



HAL
open science

Finite Element Modeling of Cell Exposed To Harmonic and Transient Electric Fields

Yvan Meny, Noël Burais, François Buret, Laurent Nicolas

► **To cite this version:**

Yvan Meny, Noël Burais, François Buret, Laurent Nicolas. Finite Element Modeling of Cell Exposed To Harmonic and Transient Electric Fields. *IEEE Transactions on Magnetics*, 2007, 43 (4), pp.1773–1776. 10.1109/TMAG.2007.892517 . hal-00136656v1

HAL Id: hal-00136656

<https://hal.science/hal-00136656v1>

Submitted on 19 Mar 2007 (v1), last revised 10 Apr 2007 (v2)

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Finite Element Modeling of Cell Exposed To Harmonic and Transient Electric Fields

I. Meny, N. Burais, F. Buret, and L. Nicolas

Abstract—The transmembrane potential (TMP) of a cell exposed to harmonic or transient electric fields is the main parameter for a successful permeabilization of a cell. Obviously, TMP can be computed with a Finite Element Method, but the high contrast between sizes and electromagnetic properties of the cytoplasm, the membrane, and the extra-cellular medium leads sometimes to inaccurate numerical results. Influences of membrane conductivity and frequency on the accuracy are studied. Optimization of transient waveforms is proposed for various shapes of cells.

Index Terms— Biological cells, Bioelectric phenomena, electromagnetic field computing, Finite Element Method.

I. INTRODUCTION

Electropermeabilization is an effective method for achieving transmembrane transport of molecules which otherwise cannot cross cell membrane: it can be used in particular for gene transfection and electrochemical therapy [1]. Theory and experiments have shown that the extent of permeabilization depends on cell size [2], shape, orientation [3, 4] and interaction with surrounding cells [5]. However, the efficiency of electropermeabilization depends above all on effective tissue conductivity and on the parameters of applied electric pulses. Investigations of the role of the amplitude, number, duration and shape of these pulses have been the subject of several experimental studies [6, 7, 8, 9]. However, the role of pulse shape in electroporation has not yet been studied with a transient modelling at the cell level.

The induced transmembrane potential (TMP) which causes permeabilization depends on the local electric field and not on the average applied field usually reported in experimental studies or predicted by tissue-level simulations. For spheroidal cells, the potential distribution can be obtained through analytical solutions of the Laplace's equation [4, 10, 11]. These analytic solutions have yet limited use in estimating TMP, as they can be obtained only for very simple shapes of cells. The application of numerical methods to cell problems provides the ability to model more complex and more actual geometries. Nevertheless, the very small thickness

of the cell membrane and the high contrast between material properties make difficult to obtain an accurate numerical modelling. The Finite Element Method (FEM) is well suited to model the geometry of actual cells and also permits the membrane to be modelled in detail without increasing the resolution over the entire problem space. Therefore, this method has been used in order to get an accurate insight of the electric field distribution inside cells with complex geometries [3, 12, 13], to make studies at the tissue scale [14, 15] or transient analyses with a wide variety of applied voltage waveforms [16].

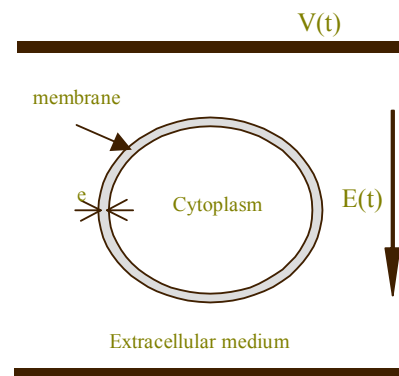


Fig. 1. Typical simulated cell problem

In this paper, FEM is used to calculate the TMP in a single cell exposed to harmonic or transient electric fields induced by a voltage applied between two parallel plane electrodes. The influence of the membrane conductivity and the frequency on the accuracy is investigated. It must be noticed that most of the time this aspect is not taken into account by the authors who use commercial FEM packages. Next, the waveform of applied pulses is optimized by investigating the effects of the signal rising rate. The validity range of the analytical expressions is evaluated with FEM calculations. Finally the slew-rate specifications recommended for the signal generators used in experiments are deduced.

