

Modeling the non-stationary behaviour of time-varying electrical bioimpedance

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Abstract-The electrical bioimpedance (EBI) measurement of varying biological systems $Z(\omega, t)$ (e.g. the heart, the lungs, ...) by means of electrical impedance spectroscopy (EIS) remains an open challenge today. Briefly stated, the bioimpedance is widely assumed to be *time-invariant* when it is measured with the frequency sweep EIS approach. Hence, time-varying changes are thus ignored or treated as a noise source. In this work, we attempt to model the time-variant effects and obtain a simple (periodically) time-varying [(P)TV] electrical circuit model with (P)TV parameters from experimental *in vivo* EBI data using the model proposed by Fricke-Morse. The aim is then to illustrate that a limited number of harmonic components of the electrical circuit parameters, which corresponds to an integer number of the bio-system periodicity, can be used to have a realistic evolution of the bioimpedance over time as well as in frequency.

I. Introduction

Nowadays, techniques for tissue evaluation through, i.e. electrical methods, provides non-destructive valuable information for the characterization of *in vitro*, *in vivo* and *ex vivo post mortem* tissues. During the past few years, a non-invasive and nondestructive technique that has become more and more popular is the electrical impedance spectroscopy (EIS). EIS has been recently applied in a wide field of applications, where the determination of the passive electrical properties of materials was of interest. In the case when the materials under study are biological, the characterization of the biological tissues by means of the EIS is known as electrical bioimpedance (EBI). The characterization of biological materials by means of EBI provides relevant physiological information about the properties of tissues as a function of the excited frequency, which is related, at a macroscopic level, to the physiological states of tissues.

When performing the modeling of living tissues or organs, there are many different approaches to represent electrically these biological systems. As thoroughly explained in the literature [1], the electrical impedance of biological systems can be modeled using an equivalent electrical circuit. One of the most adopted is the Fricke-Morse circuit model due its simplicity and direct physical interpretation [2]. Fricke-Morse modeling approach consists in considering the tissue as a suspension of millions of cells surrounded by an extracellular liquid as given schematically in Fig.1.

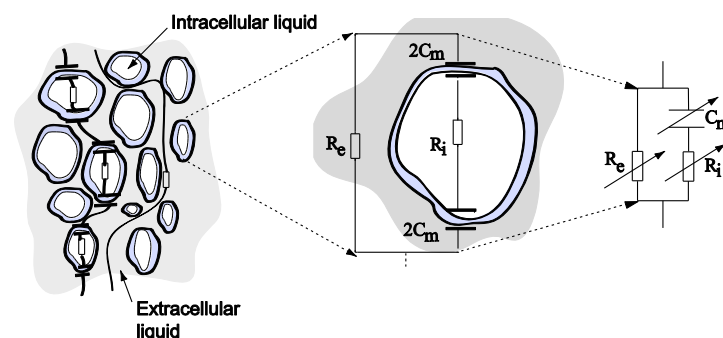


Figure 1: Simplified modeling of a biological tissue corresponding to the Fricke-Morse model as a two resistor and one capacitor ($2R-1C$) electrical circuit. The phospholipid molecules that compose the cell membrane are highly frequency dependent due to its high capacitive response. As a result, the low frequency current mainly flows through the extracellular liquid while the high frequency current flows through intra-/extra cellular liquid.

Assuming the 2R-1C model shown in Fig.1, the relation between the current through the tissue, $i(t)$, and the voltage across the tissue, $v(t)$, is given in the time domain by the following first order Ordinary Differential Equation (ODE):

$$c \frac{dv(t)}{dt} + v(t) = a \frac{di(t)}{dt} + bi(t) \quad (1)$$

where $a = R_e R_i C_m$, $b = R_e$ and $c = (R_e + R_i) C_m$ are the model parameters that are assumed to be constants (in a first stage). Note that given the model parameters a , b and c in Eq. 1, the circuit parameters R_e , R_i and C_m can readily be found as:

$$\begin{cases} R_e = b \\ R_i = \frac{ab}{bc - a} \\ C_m = \frac{bc - a}{b^2} \end{cases} \quad (2)$$

where R_e is related to the resistance of the extracellular liquid, R_i is the resistance of the intracellular liquid and C_m models the capacitance of the cell membrane. The electrical bioimpedance, $Z(\omega)$, which is a function of the (angular) frequency ω and can straightforwardly be obtained from the model parameters of the ODE model in Eq. 1, viz.

$$Z(\omega) = \frac{j\omega a + b}{j\omega c + 1} = \frac{j\omega R_e R_i C_m + R_e}{j\omega (R_e + R_i) C_m + 1} \quad (3)$$

with $j^2 = -1$ the imaginary unit of complex numbers. Converting the ODE model in Eq. 1 to the frequency domain using the Fourier transform gives Eq. 3, where $Z(\omega) = V(\omega) / I(\omega)$ with $V(\omega) = F\{v(t)\}$ the voltage spectrum and $I(\omega) = F\{i(t)\}$ the current spectrum ($X(\omega) = F\{x(t)\}$ with $x(t)$ the time signal and $F\{\square\}$ the Fourier transform operator).

