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Modelling the Cell Transmembrane Potential Dependence on the Structure of the Pulsed Magnetic Field Coils

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***Abstract*—During high power pulsed magnetic field treatment of biological samples the cells are subjected to both the high magnetic and induced electric fields. The extent of the influence of each treatment component is poorly studied. The work presents the finite element method analysis of pulsed inductive coils that are used for generation of pulsed magnetic and induced electric fields. The simulated coils, electrical parameters and the output characteristics are evaluated in respect to the induced cell transmembrane potential. The model of the Jurkat T lymphocyte cells is introduced in the analysis. The study includes finite element method analysis of four solenoid coils with different structure and inductance in the range of 2.8 μH to 62 μH. Pulsed magnetic field amplitudes up to 5 T are investigated in this work.**

***Index Terms*—Biological cells, electroporation, inductor, magnetic fields.**

I. INTRODUCTION

Application of pulsed power technological setups in biomedical and biotechnological sciences has become a common practice in the past 10 years [1]–[3]. Introduction of the high voltage pulses ranging from tens of volts to several kV in the treatment of biological tissues or cells has resulted in the formation of the biomedical technique, known as electroporation [4]–[7].

There are multiple reports showing that the controlled exposure of biological samples to the high intensity pulsed electric field results in the different effects on the cell plasma [8]–[9]. The uptake of drugs, proteins or other molecules by the cell could be successfully controlled with the pulsed power setups [10]. High intensity treatment results in necrosis of the tissue, which has found application in the cancerous tumour treatment area [11]. Also electroporation has already reached medical facilities as a new tool for treatment of cancer [12].

However, at the same time pulsed magnetic field application in the biomedical field is very limited. The area of study is very new and lacks both the experimental and analytical data. Nevertheless, in the past 3 years there are multiple studies showing the effects of high pulsed magnetic fields on the biological samples [13]–[16]. The experimental studies present different magnetic field facilities and experimental data showing that due to pulsed magnetic field treatment the permeability of biological cells was altered [17]. Towhidi *et al.* demonstrated that the subjection of CHO cells to pulsed magnetic field results in the transfer of the fluorescence dye Lucifer Yellow that was used as a marker [18]. Also in 2013 Shankayi *et al*. demonstrated that the application of low repetition frequency (0.25 Hz–10 Hz) pulsed magnetic field in the range of 2.2 T results in the increased molecular uptake and the increase of the cell medium conductivity [19]. In the studies it has been shown that the pulsed magnetic field treatment is causing effects similar to electroporation; therefore, the works are evaluating induced electric field as one of the main parameters affecting the treatment.

One of the most important factors in the magnetic field experiments is magnetic field homogeneity in the effective volume where the cells are stored. Otherwise the evaluation of the experimental data involves high error rates and poor experiment repeatability with biological samples. The requirement introduces several limitations to the inductive coil structure. A typical solution is application of solenoid type coils, which ensures high magnetic field homogeneity in the inner volume [20]. However, even though the application of the solenoid coils is straightforward and preferable, determination of the optimal coil structure is required. In order to develop such a coil, the major factors that are affecting the treatment must be studied.

In this work the evaluation of the extent of the influence of the each treatment component is performed. Determination of the solenoid structure could improve the pulsed power devices that are used in the area of magnetic field treatment to increase the efficacy of biological experiments. The number of windings, layers and the final dimensions of the inductor have high influence on the output magnetic pulse parameters [21]. The investigation of the inductive coils is required for understanding of the treatment intensity change due to various pulse parameters. Therefore, how the magnetic coil structure influences the pulse rise time, fall time, magnetic and induced electric field amplitudes, etc. in respect to the transmembrane cell potential must be evaluated.

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The results could allow better understanding of the biological effects of the high pulsed magnetic fields.