II. ELECTROMAGNETIC MODEL OF A SINGLE CELL

The studied structure (fig. 1) is a single (spherical or elliptical) cell exposed to harmonic or transient electric fields induced by a voltage applied between two electrodes. TMP is calculated by solving the electro-quasi static equation which is formulated under complex form for time-sinusoidal electric field:

$$(\sigma + j\epsilon\omega)\Delta V = 0 \quad (1)$$

Manuscript received April 21, 2006.

I. Meny, F. Buret, L. Nicolas are with the CEGELY (Centre de Genie Electrique de Lyon) at the Ecole Centrale de Lyon, 69134 Ecully, France. (email : ivan.meny@ce-lyon.fr, francois.buret@ec-lyon.fr, Laurent.nicolas@ec-lyon.fr)

N. Burais is with the CEGELY at the Université Claude Bernard Lyon 1, 69622 Villeurbanne, France. (phone: +33 472448510; fax: +33 472431193; e-mail: burais@cegelely.univ-lyon1.fr).

Or a time step form for transient field (implicit scheme):

$$(\sigma + \varepsilon/dt)\Delta V^{(t)} = (\varepsilon/dt)\Delta V^{(t-dt)} \quad (2)$$

where $\varepsilon = \varepsilon_0 \cdot \varepsilon_r$, and dt the time step.

Equations (1,2) are solved by 3D axisymmetrical FEM.

Typical electric and size parameters of cytoplasm, membrane and extracellular medium are defined in table 1 for a spherical cell.

TABLE 1
ELECTRIC AND SIZE PARAMETERS OF A SPHERICAL CELL

Parameters	Denotation and value
Cytoplasmic conductivity	$\sigma_i = 0.53$ S/m
Cytoplasmic permittivity	$\varepsilon_i = 4.42 \times 10^{-10}$ As/Vm
Membrane conductivity	$\sigma_m = 5 \times 10^{-7}$ S/m
Membrane permittivity	$\varepsilon_m = 7.96 \times 10^{-11}$ As/Vm
Extracellular medium conductivity	$\sigma_o = 10^{-2}$ S/m (low-conductivity medium)
	$\sigma_o = 0.12$ S/m (physiological medium)
	$\sigma_o = 1.2$ S/m (blood serum)
Cell radius	R=10 μ m (eukaryote cell) R=1 μ m (prokaryote cell)
Membrane thickness	e=5 nm
Distance between electrodes	d=50 μ m

III. HARMONIC SIMULATION

Because of the great difference between cell size and membrane thickness ($\approx 1/2000$), particular attention must be paid to the FEM mesh structure.

For very low conductivities of the membrane compared with cytoplasmic and extracellular conductivities, TMP curve can exhibit anomalies in harmonic simulation. This “phenomena” appears only for frequencies below 1 kHz and doesn’t influence the results for frequencies range used classically in electroporation process.

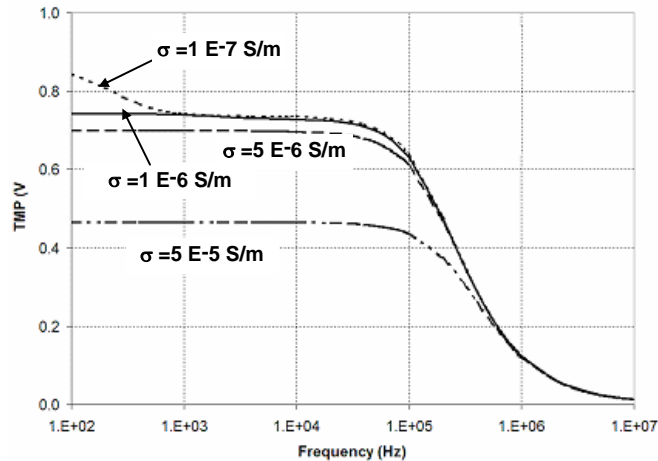


Fig.2. Frequency variations of TMP for various conductivities of membrane.

IV. TRANSIENT SIMULATION STUDY

The parametric study is performed in order to investigate the influence of the slope dV/dt of the applied signal on the permeabilization efficiency. The TMP threshold voltage V_s which allows to obtain a reversible permeabilization is ranging from 0.25 V to 1 V, depending on the type of cell. For example, a rather precise estimate gives V_s equal to 0.5 V for

hepatocytes [15]. In this study the threshold value is set to 0.4 V. The signal applied between the electrodes is a step turn-on, with a rising time greater than the time t_s required to reach V_s . In this way, the only relevant parameter for the applied signal is the slope dV/dt .

