shows an average error of about 1.9% and a measuring test of human fibroblast cells shows a good performance of the system. The proposed system is an introductory step in the study of cells related to fibrous tissue induced by implants showing to be a viable and reproducibility-improving approach for such analysis.**

I. INTRODUCTION

Today's implantable devices are designed with more and more integrated functionalities which require the use of electrodes that allow the transmission of the signals from and to the biological tissue. However, these devices may stimulate a range of immune mechanism, inflammation and a production of cells population in the local area that may cover the electrodes until they become encapsulated in a dense layer of fibrous connective tissue. This fibrotic capsule isolates the electrode from the targeted tissues by physical and electrical means, therefore causing the malfunction of the device beside of introducing medical complication to the patient.

Since the electrodes are affected by their surroundings, it is crucial to detect and measure the evolution of the fibrotic capsule. However, from a scientific point of view, the systematic characterization and monitoring of cells or tissues is still an open issue. This is a real obstacle to the development of clinically-applicable diagnostic, preventive and therapeutic measures.

In this article we start by proposing the method of Electrochemical Impedance Spectroscopy (EIS) as a practical approach to study the electrical behavior of the fibrotic capsule phenomena. In Addition, a custom portable system that perform wireless EIS measurements on cells and biological medium is described. Finally, some results from experimentation are discussed.

The electrical properties of tissue were previously studied by Schwan who identified three different regions in the spectrum, also named "regions of dispersion", labeled: α (Alpha dispersion) from 10Hz to few KHz, β (Beta dispersion) from 1KHz to several MHz, and ϒ (Gamma dispersion) above 10GHz [2]. Each of the dispersion regions is attributed to different frequency dependent phenomena in the tissue.

In this work we are focusing the design in the Alpha and Beta regions due to the fact that they are associated with tissue interface and cells with membrane [3]. Others works have been reported for the study of electrical impedance of cells culture, however either these systems do not measure at the Alpha region or the measuring frequency is fixed or without sufficient frequency points [7].

II. MATERIALS AND METHODS

The Electrical Impedance Spectroscopy (EIS) technique has been shown to be a powerful technique to study frequency dependent electrical behaviors of biological tissues that may lead to a phenomena understanding applicable in the medical field [4]. An EIS setup usually contains an electronic system, that generates a stimulation voltage of different frequencies and that captures the electrical signal, coming from the Impedance Under Test (IUT), typically by using a metallic electrode that has a physical contact with the IUT.

The proposed system was designed to perform EIS measurements of *in-vitro* cells culture with all required capabilities needed for the proper sensing without considerable affecting both electrode integrity and cells growth. During experimentations the saline solution is commonly used for system calibration. Futhermore, the measurement on Dulbecco's Modified Eagle's Medium (DMEM) is used as control impedance for cell measuring comparison. As cells, we measure human fibroblast cells since they are connective tissue cells which secrete an extracellular matrix rich in collagen and other macromolecules that compose a great percentage of the fibrous capsule [1].

The system consists of an electronic board and a computer software graphical interface. This hardware-software set is called here the ISMI System. The electronic board is based on the AD5933, the first commercially available impedance converter implemented in a single integrated circuit (IC). With the addition of a digital programmable oscillator LTC6904, which functions as external clock, the system is able to generate stimulations signals with frequencies between 64Hz to 200KHz, with a 0.1Hz of resolution and a maximum of 255 different equally spaced frequency points per sweep.

In addition, the electronic board has the Simblee microcontroller with Bluetooth Low Energy (BLE) communication capabilities that may well be linked to a PC via another Simblee microcontroller, or to a Mobile device. Finally, the board includes an Analog Front End (AFE) that reduces the output impedance and removes DC offset from the signal and also a 1-to-8 multiplexer to measure up to eight different impedances. A diagram of the functional block of the system is shown in Fig. 1.

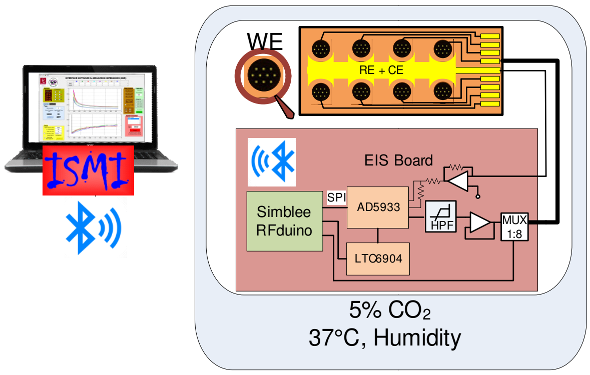

Figure 1. Block diagram of ISMI System. The custom board measures up to 8 bioimpedances wirelessly controlled by the ISMI software interface.