II. THEORETICAL APPROACH

A. *Induced Membrane Potential*

In order to estimate the change of the transmembrane potential of a biological cell the analytical model of the cell must be introduced. Currently, the spherical model of the cell is mostly used. The cell is approximated as a conducting sphere where the membrane thickness is much smaller than the cell radius [22]. This approximation allows application of the Maxwell equations for the estimation of the effective conductivity of the cell suspension [23]. The model allows evaluation of the polarization effects happening during electrical pulses. It has been chosen that the cells that were used in the model are the human Jurkat T lymphocyte cells. The parameters of the Jurkat T cells are summarized in Table I.

TABLE I. JURKAT T PARAMETERS.

Parameter	Value	Denotation
Radius	8	*r*, μm
Membrane thickness	10	*m*, nm
Membrane conductivity	50	σ_m, μS/m
Inner cell volume conductivity	1	σ_i, S/m
Outer medium conductivity	1.2	σ_o, S/m

Based on the approximation the polarization time has been evaluated. For the selected type of the cells according to the methodology described by Schwan *et al.* the pulse width of the induced electric field must be in the range of 1 μs [24].

The induced electric field ***E*** is estimated according to the Maxwell-Faraday equation

$$\nabla \times \mathrm{E} = \frac{-\partial \mathrm{B}}{\partial t}, \tag{1}$$

where ***B*** is the magnetic flux density and *t* is the time. The transmembrane potential that is induced due to the external electric field is derived from Laplace equation. For the medium that is used in our approximation the transmembrane potential equation could be simplified to [25]

$$V_T = 1.5\boldsymbol{E} r \cos\theta, \tag{2}$$

where θ is the angle between the induced electric field and the point vector on the cell membrane, *r* is the cell radius. From (1) and (2) it can be seen that the induced electric field amplitude is proportional to the magnetic field alteration rate. Also it is reported that the critical threshold voltage is when V_T = [0.2 V–1 V] [26]. At the marginal case according to (2) to get the potential of 0.2 V the minimum induced electric field must be at least 16.7 kV/m for the selected cells.

B. *Magnetic Field Pulse*

Generation of high pulsed magnetic fields requires high pulsed currents. Therefore, one of the most popular semiconductor switches, that are used for high magnetic field generation are thyristors [25]. High current handling capability compared to other semiconductor technologies and the simplicity of driving makes the thyristor switch advantageous in the area. For analytical approximation of the magnetic field pulse that is generated in the coils with different parameters, methodologies applied in References [26]–[27] are used. The shape of the magnetic field pulse *B(t)* for a long solenoid could be approximated as

$$B(t) = \text{«} \frac{Un}{\mu La} e^{\left(-\frac{R}{2L}t\right)} \sin \mu t, \tag{3}$$

where *U* is the capacitor voltage value, *R* – sum resistance of the line, *L* – sum inductance of the line, *ω* is the oscillation frequency, which is *R*, *L* dependent; *n* – number of windings, *a* – length of the solenoid, *μ* – magnetic permeability. However, this approximation does not include such parameters as layer insulation, form factor etc., which results in the decrease of the simulation accuracy. Also multilayer coil analysis becomes complex and time consuming. Therefore, finite element method analysis has to be applied.

III. FINITE ELEMENT METHOD ANALYSIS

For the finite element method (FEM) analysis ANSYS and Matlab software have been used. The summary of the coils investigated in the study is presented in Table II.

TABLE II. COILS PARAMETERS

Parameter	Value	Denotation
Coil length	[2–4]	*a*, mm
Outer diameter	[4.5–8]	*b*, mm
Inner diameter	1	*c*, mm
Number of layers	[5–10]	n_L
Number of windings	[25–100]	n_W
Wire diameter	0.3	d_W, mm
Insulation thickness	0.04	i_W, mm
Cuvette diameter	0.8	*d*, mm

The schematic of the vertical slice of the 25 windings (5 × 5) coil that was used in the model is shown in Fig. 1.