A. Analytical and FEM study of TMP for spherical cell

The classical theory of TMP developed by H.P. Schwan [17] leads to a temporal description of this phenomenon as a first-order process. The expression of the TMP V_m as a function of the time during the rising edge of the signal is:

$$V_m(t) = K \frac{dV}{dt} (t - \tau + \tau e^{-\frac{t}{\tau}}) \quad (3)$$

by assuming that TMP is measured along the cell axis.

The DC gain K can be calculated by using the approximate expression of the TMP:

$$V_m = \frac{3}{2} ER \quad E = \frac{V_{app}}{d} \quad K = \frac{3R}{2d} \quad (4)$$

where E is the strength of the electric field and V_{app} the applied voltage between the two electrodes.

A more accurate analytical expression of the TMP [11] leads to the equation:

$$K = \frac{3e\sigma_o(\sigma_i(3R^2 - 3eR + e^2) + \sigma_m(3eR - e^2))}{2R^3(\sigma_m + 2\sigma_o)\left(\sigma_m + \frac{1}{2}\sigma_i\right) + 2(R - e)^3(\sigma_m - \sigma_o)(\sigma_i - \sigma_m)} \frac{R}{d} \quad (5)$$

With the numerical values given in Table 1, by taking $R=10\mu$ m and $\sigma_o=0.12$ S/m, we find $K=0.3$ with equation (4) and $K=0.298$ with equation (5). As the difference between these two results is very low, equation (4) will be used for analytical calculations.

The time constant τ of the membrane is given [18] by:

$$\tau = \frac{R \frac{\varepsilon_m}{e}}{\frac{2\sigma_o\sigma_i}{2\sigma_o + \sigma_i} + \frac{R}{e} \frac{\sigma_m}{\sigma_m}} \quad (6)$$

TMP values are calculated with FEM and with equation (3) by taking $R=10\mu$ m, $\sigma_o=0.12$ S/m and $dV/dt=6$ V/ μ s. Equivalent results are obtained. So, the first-order theory seems to be valid during the rising phase of the signal.

In order to investigate the influence of the slope dV/dt , we focus on the time t_s required to reach V_s . Experiments show that the time during which the amplitude of the applied pulse exceeds a certain critical value, has a major role in the efficiency of electroporation [6]. It is assumed here that this critical value is linked with the reversible threshold V_s of permeabilization.

TABLE 2.

Values of t_s for $\tau=0.96$ μ s.	
dV/dt (V/ μ s)	t_s (μ s)
6	0,73
3	1,1
1	2,2
0,5	3,6
0,2	7,7
0,06	23,6
0,03	46
0,01	138

An analytical expression of t_s needs the reciprocal of the function $V_m(t)$ written in (3) to be determined. As V_m^{-1} cannot be directly calculated, (3) is simplified by noticing that t_s is much greater than τ in most of the cases, especially for the lowest values of dV/dt : in Table 2, we show some values of t_s obtained with $R=10\mu\text{m}$ and $\sigma_0=0.12\text{ S/m}$, i.e. $\tau=0.96\mu\text{s}$. The exponential term in (3) may be neglected, and an expression of t_s as a function of V_s and dV/dt would be:

$$t_s = \frac{V_s}{K \frac{dV}{dt}} + \tau \quad (7)$$

In fig. 3, values of t_s given by FEM calculations are compared with analytical values given by (7) for $R=10\mu\text{m}$ (order of magnitude of eukaryote cells sizes). Others calculations are performed for $R=1\mu\text{m}$ (prokaryote cells), but the FEM and analytical curves are quite similar. Different values of τ are obtained by varying the extracellular medium conductivity: for $R=1\mu\text{m}$ and $R=10\mu\text{m}$, τ is respectively equal to: $0.82\mu\text{s}$ and $7.9\mu\text{s}$ for $\sigma_0 = 10^{-2}\text{ S/m}$, $0.096\mu\text{s}$ and $0.96\mu\text{s}$ for $\sigma_0 = 0.12\text{ S/m}$, $0.037\mu\text{s}$ and $0.37\mu\text{s}$ for $\sigma_0 = 1.2\text{ S/m}$.