However, in practice the Fourier integral transformation cannot be performed because of two major reasons: (i) the current and the voltage signals, $i(t)$ and $v(t)$, are only available in a certain time window of the measurements, say $t \in [0, T]$, with T the measurement time; (ii) the input-output signals are only accessible as sampled signals, $i(nT_s)$ and $v(nT_s)$, with T_s the (constant) sampling period of the input-output signals and n an integer. Therefore, the Fourier integral should be replaced by the (normalized) Discrete Fourier Transform (DFT):

$$X(k) = \frac{1}{N} \sum_{n=0}^{N-1} x(nT_s) e^{-j2\pi kn/N} \quad (4)$$

with $x = \{i, v\}$, $X = \{I, V\}$, $N = T / T_s$ the number of time domain samples that are collected during the measurement process and the index k in $X(k)$ in Eq. 4 is the frequency bin corresponding to the k^{th} DFT frequency $\omega_k = 2\pi k / T$. In practice, the DFT of a signal can efficiently be computed by the Fast Fourier Transform (FFT), which is, nowadays, offered by numerous numerical packages.

Reaching the steady state situation can be a weak assumption when characterizing the properties of time-varying bio-systems, as for example for the in vivo myocardium. It can be seen from Fig.1 in [3] that the transients fully die out after 40 μ s. Hence, when performing electrical impedance spectroscopy measurements with a periodic signal, the gathered measurements of the current and voltage signals might fall in steady state conditions. The reader is referred to [4] to obtain insight in the approaches for measuring time-varying bioimpedance.

I. Simplified modelling of time-varying bioimpedance systems

Adopting the Fricke-Morse $2R-1C$ electrical model shown in Fig.1, the relation between the current flowing through the tissue, $i(t)$, and the voltage drop across it, $v(t)$, is given in the time domain by the following 1st order Ordinary Differential Equation (ODE):

$$(R_e(t) + R_i(t))C_m(t) \cdot \frac{dv(t)}{dt} + v(t) = R_e(t)R_i(t)C_m(t) \cdot \frac{di(t)}{dt} + R_e(t) \cdot i(t) \quad (5)$$

Once the time-varying circuit parameters, i.e. $R_e(t)$, $R_i(t)$ and $C_m(t)$ in (1), are *frozen* at a certain time, say at $t = t^*$, the *frozen impedance spectrum* (FIS), denoted by the subscript f in $Z_f(\omega, t)$, can be computed from (1). The FIS, $Z_f(\omega, t^*)$, follows easily from (1) at $t = t^*$ and is mathematically written down as:

$$Z_f(\omega, t^*) = \frac{R_e(t^*)R_i(t^*)C_m(t^*)j\omega + R_e(t^*)}{(R_e(t^*) + R_i(t^*))C_m(t^*)j\omega + 1} \quad (6)$$

Although the frozen impedance spectrum is continuous over time, there exists no direct mathematical relationship between the current spectrum $I(\omega)$ flowing through the tissue, the voltage spectrum $V(\omega)$ across the tissue and the frozen impedance spectrum $Z_f(\omega, t)$. The mathematical property that relates $V(\omega)$ and $I(\omega)$ is through the *instantaneous impedance spectrum* [5], denoted as $Z_i(\omega, t)$, and differs in general from the frozen impedance spectrum at $t = t^*$ [6–8]. Nevertheless, it can be proven that for slowly varying biological tissues the difference between the two impedance concepts (frozen and instantaneous) is negligible [7].

