Magnetic Induction of Electroporation: Numerical Analysis and Technical Limitations

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Abstract— **Electric fields delivered across biological cells can cause structural and functional changes to the cell membrane, such as electroporation. An important application of electroporation is in the permeabilization of skin cells. Currently these cells are electroporated with contact electrodes. In this study we explore the feasibility of using electromagnetic induction for non-contact electroporation of skin cells, and the effect of various design parameters on the process. We derived a simple analytical solution that lends itself to a systematic study of design parameters and verified the solution with a numeric solution of the Maxwell equations using finite elements. A short feasibility study of the system implementation is done, concluding that there are technological limitations that must be met in the future in order to build such a device.**

I. INTRODUCTION

Transmembrane electric fields in biological cells cause transient structural and functional changes, from ionic channels conductance changes, to permeabilization of the cell membrane. Membrane permeabilization is theoretically understood as membrane pores which allow cross-membrane material flow, and is known as electroporation; phenomenon that has been used since 1983 for research, laboratory practice and clinical applications [1].

During the application of an electrical pulse (approximately 400 mV [2]) across the cell membrane, charges accumulate due to migration of ions both inside and outside the cell medium. When a critical transmembrane voltage is reached, the lipids rapidly rearrange and their polar heads fold over, creating a hydrophilic interface between the inner and the outer medium. This phenomenon is theoretically modeled as the formation of a conductive pore, which will allow the diffusion of hydrophilic macro-molecules across the cell membrane. Finally, depending on the electrical pulse amplitude, exposure time, and critical defect size, the lipids may rearrange to its natural structure, resealing the lipid bilayer (reversible electroporation), or remain in the new structure, resulting in an irreversible electroporation (IRE) [2].

Since for IRE the cell membrane remains permeable, diffusion among the inner medium and the outer medium leads the cell to finally lose its homeostasis making it suitable for tissue ablation [2].

Conventional electroporators basically consist of two electrodes (separated a distance of few *mm*). These electrodes deliver sequences of short (*ns* to *ms*) pulsed electric fields which are delivered across the tissue to produce the desired electroporation. However, it has been long known that while alternating currents (AC) have various effects on biological cells they can also produce phenomena akin to electroporation, as suggested in [3]. From his own observations, McKinley concludes that damage caused to living tissues by high frequency electric fields (10 to 100 *MHz*) cannot be only from thermal origin, particularly in the case of nervous tissue.

It occurred to us that electromagnetic induction with alternating currents (AC) could be used for non-contact electroporation of tissue. This would be particularly relevant to electroporation enabled gene vaccines of the skin cells.

Our goal is to assess, theoretically, the feasibility of non-contact electromagnetic induction electroporation in tissue and to determine the effects of various design parameters on the process. To this end we have developed a simplified theoretical model of the process and have verified it with the full solution of the Maxwell's equations obtained using finite element based numerical analysis. We have also studied the feasibility of such a device and have found a list of current technological limitations for its development and implementation.

II. SIMPLIFIED ELECTROMAGNETIC MODEL

A. Induced magnetic field

Our goal is to obtain an expression for the magnetic induction produced in the tissue by a long multilayer coil wound around it. The analysis is for a coil made of wires with radius r_{wire}, wound in such a way that at every axial location there are N turns, and the length of the coil is l_c. It is acceptable to assume that inside a coil, the magnetic field is quasi-uniform [4]. The relative magnetic permeability of biological tissue is considered by the literature to be $\mu_r = 1$ [5].

Faraday's equation gives that the axial magnetic field induced by a single circular turn of the coil, is given by (1)

$$\boldsymbol{B}(z) = \frac{\mu_0 \cdot I}{2} \cdot \frac{a^2}{(z^2+a^2)^{3/2}} \cdot \boldsymbol{k}.$$ (1)

where μ_0 is the magnetic permeability of the vacuum, I is the driving current, a is the turn radius, z is an arbitrary point on the coil axis, and $\boldsymbol{k}$ the direction vector.