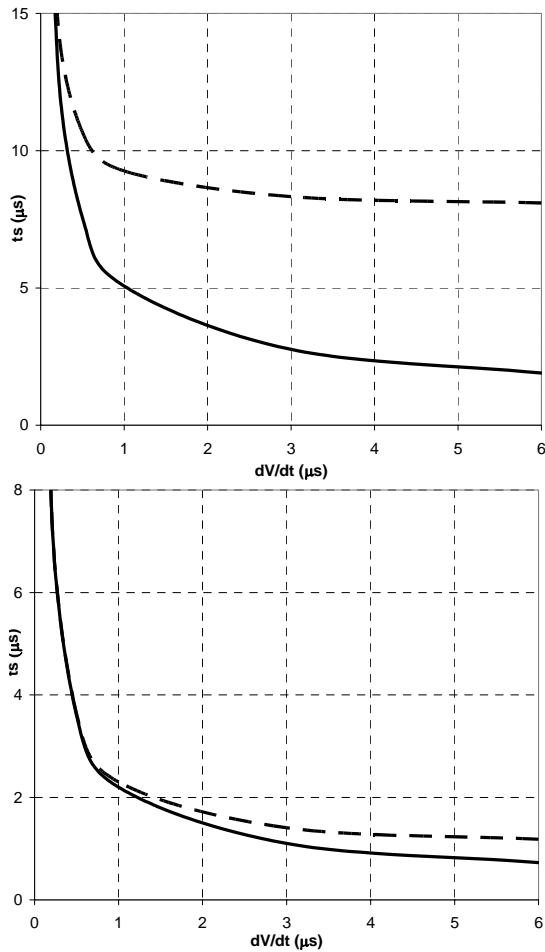


Fig. 3. t_s vs dV/dt : FEM values (solid curve) and analytical values obtained from expression (7) (dashed curve): $R = 10\mu\text{m}$, $\sigma_0 = 10^{-2}\text{ S/m}$ (up) $\sigma_0 = 0.12\text{ S/m}$ (down),

The accuracy of the analytical expression of t_s improves when the slope dV/dt and τ present low values. For $R=10\mu\text{m}$, it can be noticed that for a given value of dV/dt , values of t_s change with σ_0 , when t_s remains almost unchanged whatever σ_0 may be. When the distance between electrodes is in the same order of magnitude as the cell radius (e.g. $R=10\mu\text{m}$ and $d=50\mu\text{m}$), t_s is influenced by the cytoplasm and the extracellular medium conductivities: τ is not negligible in (7) and becomes even predominant for high values of dV/dt . On the other hand, when R is much smaller than d (e.g. $R=1\mu\text{m}$ and $d=50\mu\text{m}$), t_s depends first of all on applied signal. So, the spherical-cell model makes possible to establish analytical relations, from which we deduced (7).

B. FEM study of TMP for elliptical cell

By using FEM, the TMP evolution for elliptic cells can be calculated, this shape being closer to reality. Fig. 4 shows values of t_s obtained with prolate ("cigar-shaped"), oblate ("disk-shaped") and spherical cells.

For the spherical cell: $R=10\mu\text{m}$, for the prolate cell: $R_1=15\mu\text{m}$ and $R_2=10\mu\text{m}$, for the oblate cell: $R_1=10\mu\text{m}$ and $R_2=15\mu\text{m}$, R_1 and R_2 being respectively the radius along the axis of rotational symmetry and the radius perpendicular to this axis.

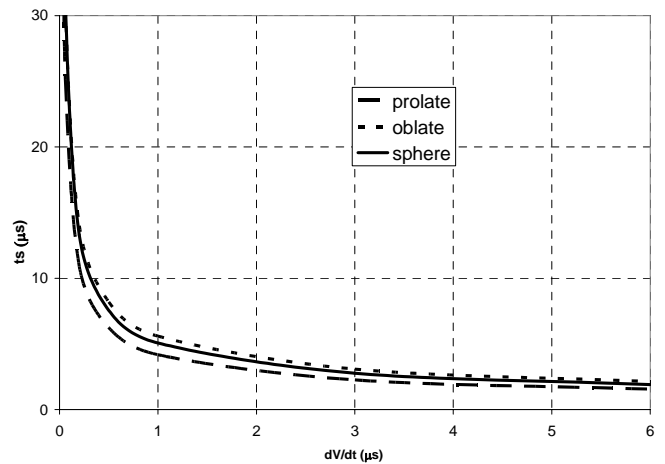


Fig. 4. Time t_s vs dV/dt for spherical and elliptic cells ($\sigma_0=10^{-2}\text{ S/m}$)

The evolution of t_s is the same with the three cell shapes: we can distinguish a sharp decrease and a very slow decrease area, the transition between these two zones takes place for the same values of dV/dt . The two areas can be delimited with the curve point where the derivative is equal to -1. By taking the spherical-cell as a reference and using (7), we find that this value of the derivative occurs for:

$$\left(\frac{dV}{dt}\right)_1 = \sqrt{\frac{V_s}{K}} \quad (8)$$

C. Optimization of the applied signal

Pulses used for electropermeabilization can be very short, especially for eukaryote cells, on which single rectangular pulses of $100\mu\text{s}$ duration are often applied.