II. Experimental results and discussion: extracting the periodic features from the time-evolution of the $2R-1C$ model parameters of *in vivo* myocardium

Fig.2 illustrates the estimated time-varying Fricke-Morse circuit parameters (i.e. $R_e(t)$, $R_i(t)$ and $C_m(t)$) using differential impedance analysis (DIA) [9–11] for the 10 cycles of *in vivo* myocardial impedance. The estimated cardiac cycle periodicity is $T_{cc} = 0.946$ s. The periodic reconstruction of the circuit parameters, which is shown in grey in the figure, i.e. $R_e(t + T_{cc}) = R_e(t)$, $R_i(t + T_{cc}) = R_i(t)$, $C_m(t + T_{cc}) = C_m(t)$, are obtained as follows. First, the mean periodicity of the time-variation is estimated. Next, the DFT of the 10 cardiac cycles, $T = 10T_{cc}$, is calculated. Then, only the harmonics corresponding to an integer number of the cardiac cycle ($\dots, -2/T_{cc}, -1/T_{cc}, 0/T_{cc}, 1/T_{cc}, 2/T_{cc}, \dots$) are retained, and the leftovers of the DFT spectrum are set to zero. Finally, the reconstructed periodic time domain signal is then finally obtained using the inverse of the reconstructed DFT spectrum.

It follows from Fig. 2 that the circuit parameters $R_e(t)$ and $R_i(t)$ vary more or less periodically over time. Indeed, the periodic changes dominate the arbitrary time-variations. As for the case study presented, the periodic features in the *in vivo* myocardium are due to the morphological change of the myocardial cells during the different cardiac phases, which influence the intra-extracellular resistances shown in Fig. 1. The cells in the heart undergo a contracting as well as a relaxing phase within each cardiac process. The corresponding frequency spectrum (A-B, bottom) exhibits the characteristic frequencies related to these periodic phenomena occurring in the heart.

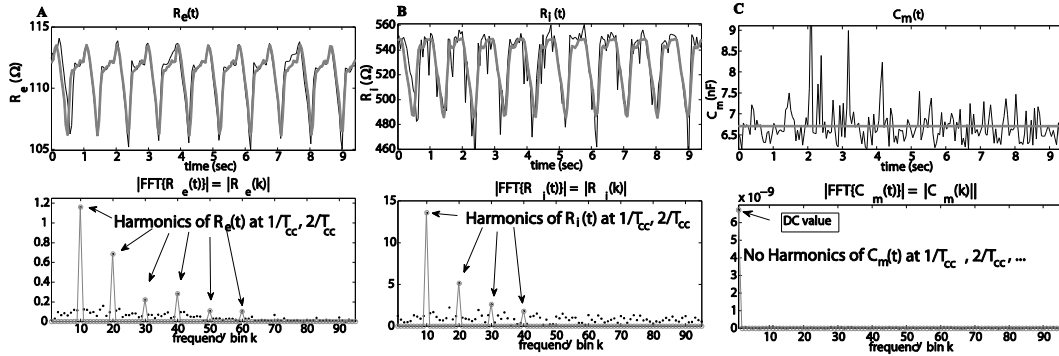


Figure 2: The time-evolution of the *in vivo* myocardium electrical circuit parameters $R_e(t)$, $R_i(t)$ and $C_m(t)$ of the $2R$ - $1C$ circuit shown in Fig.1. Time (top) and frequency (bottom) dependencies of the estimated circuit parameters (black) and the periodic reconstruction (periodicity of $T_{cc} = 0.946$ s) (grey) (A-C). DC-values are not shown in the DFT-plot for convenience (except for $C_m(t)$).

It can be observed from Fig. 2 that the Periodic Reconstruction (PR) of the data follows quite well the estimated time-waveforms of the Fricke-Morse model parameters. Only a significant difference in the first cycle can be observed, where the periodically reconstructed signal is lagging w.r.t. the measured one. This is because during the measurement, the myocardium was not perfectly stable (heart rate variability was present) while the system's periodicity T_{cc} was assumed to be constant. However, this occurrence is not present in the other 9 consecutive cycles. This plot motivates the use of (periodically) time-varying [(P)TV] tools to model, better analyze and simulate the behavior of the bio-system within one or several cycle(s) [4]. Once the periodicity of the cycle is known or estimated, the PR of (1)-(2) can readily be constructed from the harmonics in Fig. 2 (bottom). The obtained frozen PTV model, $Z_f(\omega, t)$, is continuous in frequency as well as in the time variable.

