Effects of Pulse Addition in Electropermeabilization: Theoretical Insights on the Electric Conductivity

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Abstract— **The electrochemical treatment (ECT) of solid tumors is an electropermeabilization technique firmly established and widely used. In ECT protocols, pulse intensity as well as tissue electric conductivity are of utmost importance for assessing the final electropermeabilized area. Present ECT mathematical modeling based on the solution of the nonlinear Laplace equation for the electric field with a conductivity coefficient depending on the electric field and the temperature have greatly contributed to ECT protocol optimization. However, experimental results from literature report that a succession of pulses may increase tissue electric conductivity and the extent of tissue permeabilization, a phenomenon that present models fail to describe. Here we present new insights of a recently introduced ECT theoretical model that takes into account the effect of pulse addition on tissue electric conductivity. The model describes the electric field with the nonlinear Laplace equation with a conductivity coefficient depending on the electric field, the temperature and the quantity of pulses applied. ECT theoretical predictions show that the rise in the electric current density during the addition of pulses is due solely to an increment in the tissue electric conductivity with no significant changes in the electric field. A potential consequence of these results is that, under certain conditions, it would be possible to obtain larger electropermeabilized areas with the same pulse amplitude simply by increasing the number of pulses. The theoretical implications of this new model lead to a more realistic description of the EP phenomenon, hopefully providing more accurate predictions of ECT treatment outcomes.**

Keywords— **Electropermeabilization, electroporation, electric conductivity, pulse addition, mathematical modeling**

I. INTRODUCTION

EP-based technologies are at present being widely explored due to their broad spectrum of potential biotechnological applications, including not only the treatment of solid tumors but also food processing and environmental management. Among medical implications of electroporation-based technologies (EP), Electrochemotherapy (ECT) [1], gene electrotransfer [2], irreversible electroporation [3] and nanoelectroporation [4] are the main ones. All of them share the application of electric pulses to permeabilize, transiently or permanently, the cell outer membrane. ECT is one of the most explored approach among all EP techniques and is nowadays of standard clinical use in Europe for cutaneous and subcutaneous tumors [5]. It consists in the transient permeabilization of the cell membrane to increase significantly the introduction of a specific drug. The amount of permeabilization, and thus the efficiency of the EP protocol, depends on the local electric field but also on the tissue electric conductivity [6]. It was experimentally established for certain EP protocols that the addition of pulses rise tissue electric conductivity. Even more, the amount of pulses applied would affect the permeabilization level [7].

During the last decade many mathematical models have been evolving to achieve good pretreatment planning of EP-based medical interventions in tumors [8,9]. Initial models consider conductivity as a constant parameter derived from tissue characteristics, but soon models evolve to include a non-linear conductivity first dependent on the electric field [10] and later also on the temperature [11]. We introduced recently a new conductivity formulation dependent on the electric field, the temperature and the train of pulses [12]. Now we present new theoretical implications of this model concerning the evolution and spatial distribution of main variables during a given EP protocol.

II. MATERIALS AND METHODS

A. *In Vitro Model*

Potato tuber slices (4x5x2 cm) were electroporated with an arrange of three pair of parallel surgical steel electrodes 2 cm long and 1 mm diameter, immersed 1 cm in the tissue, separated 1 cm from anode to cathode and 0.5 cm between two electrodes of the same polarity (a typical type II configuration used in clinics [13]). Figure 1a shows the experimental setup. Twenty four square electric pulses (500, 800, 1000, 1500 and 1700 V with a duration of 100 μs at 1 Hz) were applied by means of a square wave electroporator. Pulse amplitudes were chosen to correspond to those used in standard ECT and IRE protocols. Total electric currents were recorded all along the treatment by an oscilloscope

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T. Jarm and P. Kramar (eds.), *1st World Congress on Electroporation and Pulsed Electric Fields in Biology, Medicine and Food & Environmental Technologies (WC 2015)*, IFMBE Proceedings 53,
DOI: 10.1007/978-981-287-817-5_48

DSOX2012A, 100 MHz, 2 channels, connected to the wire powering the 3 cathodes. Experiments were repeated 3 times independently. Electric current density derived from electropermeabilization experiments was determined at the end of each pulse.