On one hand, it seems necessary in this case to use pulse generators able to deliver signals with slopes greater than $(dV/dt)_1$, otherwise the TMP would remain below the

reversible threshold during a time t_s which is not negligible in comparison with the total pulse duration. Moreover this time t_s would not be precisely controlled: it depends particularly on the gain K and the threshold value V_s , which are generally imprecisely known and present heterogeneous values. Then for low values of dV/dt , t_s could be very different from a cell to another; the effective duration of the applied pulses being not known, the experiments would not be fully repeatable. On the other hand, generator pulses with slew-rates much greater than $(dV/dt)_m$ seem unnecessary, at least for high values of K : the gain achieved on t_s with very high dV/dt is minor in comparison with the total pulse duration.

The threshold V_s being estimated less than 1 V, (8) is upper-bounded by:

$$\left(\frac{dV}{dt}\right)_m = \sqrt{\frac{1}{K}} = \sqrt{\frac{2d}{3R}} \quad (9)$$

This value would then be the minimum acceptable slope for the applied signal. However, the distance between electrodes is often in the order of one millimetre in experiments. Low values of K can then be reached and t_s becomes significant in comparison with the total pulse duration, even if dV/dt is greater than $(dV/dt)_m$. Considering a pulse of 100 μs duration, if we want t_s to remain less than 10 μs for example, the minimum slope for $K < 0.01$ has to be:

$$\left(\frac{dV}{dt}\right)_{m_{K < 0.01}} (V / \mu s) = \frac{(0.1)}{K} = \frac{(0.2)d}{3R} \quad (10)$$

Fig. 5 shows values of $(dV/dt)_m$ in case of spherical cells with a radius $R=1 \mu m$ and $R=10 \mu m$, for a distance d between electrodes included in [50 μm ; 2mm]. It can be seen that high values of slew-rate can be required for $R=1 \mu m$. In this case, special generators or reduction of the distance between electrodes may be necessary.

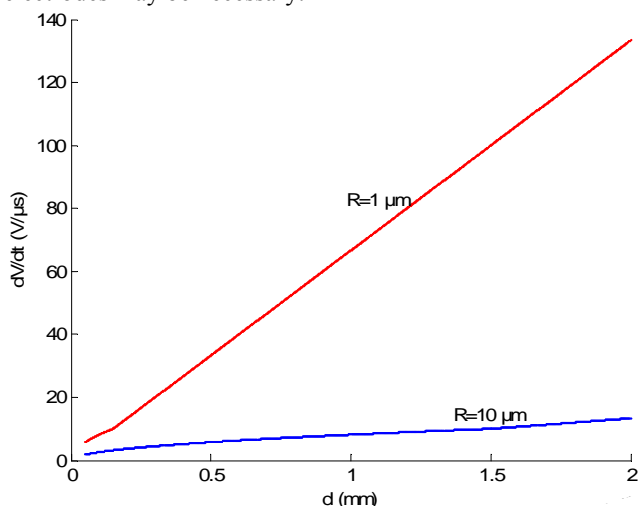


Fig. 5. $(dV/dt)_m$ vs distance between electrodes

V. CONCLUSION

Electro-quasi static formulation and FEM resolution can be used to calculate harmonic and transient TMP, but because of the very low thickness of membrane, particular attention must be paid to the mesh structure. FEM and analytical

calculations of TMP has been performed for spherical cells in order to obtain optimization parameters of signal (threshold time t_s and slope dV/dt). For elliptical cells, FEM studies show that the results are similar, and the same analytical expressions can also be used to optimize the applied signal. Next works will be devoted to FEM study of inhomogenous cytoplasm in cell, to membrane modeling by "shell element" and optimization of other waveforms.