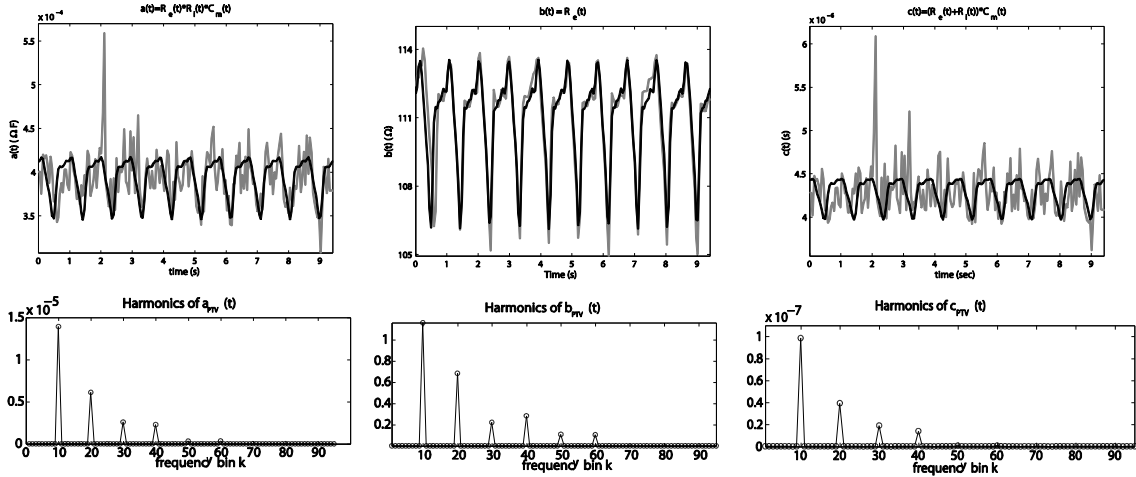


Figure 3: Time dependencies of, respectively, (black) the time-varying model parameters $a(t) = R_e(t)R_i(t)C_m(t)$, $b(t) = R_e(t)$ and $c(t) = (R_e(t) + R_i(t))C_m(t)$, (grey) the PTV model parameters $a_{PTV}(t) = R_e^{PTV}(t)R_i^{PTV}(t)C_m^{PTV}(t)$, $b_{PTV}(t) = R_e^{PTV}(t)$ and $c_{PTV}(t) = (R_e^{PTV}(t) + R_i^{PTV}(t))C_m^{PTV}(t)$.

Since it turned out from Fig.2 (A-C) that the periodic variations are dominant in the data, we will impose the periodicity in the model parameters and the bioimpedance. The main reason for this is that a (Linear) Periodically Time-Varying [(L)PTV] model is also usable outside the measurement window (by definition), while there is no guarantee that the non-periodic time-variations are the same outside this measurement interval. This statement is justified in Fig.3 by the fact that the arbitrary variations differ from one cardiac cycle to the other (10 cardiac cycles are depicted), while the periodic variations are still dominating over most of the signal. In order to extract the PTV part of the time-varying ODE model in Eq. 5, the PTV model parameters, $a_{PTV}(t) = a_{PTV}(t + T_{cc})$, $b_{PTV}(t) = b_{PTV}(t + T_{cc})$ and $c_{PTV}(t) = c_{PTV}(t + T_{cc})$, are obtained using the periodic

reconstruction, as explained above. The results from the periodic reconstruction of the PTV ODE parameters are shown in Fig. 3.

It can be seen from the temporal and frequential representation of the impedance spectrum in Fig.4 that the PR of the data describes fairly well the measured time-varying impedance. However, it is difficult at this stage to know, by visual inspection, how accurate the periodic reconstruction is w.r.t. the time evolution of the estimated myocardial impedance.