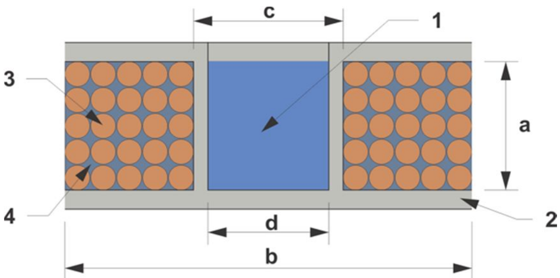

Fig. 1. The schematic of the vertical slice of the 25 windings (5 × 5) coil that is used in the model, where 1: cell medium; 2: plastic coating of the cuvette; 3: insulated copper wire; 4: epoxy insulation.

It should be noted that for comparison purposes of the coils with different structures the discharge energy of single pulse was kept constant (0.4 J, *U* = 1650 V, *C* = 0.3 μF).

Application of FEM analysis involves high demands for computational power increasing with the increase of separate finite elements. In our case each simulation had from 60 to 100 thousands of finite elements. Triangular mesh has been chosen. The edge size of each finite element varied in the range of 0.2 μm–50 μm.

During FEM analysis such parameters as inductance, active resistance, generated pulsed magnetic field, induced electric field and the change of the transmembrane cell potential was evaluated.

IV. Results

A broad range of coils with different parameters has been evaluated using FEM analysis (Table II). The typical resultant pulse characteristics dependent on the structure of the coil are summarized in Fig. 2.

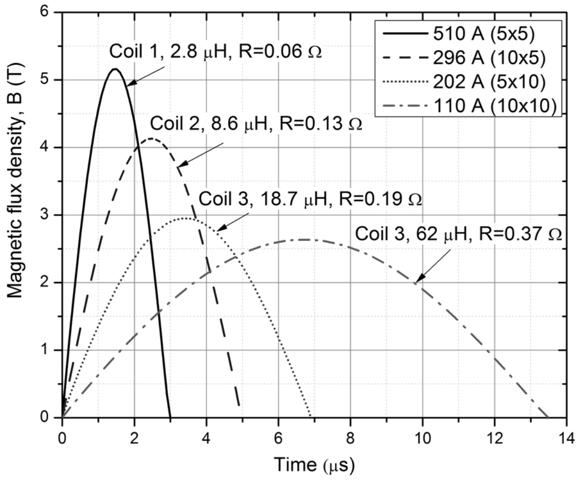

Fig. 2. FEM modelled pulse characteristics of the coils, where Coil 1 – 5 layers with 5 windings each; Coil 2 – 10 layers with 5 windings each; Coil 3 – 5 layers with 10 windings each; Coil 4 – 10 layers with 10 windings each.

With the selected single pulse energy (0.4 J) a variety of magnetic field values could be achieved ranging from 2.5 T to 5.2 T dependent on the coil structure. However, according to (1) the induced electric field is *dB/dt* dependent, therefore short pulses with small rise time are preferable (Coil 1).

Each coil model included induced electric field distribution. The induced electric field distribution of the Coil 1 during highest dB/dt is presented in Fig. 3.

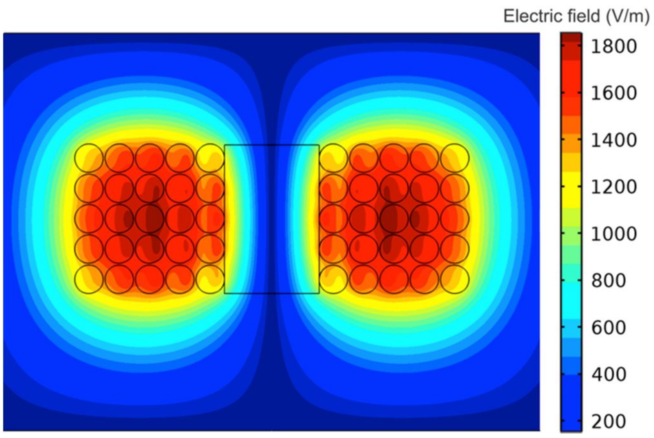

Fig. 3. Distribution of the induced electric field during highest *dB/dt* of the 5 × 5 coil.