Assuming that at a single axial location the coil has multiple layers (N turns) and that the difference between the outer and inner radii of the coils is not negligible, the total magnetic field induced in the coil is the sum of the magnetic

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field that each layer alone would induce. Considering that the wire radius is negligible relative to the coil's size, an infinitesimal approximation of the sum can be done by means of integration. After calculating the integral, we evaluate the magnetic field at $z_0 = {}^{l_c}\!/_2$ since that is the point of maximum $B(z)$ [4] and we get (2). Where a_{out} and a_{in} are the coil's outer and inner radii respectively.

$$\boldsymbol{B}(z) = \frac{\mu_0 \cdot I}{8 \cdot r_{wire}^2} \cdot l_c \cdot \ln\left(\frac{\sqrt{a_{out}^2 + \left({}^{l_c}\!/_2\right)^2} + a_{out}}{\sqrt{a_{in}^2 + \left({}^{l_c}\!/_2\right)^2} + a_{in}}\right) \cdot \boldsymbol{k}. \quad (2)$$

B. Simplified expression for the induced electric field

A general expression, for the electric field as a function of the physical characteristics of the coil and the driving current, can be developed. Consider a cylindrical body (tissue) inside the cylindrical coil (see Fig. 1). Due to the intrinsic symmetry of the problem being modeled, an equation for the induced electric field in cylindrical coordinates was developed. The electric field has no component in the z coordinate. Being γ any circle in an orthogonal section of the cylindrical body (concentric with the cylinder), it can be shown that the maximum value in time for the induced electric field is given by (3), when exciting the system with AC: $I = I_0 \cdot \cos(\omega t)$.

$$\left|\vec{E}(r_\gamma)\right| = \frac{\mu_0 \cdot I_0 \cdot \omega}{8 \cdot r_{wire}^2} \cdot l_c \cdot \ln\left(\frac{\sqrt{a_{out}^2 + \left({}^{l_c}\!/_2\right)^2} + a_{out}}{\sqrt{a_{in}^2 + \left({}^{l_c}\!/_2\right)^2} + a_{in}}\right) \cdot \frac{r_\gamma}{2}. \quad (3)$$
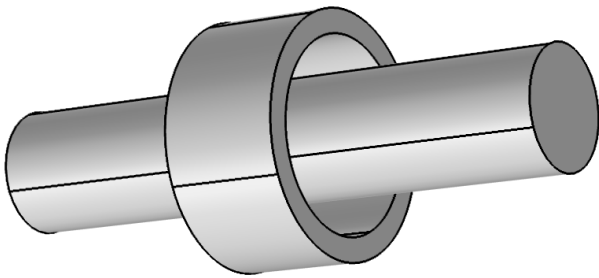

Figure 1.   Schematic representation of the coil and tissue system

As stated above, in this simplified model it is assumed that the electric field is uniform inside the coil. This is not physically accurate, but would provide a straight-forward method to calculate the dimensions of the coil roughly and afterwards fine tune it using Finite Elements methods.

III.   DESIGN PARAMETERS

The design was based on parameters of other electro-magnetic induction systems used in medicine. For instance, a driving current of $I_0 = 5\,kA$ at $4 - 10\,kHz$, is commonly used for transcranial magnetic stimulation systems [5]. Then, a parametric study was performed, in which the geometry of the coil and the frequencies of the driving current (between 1 kHz to 10 kHz) are varied. This frequency corresponds to electric pulses in the range from 100 μs to 1 ms, which is a commonly used range in electroporation.

Since initially the intention of this study is to perform electroporation on skin *in vivo*, the cylindrical body was considered to have a diameter similar to that of a mean forearm diameter, which is approximately 90 mm [6]. The design goal is to perform reversible electroporation in the outer 2 mm layer: the epidermis and dermis [6]. In order to induce reversible electroporation we need to induce a minimum electric field of $3.6 \cdot 10^4\,{}^V\!/_m$ [2].

