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Preliminary Investigation Towards Embedded Impedance Spectroscopy in Implanted Stimulators

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Abstract— This paper presents a preliminary study of impedance spectroscopy compatible with cardiac pacing implants, for the long-term monitoring of the fibrosis around electrodes. The multisine broadband technique have been implemented successfully in a characterization bench centered on a typical neuro-stimulator, with a high level of precision in measuring impedance of cardiac cells *in vitro*.

Keywords—Bioimpedance spectroscopy, implanted stimulators, implant-induced fibrosis, multi-sine stimulus

I. OBJECTIVE AND CONTEXT

Long-term efficacy of implantable devices is affected by fibrosis, a sustained inflammatory response that encapsulates the implant in a dense layer of fibrotic connective tissue [1]. In the case of active stimulation implants, the modification of the electrode-tissue interface has several consequences: fibrotic attachments, higher stimulation thresholds and lower battery lifespan. Fibrosis at the myocardium-electrode interface has been known for a long time and has already led to a major breakthrough in the 1980s, when steroid-eluting leads appeared [2]. Despite this revolution, fibrosis remains an issue for the latest devices such as leadless pacemakers or resynchronization devices. As fibrotic encapsulation is due to a remodeling of the tissue surrounding the electrode, it must be reflected in the impedance of the electrode-tissue interface. We then propose to investigate bioimpedance spectroscopy applied to cardiac cells and tissues, with the objective to develop a characterization method that could be embedded *in vivo*. We will carry out investigations in two directions: (1) impedance spectroscopy with dedicated commercial instruments, conducted at the tissue or cell level, in order to highlight impedance modifications in conditions mimicking fibrosis; (2) feasibility study of embedded impedance spectroscopy measurement in implanted stimulators.

It has been shown that *in situ* measurements of myocardium electrical impedance allow the differentiation among normal, ischemic, and infarcted tissue [3]. *In vivo* myocardium impedance characterization requires a short measuring time that can be reached with broadband excitation signals [4].

The advantage of active implants is that they naturally include a circuit that generates an electrical excitation. The first question is how this excitation source could be adapted to “broadband” impedance spectroscopy and second what should be the sensing and post-processing strategy that allows accurate and low-consumption impedance measurement. In this paper,

we describe the experimental bench, centered on a custom integrated neuro-stimulator, and we evaluate its performances on *in vitro* cardiac fibroblasts.

II. EXPERIMENTAL BENCH

A. Optimal excitation source

An extensive study on broadband impedance spectroscopy using periodic excitations reported that the multisine signal was an optimal candidate [4]. In the time-domain, it has a minimal crest factor (CF), maximizing the signal to noise ratio (SNR) [5]. In the spectral domain, the frequency distribution can be optimized by using a bilateral quasi-logarithmic set (BQL), centered on cut-off frequencies [5].

B. Material constraints

1) Two-point electrode

Our long-term objective being to add a monitoring functionality to *in vivo* cardiac pacing technologies, we are constrained to use a two-point impedance measurement technique, as human pacing/sensing leads are bipolar, with one proximal and one distal electrode, separated by few millimeters.

2) A neurostimulator as excitation source

Typical excitation signal in neural electrical stimulation is a balanced biphasic current impulse, with a pulse width of tens of μs to tens of ms, with a repetition frequency reaching few hundreds of Hz at maximum [6]. In a previous study, we developed a stimulation system, centered on a custom integrated circuit (IC) and controlled by a dedicated digital architecture implemented on an FPGA (Field Programmable Gate Array). It provides 8 stimulation channels with high-voltage compliance, to adapt to a wide range of experiments. Its real-time, open-loop and closed-loop capabilities have proven their efficacy in respiratory muscles stimulation experiments [7]. In the present study, we developed a second version of the digital architecture, in order to explore arbitrary stimulation waveforms, including adequate excitation for impedance measurement. Arbitrary waveforms are stored in binary format in a 32 bit-RAM and the FPGA architecture triggers the stimulation sequence of the 8 output channels, through an 8-bit, 1MSa/s DAC (Digital to Analog Converter). Each channel is a current source delivering 1 mA at maximum, with a 4 μA resolution. Its measured static output resistance is of the M Ω order. The characterization of the excitation source has been extended in a frequency domain ranging from few Hz

up to 250 kHz, an interval exceeding largely the usual neurostimulation bandpass. We observed the proper operation of the current generation up to 100 kHz but a decrease in the output impedance at high frequencies, resulting in a 10% current error at 100 kHz for load impedance reaching 1 k Ω . This obliged us to add an interface circuit measuring the real current.

In the current version of the system, the minimal sampling period is 1 μ s and each channel can generate a unique tone, with a chosen amplitude and frequency. It limited the multi-tone exploration to 8 frequencies but allowed to conduct a feasibility study.