The ISMI System is validated by means of simulations and comparison with reference instruments. This results in a contour accuracy plot with a minimum of 98% accuracy when 100mVpeak signal is applied to a calibration electrical circuit as shown in Figure 2.

III. Demonstration

The real time impedance measurements of the DMEM solution in a well with ten 250µm of diameter electrodes of gold is shown in Figure 3. It is noticeable the module and phase of the impedance from both system: the ISMI and the reference instrument. The values of the impedance magnitude and phase have their major difference of about 1.9% at both ends of the spectrum in conformity to the accuracy margin of 2% presented previously for the ISMI accuracy contour plot.

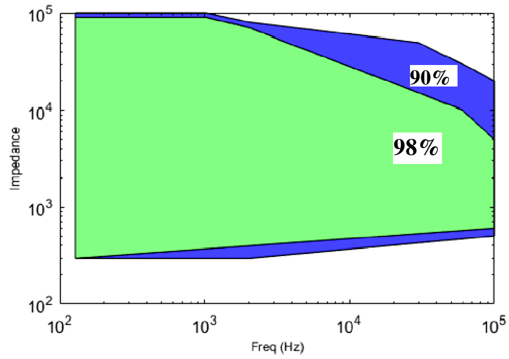

Figure 2. ISMI accuracy contour plot. The stimulation signal amplitude is 100mVpeak. Green represents 98% and blue 90% accuracy.

The speed of a measurement point in the ISMI system depends of the stimulation signal frequency, the clock rate and the wireless data transfer speed. Each measurement interval takes about 200ms in total.

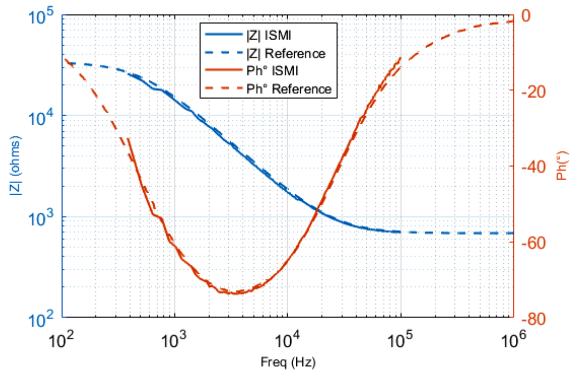

Figure 3. Comparison between ISMI and the Reference Instrument. The DMEM impedance is measured using a 10 electrodes well. The plot shows the impedance module (blue) and phase (red).

References

[1] "Connective Tissue Study Guide," Electronic publication: http://www.siumed.edu/~dking2/ intro/ct.htm#blood.

[2] H. P. Schwan, "Electrical properties of tissue and cell suspensions," Adv. Biol. Med. Phys. V, 1957, pp. 147–209.

[3] D.A. Dean, T. Ramanathan, D. Machado, and R. Sundararajan, "Electrical impedance spectroscopy study of biological tissues," Journal of Electrostatics, Volume 66, Issues 3–4, March 2008, pp. 165-177.

[4] B. Kloesgen, C. Ruemenapp, and B. Gleich, "Bioimpedance spectroscopy," in BetaSys, System Biology Vol. 2, edited by B. Booß-Bavnbek et al. (Springer-Verlag GmbH, Berlin, 2011), pp. 241–264.

[5] J. E. B. Randles, "Kinetics of rapid electrode reactions," Discussions of the Faraday Society, 1947, doi:10.1039/df9470100011.

[6] E. T. McAdarns, A. Lackermeier, J. A. McLaughlin & D. Macken, " The linear and non-linear electrical properties of the electrode-electrolyte interface," Biosensors & Bioelectronics 10, 1995, pp. 67-74, doi:10.1016/0956-5663(95)96795-Z.

[7] M. Terosiet, A. Histace, O. Romain, M. Boissiere, E. Pauthe, "Toward an embedded System for the In-Vitro and In-Situ Cell Proliferation Characterization by Impedance Spectroscopy," Biomedical Circuits and Systems Conference (BioCAS), 2015, doi:10.1109/BioCAS.2015.7348400