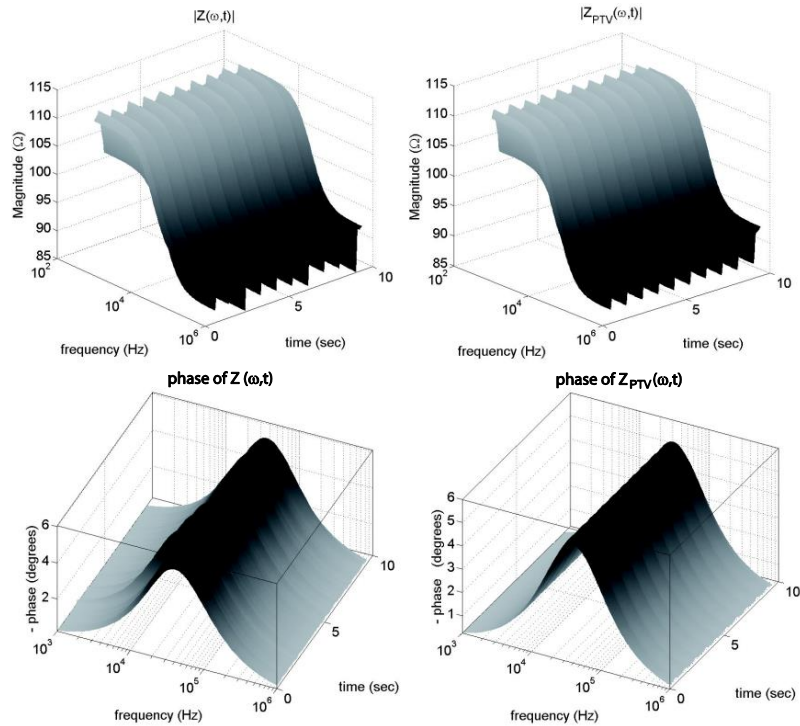


Figure 4: 10 cardiac cycles of the magnitude and phase spectrum of the time-varying electrical bioimpedance and its PTV reconstruction derived from Fig. 3.

To determine a measure of discrepancy between the estimated myocardial impedance and the PR *in vivo* myocardial impedance model, the Root Mean Squared Error over Time (RMSEoT) is calculated as:

$$\left\{ \begin{array}{l} \text{RMSEoT}_{|Z|} = \sqrt{\frac{1}{10T_{cc}} \int_0^{10T_{cc}} (|Z(\omega, t)| - |Z_{PTV}(\omega, t)|)^2 dt} \\ \text{RMSEoT}_{\phi_Z} = \sqrt{\frac{1}{10T_{cc}} \int_0^{10T_{cc}} (\angle Z(\omega, t) - \angle Z_{PTV}(\omega, t))^2 dt} \end{array} \right. \quad (7)$$

The RMSEoT introduced in Eq. 7 and shown in Fig. 5 allows one to ease the comparison of 2D magnitude and phase spectra, showing the frequency distribution of the averaged power-error over time.

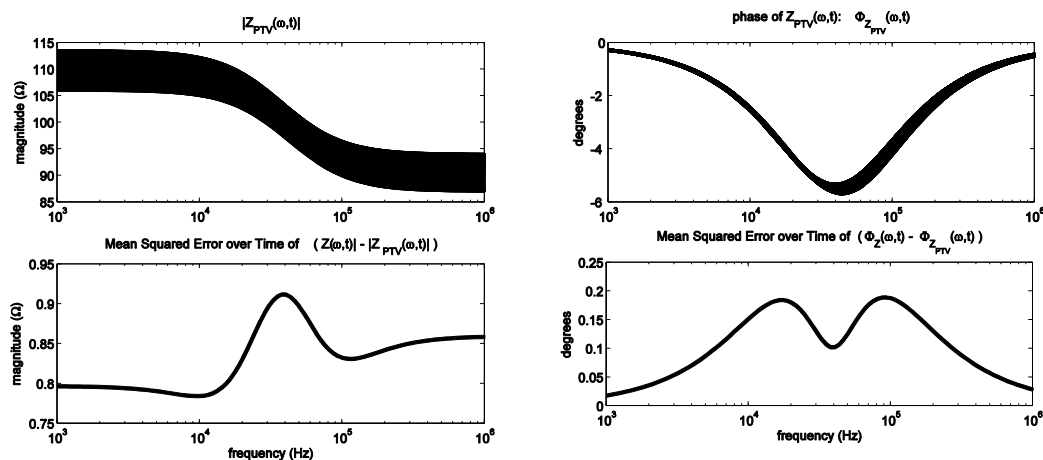


Figure 5: Magnitude and phase spectrum originating from the PR of an *in vivo* myocardial impedance fit. The bottom figures are respectively the RMSEoT of the magnitude and the phase spectrum over the 10 cardiac cycles.

III. Conclusions

When performing the experiments of time-varying impedance spectra, e.g. to characterize pathological *in vivo* tissues, the non-stationary nature of the bio-system under study has usually been discarded, as, for example, the case in [12–14]. Special attention should be paid when measuring (P)TV bioimpedance spectra using frequency-sweep EIS technique. The total measuring time to acquire a complete spectrum might be larger than the bioimpedance periodicity, limiting the accuracy of current frequency sweep-based impedance monitoring systems [15]. From the reported results, it can be concluded that it is preferable to benefit from the intrinsic (periodic) non-stationary information of the bioimpedance, e.g. to study accurately the influence of the cardiac and respiration activities in human thorax measurements, or to obtain information about morphological changes with the goal of detecting differentiation in stem cell cultures. In a view of the time dependencies shown, it has been demonstrated that is feasible to use only a limited number of harmonics to describe the *in vivo* myocardial impedance. The root mean square error over time (RMSEoT) for the periodically reconstructed model is bounded to 1 Ω and 0.2° in the frequency band 1 kHz – 1 MHz.

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