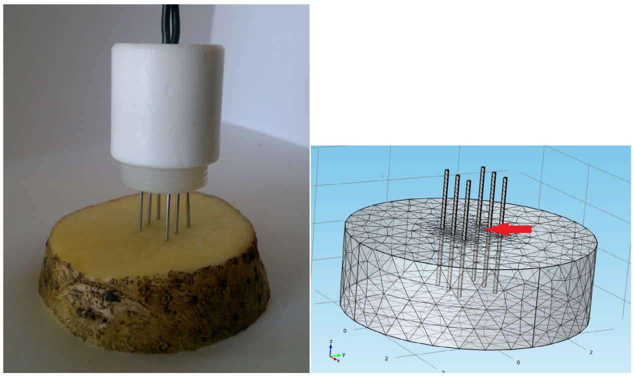

Fig. 1 In vitro and in silico models. a) Experimental setup. Arrangement of six electrodes inserted in a potato slice. b) Domain and mesh of the mathematical model generated by Comsol.

B. In Silico Model

The three-dimensional mathematical model introduced here describes the electric field distribution by a nonlinear Laplace equation with variable conductivity depending on the electric field, the temperature and the number of pulses; and the Penne's Bioheat equation for temperature variations:

$$\nabla.(\sigma\nabla\varphi)=0 \tag{1}$$

$$\nabla.(\kappa\nabla T)+q^{m}+\sigma|\nabla\varphi|^{2}=\rho C_{p}\frac{\partial T}{\partial t} \tag{2}$$

being σ the electric conductivity, φ the electric potential, k the thermal conductivity, T the temperature, q^{m} the metabolic heat generation, ρ the tissue density, C_p the tissue heat capacity and t the time. In [12] we introduced a new formulation for the electric conductivity dependent on the electric field (E), the temperature (T) and the amount of applied pulses (p):

$$\sigma(E,T,p)=\sigma_{b}(1+F_{f}(E)+F_{t}(T)+F_{p}(U,p)) \tag{3}$$

where σ_b is the basal electric conductivity of the tissue (0.03 S/m for potato). Ff(E), Ft(T) and Fp(U,p) are the terms dependent on the electric field, the temperature, the voltage applied to the electrodes (U) and amount of pulses, respectively. The system was solved, for each time step, in a fixed domain on a three-dimensional variable triangular mesh using finite elements and deterministic relaxation techniques. The model was solved by a Fortran 95 code developed at our lab and executed on a I7-class computer under Linux. It was also solved using the commercial finite element package Comsol (Stockholm, Sweden) under Windows 7. The model was calibrated with experimental measurements of electric currents in potato tissue during different EP protocols.

III. RESULTS AND DISCUSSION

Figure 2 shows experimental measurements on potato tissue and theoretical predictions (with or without the pulse-dependent conductivity term) of the electric current density, electric conductivity, electric field and temperature in the measurement area (arrow in figure 1b) as a function of the amount of pulses, for different applied voltages. Experimental data (figure 2a, dashed lines) show that, at applied voltages higher than 1000 V, electric current density increases with a higher number of pulses. Electric current density is not homogeneous in the electropermeabilized tissue [14], as neither is the electric field, the conductivity and the temperature; so we calculated and reported all these variables in a defined area close to the central cathode (measurement area, arrow in figure 1b).

Theoretical predictions with the pulse-dependent conductivity term (circles) describe how, at applied voltages higher than 1000 V, electric current density (figure 2a) and conductivity (figure 2b) rise during the train of pulses. Nevertheless, the electric field remains constant (figure 2c). These predictions are quantitatively close to experimental results of electric current density, both regarding initial values and slopes (figure 2a). In contrast, predictions obtained without this term (solid lines corresponding to 1700 V) compare unfavourably with experimental measurements. Although they present constant electric field values (figure 2c), they do not reflect the increment in the electric current density (figure 2a) nor in the electric conductivity (figure 2b). All numerical results presented in figure 2 were derived from the Fortran code. Comsol curves were omitted for clarity but they were very similar concerning both origin ordinates and slopes to the Fortran ones.

Figure 3 presents theoretical predictions of the electric potential, electric field and electric current distribution after eight pulses of 1500 V, 100 µs, 1 Hz, derived from the model implemented in Fortran. Figure 4 shows numerical predictions of the electric potential, electric conductivity and temperature distribution after eight pulses of 1500 V, 100 µs, 1 Hz, derived from the model implemented with the Comsol package. It can be observed a good correlation between Fortran and Comsol electric potential distributions (figures 3a and 4a, respectively).