REFERENCES

- [1] K.H. Schoenbach, S. Katsuki, R.H. Stark, E.S. Buescher, S.J. Beebe, "Bioelectrics-New applications for pulsed power technology", *IEEE Trans. on Plasma Science*, vol.30, n°1, pp. 293-300, february 2002
- [2] S. Hojo, K. Shimizu, H. Yositate, M. Muraji, H. Tsujimoto, W. Tabebe, "The relationship between electroporation and cell cycle and cell size of *Saccharomyces Cerevisiae*", *IEEE Trans. on nanobioscience*, vol.2, n°1, pp. 35-39, march 2003
- [3] B. Valic, M. Golzio, M. Pavlin, A. Schatz, C. Faurie, B. Gabriel, J. Tessié, M.P. Rols, D. Miklavcic, "Effect of electric field induced transmembrane potential on spheroidal cells: theory and experiment", *Eur. Biophys. Journal*, vol. 32, pp. 519-528, september 2003
- [4] J. Gimsa, D. Wachner, "Analytical description of the transmembrane voltage induced on arbitrarily oriented ellipsoidal and cylindrical cells", *Biophysical Journal*, vol. 81, pp. 1888-1896, october 2001
- [5] T.R. Gowrishankar, J.C. Weaver, "An approach to electrical modeling of single and multiple cells", *PNAS*, vol. 100, pp. 3203, march 2003
- [6] T. Kotnik, G. Pucihar, M. Rebersek, D. Miklavcic, L.M. Mir, "Role of pulse shape in cell membrane electroporation", *Biochimica et Biophysica Acta*, n° 1614, pp. 193-200, august 2003
- [7] M.P. Rols, J. Tessié, "Electroporation of mammalian cells to macromolecules: control by pulse duration", *Biophysical Journal*, vol. 75, pp. 1415, september 1998
- [8] N. Eynard, F. Rodriguez, J. Trotard, J. Teissie, "Electrooptics Studies of *Escherichia coli* Electroporation: Orientation, Permeabilization, and Gene Transfer", *Biophysical Journal*, vol. 75, pp. 2587-2596, november 1998
- [9] R.P. Joshi, Q. Hu, K.H. Schoenbach, "Dynamical modeling of cellular response to short-duration, high-intensity electric fields", *IEEE Trans. on Dielectrics and Electrical Insulation*, vol. 10, n°5, pp. 778-787, october 2003
- [10] T. Kotnik, F. Bobanovic, D. Miklavcic, "Sensitivity of transmembrane voltage induced by applied electric fields- a theoretical analysis", *Bioelectrochemistry and Bioenergetics*, n°43, pp. 285, 1997
- [11] T. Kotnik, D. Miklavcic, T. Slivnik, "Time course of transmembrane voltage induced by time-varying electric fields- a method for theoretical analysis and its application", *Bioelectrochemistry and Bioenergetics*, n°45, pp. 3-16, 1998
- [12] E.C. Fear, M.A. Stuchly, "Modeling assemblies of biological cells exposed to electric fields", *IEEE Trans. on Biomedical Engineering*, vol. 45, n°10, pp. 1259-1271, october 1998
- [13] C.E. Miller, C.S. Henriquez, "Three-dimensional finite element solution for biopotentials: Erythrocyte in an applied field", *IEEE Trans. on Biomedical Engineering*, vol. 35, n°9, pp. 712-718, september 1988
- [14] D. Miklavcic, D. Semrov, H. Mekid, L.M. Mir, "A validated model of in vivo electric field distribution in tissues for electrochemotherapy and for DNA electrotransfer for gene therapy", *Biochimica et Biophysica Acta*, n° 1523, pp. 73-83, september 2000
- [15] D. Sel, D. Cukjati, D. Batuskaite, T. Slivnik, L.M. Mir, D. Miklavcic, "Sequential finite element model of tissue electroporation", *IEEE Trans. on Biomedical Engineering*, vol. 52, n°5, pp. 816-827, may 2005
- [16] S. H. Jayaram, S. A. Boggs, "Optimization of electroporation waveforms for cell sterilization", *IEEE Trans. on Industry Applications*, vol. 40, n°6, pp. 1489-1497, november/december 2004
- [17] H.P. Schwan, "Electrical properties in tissue and cell suspensions", *Adv. Biol. Med. Phys.*, vol. 5, pp. 147-209, 1957
- [18] H. Pauly and H.P. Schwan, "Impedance of a suspension of ball-shaped particles with a shell ", *Z. Naturforsch.*, vol. 14B, pp. 125-131, february 1959.