C. Sensing method and triggers management

With a current-mode excitation source, the voltage drop across the electrode must be acquired. For this study, we used the Keysight MS0X2024A oscilloscope (200MHz, 2GSa/s, 8 bits). Despite this poor ADC resolution, the embedded post-processing uses oversampling and dithering methods that greatly improve the SNR (10 Effective Number of Bits). Oscilloscope time base is chosen to acquire five periods of the minimal frequency tone. Sampling frequency and vertical time scale are automatically adjusted. Triggering of stimulation and acquisition are controlled by a microcontroller (Atmel SAM3X8E, 32bits ARM-Cortex M3, on Arduino Due card), with a constant delay of 10 ns between the stimulation source and the acquisition. The microcontroller also controls the stimulus duration and repetition. A Matlab script drives every device and retrieves the current and voltage data, from a single interface.

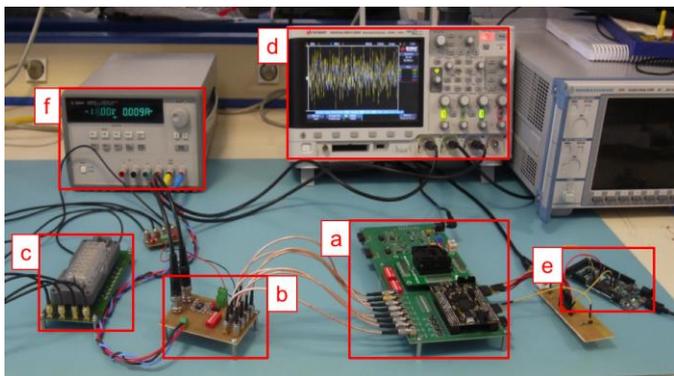


Fig. 1. Photograph of the measurement bench. (a) Stimulation system, (b) Interface circuit for current sensing, (c) 16-well culture plate, (d) Oscilloscope, (e) Microcontroller, (f) Stimulator power supply.

D. Post-processing for impedance spectrum

Each acquisition set is post-processed following these steps: 7-term Blackman-Harris windowing, Discrete-Time Fourier Transform based on the known frequencies of the excitation signal, impedance spectrum computation. Furthermore, the variance of the results is calculated on a sequence of 5 successive acquisitions. Based on this statistical calculation, we estimate the SNR_z of the impedance measurement [4], to evaluate the repeatability of measurement.

III. PRELIMINARY RESULTS

A. In vitro experiment and measurement protocol

Cardiac fibroblasts were isolated from neonatal Sprague-Dawley rats (Charles River, France) and cultured in

xCELLigence E-Plate 16 (Ozyme, France) at 75000 cells per well. These plates contained 16 culture wells with golden electrodes at the bottom which interdigitated electrodes allowing 2-point impedance measurements. Cells were maintained at 37°C, 5% CO₂ and 95% humidity during the measurements. First, a reference measurement was made with Solartron 1260 (Ametek, USA), at 100 mV, on the 1Hz-1MHz frequency range, which was used to generate the proper BQL distribution of the frequency points, from 5 kHz to 100 kHz. The duration of the multisine signal is 5 ms, corresponding to 5 periods of the minimal sinus frequency.

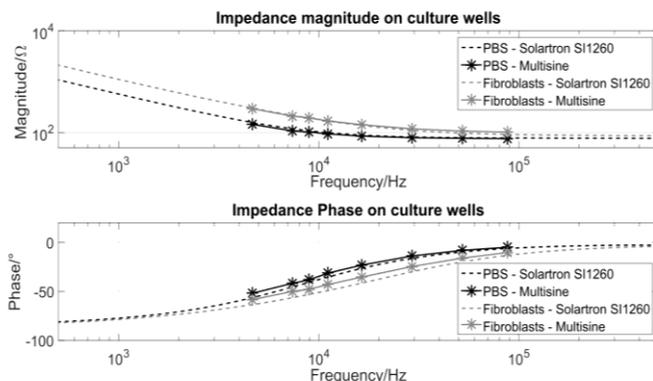


Fig. 2. Impedance magnitude and phase graphs for one well at day 7 of fibroblasts culture

First, the multisine measure is highly repeatable as SNR_z is always higher than 72 dB. For each of the 16 wells, the custom multisine spectrum reproduces the Solartron reference spectrum with a maximal relative error of 3% for the magnitude and 5% for the phase.

IV. CONCLUSION

This preliminary investigation has proven the feasibility of embedded multisine impedance spectroscopy in a stimulator dedicated to neuro-muscular applications, with a high level of precision. Future work will encompass development of the stimulator digital architecture to generate an adaptive higher dimension multisine signal as well as *in vivo* experiments.

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