The Importance of Dielectric Dispersion for NsPEFs: a Cell Circuit Model

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Abstract — In this work, a novel passive element circuit model for microdosimetric study was presented and described. This model is able to incorporate dielectric relaxation / dispersion of the cell. The circuit cell model permits to obtain a simple and efficient method to evaluate the nsPEFs' action at the cellular level.

I. INTRODUCTION

During the last years, the biological effects due to the exposure of cells to nanosecond pulses electric fields (nsPEF) have been investigated for successful application to therapeutics scopes [1]. nsPEFs are characterized by an extremely short duration and a megavolt per meter amplitude.

The first effect induced by nsPEFs is the rearrangement of cell membrane with formation of nanometer-sized pores and this phenomenon strongly depend on the transmembrane potential (TMP) [1].

In such a context, microdosimetric studies allow to determine the TMP and provide important information on the effectiveness of nsPEF delivery to cells. For these studies, a passive cell circuit model can be advantageous, as suggest in [2].

Recently, the importance of including the dielectric dispersion of cell compartments into the microdosimetric models for short pulses (<10 ns) has been highlighted [3], [4]. In the circuit cell models, currently present in literature [1], [5], the dielectric dispersion of the cell compartments is not taken into account. In this work, we highlight the importance to incorporate the dielectric dispersion for a correct evaluation of TMP for the short nsPEF and we provide a circuit cell model able to properly include the dielectric dispersion.

To analyze the behavior of the new circuit three different types of pulses were used: the ES_nsPEF, VS_nsPEF, S_nsPEF reported in [4] with duration of 1, 3, and 10 ns respectively.

II. CIRCUIT MODEL AND PARAMETERS

In this section, we describe the new circuit model including the dielectric dispersion [4] and compare this with a classical circuit topology in which the Debye relaxation is neglected. In Fig.1 the basis element of the circuit model is shown. For a three layered model of the cell, the circuit consists in a series of five basis elements that represent in order: the extracellular medium, the membrane, the cytoplasm and again the membrane and the extracellular medium.

![Fig. 1: Basis element of the circuits with (a) and without (b) dielectric dispersion](image)

The classical circuit used for microdosimetry, in which the dielectric dispersion is neglected, consists in a series of simple RC-parallel elements (Fig. 1 (b)) representing specific cell compartments and the values of these capacitance and resistance are obtained as:

\[ R_{si} = \frac{d_i}{\sigma_i} \left[ \Omega/m^2 \right] \]  

\[ C_{si} = \frac{\varepsilon_0 \varepsilon_{si}}{d_i} \left[ F/m^2 \right] \]  

with \( i \) equal to \( e \) for the extra-cellular medium, \( m \) for the membrane, and \( c \) for the cytoplasm. \( d_i \) is the dimension, \( \varepsilon_{si} \) the static permittivity, and \( \sigma_i \) the conductivity of each compartments, and \( \varepsilon_0 \) is the permittivity of the vacuum [6].

This classical topology is modified to include the Debye relaxation phenomenon. The Debye model is a first-order model represented by and RC-series branch. Therefore a series of a resistor \( R_i^D \) and a capacitor \( C_i^D \) is added to the classical topology, where the superscript \( D \) indicated the Debye terms.

Each circuit element is dependent on the electrical properties of its cell compartment and geometry and is calculated per unit area from the parameters of the Debye model for permittivity and conductivity \( (\varepsilon_{si}, \varepsilon_{oi}, \tau_i, \sigma_i) \) with the following formula [6]:

\[ R_i = \frac{d_i}{\sigma_i} \left[ \Omega/m^2 \right] \]  

\[ C_i = \frac{\varepsilon_0 \varepsilon_{si}}{d_i} \left[ F/m^2 \right] \]  

\[ C_i^D = \frac{\varepsilon_0 (\varepsilon_{si} - \varepsilon_{oi})}{d_i} \left[ F/m^2 \right] \]  

\[ R_i^D = \frac{d_i \varepsilon_{oi}}{\varepsilon_0 (\varepsilon_{si} - \varepsilon_{oi})} \left[ \Omega/m^2 \right] \]  

where \( d_i \) is the dimension of the different compartments, \( \varepsilon_{oi} \) the residual permittivity, \( f_{res} = 1/2\pi \tau_i \) the relaxation frequency of each compartment, and \( \varepsilon_{si} - \varepsilon_{oi} \) corresponds to the dispersion strength.

The values of the geometrical and dielectric parameters are selected in accordance to [7]. This choice permits to confirm the results presented in [4] with a different dielectric model.
The circuit components represent all the physical mechanisms observable in the cell. In particular, the RC-series shunt permits to describe the dipolar polarization: when dipoles are immersed in an electric field the orientation of the polar species occurs. The capacitance $C_i^D$ takes into account the polarization phenomenon due to the orientation of the dipoles and the resistance $R_i^D$ the loss due to the energy exchanges between the dipoles in motion.

III. RESULTS

The proposed circuit model represents an accurate microdosimetric model as suggested in [4] where the data obtained with LTspice IV simulations and the analytical solution of the Laplace equation in the time and frequency domains are compared, obtaining a perfect matching of the data.

In this work, a time analysis for the two circuit topologies was carried out. Fig. 2 shows the time behaviors of the TMP with the two circuits for the three pulses.

From this figure, it is evident that the TMP time courses for the two alternative circuits tend to become similar with longer pulse duration in accordance with the results in [4]. To quantify the difference due to considering or disregarding the dielectric dispersion, a frequency analysis for the two circuit topologies was carried out. The membrane transfer function is defined as $H(f) = \frac{\text{TMP}(f)}{V_{in}(f)}$.

![Fig. 3 $\vert H(f) \vert$ for the circuit with dispersion and different dielectric model presented in [4] and [7]](image)

The $H(f)$ curve for the circuit without a dispersion presents a low-pass behavior. Instead, for the circuit with Debye relaxation there is a mitigation of the $H(f)$ low pass behavior that arrests its descending trend and starts to rise from about 100 MHz. The ascent is greater than the $H(f)$ curve in [4] due to the different membrane parameters that influence the third pole of $H(f)$ (Fig. 3). The frequency behavior confirms the importance of the dispersion for pulses with shortest duration.

IV. DISCUSSION AND CONCLUSION

In this work a new circuit able to include the dielectric dispersion was presented and the importance of the Debye relaxation phenomenon for a correct analysis of the shortest nPEFs effects was demonstrated.

The circuitual description proposed in the work is completely general. Indeed, it is possible to take into account more than one relaxation step for each cell region (e.g. membrane cytoplasm, extra cellular medium), with addiction of a further RC-series branch for each relaxation step, as well as an arbitrary number of cell compartments (e.g. including the so-called “bound water” layer or internal organelles).

REFERENCES