It can be noted that the electric field inside the coil is not uniform, which implies that only a fraction of the cells in the cuvette will be subjected to the induced electric field. Also the peak of the electric field inside the cuvette is in the range of 1450 V/m at maximum distance from the coil center. The value linearly decreases up to zero towards the center of the coil. Based on the simulation the resultant transmembrane potential of the selected cells during single magnetic field pulse has been evaluated. The results for each coil are presented in Fig. 4.

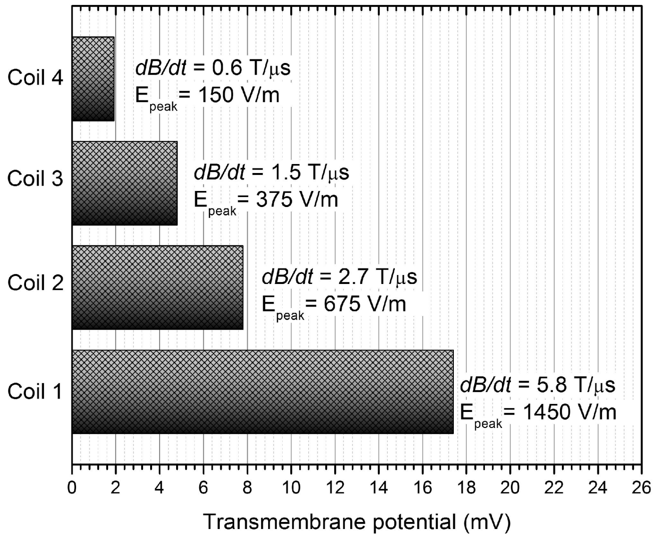

Fig. 4. Transmembrane potential during single magnetic field pulse for each coil.

As it can be seen in Fig. 4 the highest transmembrane potential due to the induced electric field was achieved when the Coil 1 is modeled. However, it is in the range of 18 mV, which is not sufficient for electroporation to happen according to the traditional theory. The other coils allowed achieving even lower induced electric field, which resulted in the transmembrane cell potential below 10 mV.

V. Discussion

Many experimental works in the past few years have been accomplished in the area of the magnetic field treatment of biological samples. Towhidi *et al.*, Shakayi *et al.*, Kardos and Rabussay, acquired experimental data showing that the pulsed magnetic and induced electric field treatment results in effects similar to electroporation [28]–[29]. The methodology described in these papers slightly varies. Even though the scientific groups use the repetitive magnetic field pulses (0.25 Hz–35 Hz), the pulse width varies from μs to ms.

In this work we have investigated the extent of each treatment component during magnetic field treatment using FEM analysis. Four different coil models have been introduced in the analysis. The inductance of the coils varied from 2.8 μH to 62 μH. The number of windings varied from 25 to 100 for each coil.

VI. Conclusions

It has been shown that the induced electric field inside the magnetic field coils is non-uniform and that the amplitude is not sufficient to cause the transmembrane potential to be in the 0.2 V–1 V region per single magnetic field pulse. It has been pointed out that it is important to have the *dB/dt* as high as possible to get high induced electric field. Nevertheless, even with 3 μs pulses (Coil 1) and the resulting magnetic field value of 5.2 T, the modeled transmembrane potential was in the range of 18 mV. Based on the results a presumption could be made that the magnetic field has an influence on the cell permeabilization process, because many contributors in the area of magnetic permeabilization apply longer and lower amplitude pulses. During application of long pulses (hundreds of μs) with rise time in the range of several microseconds and amplitude [0 T–5 T] the effects of the induced electric field could be almost neglected. Nevertheless, processes similar to electroporation still occur during the magnetic field treatment. Therefore, according to the results acquired in this work it could be concluded that the increase of the molecular uptake by the cells and the increase of the cell medium conductivity is also influenced by high-pulsed magnetic fields. The mechanism of the membrane permeability increase when subjected to pulsed magnetic field needs further research.

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