For this study, skin effects within the coil wires are neglected. It can be assumed that Litz wires are used with the necessary cooling system in order to reduce its resistivity and heating.

The aim is to find the smallest coil that will induce reversible electroporation, with the lowest possible frequency.

IV.   NUMERICAL RESULTS

A. Analytical calculations and Finite Elements Simulation

According to (3), the induced electric field increases with l_c without any local maximum. Therefore, the parametric study is done for an arbitrary $l_c = 10\,mm$ and varying the coil depth ($a_{out} - a_{in}$). When a_{in} is minimal, the induced electric field is maximal. So a_{in} was set to 50 mm, a_{out} is varied from 55 mm up to 400 mm, $r_\gamma = 43\,mm$ (epidermis and dermis [9]), $I_0 = 5\,kA$ and $r_{wire} = 0.25\,mm$.

According to (3), it is interesting to notice that using relatively higher frequencies allows the use of substantially lower outer radii of the coil.

A numerical analysis was performed using COMSOL® Multiphysics 4.1. A 2D axisymmetric Magnetic and Electric Fields (MEF) frequency domain model was used, in which the symmetry axis is that of the coil system, namely axis z. This numerical analysis was intended to verify the validity of the analytical model, to be used as a basis for parametric design of the system.

For simulation the parameters were defined as follows: $a_{out} = 85.5$ and the frequency to 4 kHz (while the other parameters are those defined above). The results are similar to those of the analytical model but slightly different. While the analytical model calculates the induced electric field to be $E_{ind} = 3.63 \cdot 10^4\,{}^V\!/_m$, the simulation results in an induced electric field $E_{ind} = 4.17 \cdot 10^4\,{}^V\!/_m$ (both RMS values). This difference of less than 15% between both induced electric fields' magnitudes comes mostly from the simplifying assumption in the analytical model, which assumes that the magnetic field is uniform inside the coil [4].

V.   TECHNICAL LIMITATIONS FOR IMPLEMENTING THE SYSTEM

The coil build with the calculated dimensions has an inductance close to 100 mH, as can be easily derived from (2). In order to drive a current of 5 kA at 4 MHz as proposed, a peak voltage of about 40 MV is needed. Such a voltage can be achieved by charging a load of capacitors which will afterwards be connected to the coil, and then an oscillation will be seen. The frequency of that oscillation can be set (theoretically) by properly calculating the overall

capacitance of the load.

Calculations were developed and the required system with commercially available capacitors was designed. But the availability fails in providing appropriate switches or relays for disconnecting the capacitors load from charging and the connecting to the coil. The time they take for disconnecting the circuit is much longer than the time needed for avoiding capacitor discharge through parasitic resistors, and much longer than the time stated above to avoid thermal damage of the tissue, which is about 70 *ms* [2].

Also, the calculated loading time for such capacitors load is more than an hour, for a discharge of 70 *ms* through the coil. While the overall energy is not big, its power consumption is about 200 *MW* (peak power) descending quickly within tens of milliseconds.

Finally, implementing this system with the existing components would require a volume of about $10^4 \, m^3$, due to the size of available components and distance between cables for insulation [7].

VI. CONCLUSION

An analytical model of an induced electric field within biological tissue was derived and used for a parametric analysis of an electromagnetic induction system for skin reversible electroporation. The analysis was based on the same currents and frequencies as those used by a magnetic stimulator. The design study has demonstrated the design parameters needed to induce electroporation in the skin layer of an arm. It was calculated that no sensitive thermal effect is generated, when applying typical AC electroporation protocols.

An implementation limitations discussion is included, concluding that nowadays building this device is not feasible due to, mainly, lack of relays with quick response time. Since other issues like building a power supply for charging the capacitors can be solved.

This paper introduces a novel application of magnetic AC electroporation, and can serve as the basis for designing electromagnetic induction electroporation systems, in the future.

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