Distribution of Electrical Conductivity in Mammalian Muscle Tissue Model on Exposed to a Pulsed Electric Field

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***Abstract*—Biological cells have natural characteristic to isolate substances between outside and inside cell by using its membranes. By applying pulsed electric field, membrane pores can be formed to facilitate the introduction of small foreign materials into cells. The success of this technique can be determined by observation of conductivity changes. The equivalent conductance can be measured but the inhomogeneous electric field results inhomogeneous conductance. The aim of this research is to compute conductivity distribution on a specific biological tissue (e.g. mammalian muscle tissue) that being electrically pulsed. The tissue is modeled as conductive medium due to its conductivity dominant. The medium as a system of electro-conductive, modeling of this system leads to get a model in the form of partial different equation problems. A finite element method is used as a tool to solve the problem. The final simulation result are graphical presentations showing the conductance. It is also shown that the intensity of the field is higher in the location near electrode and smaller in remote location. Then, electrical conductivity, derived from electric field exposure is then can be computed. It is shown that needle electrodes exibit inhomogeneous conductivity distribution. A large increase of conductivity occurs surrounding both electrodes and much smaller increase on other location. A larger conductivity change means more number and size of pores are produced. In practical aspect, the result can be further developed for designing in-vivo pulsed electric field applications.**

***Keywords*: biological tissue, conductivity, electrically pulsed**

I. INTRODUCTION

The plasma membrane of biological cells provides the isolation between the intra and extracellular media and controls the transport of small matters from or into the cell. Electroporation, also called electro-permeabilization, is a phenomenon that occurs when cell membranes are exposed to high electric field pulses. Electroporation occurs when electrical energy is induced to living cells that increases the permeability of cell membranes and form the membrane pores which further an organic molecule, gene, peptide antibody, or DNA can enter the cell. Most applications of pulsed electric field (PEF) is reversible electroporation and the in vivo application (in the body) is a challenging research [1], [2]. That is because the high risk procedure, considering that the electroporation procedures which exist today only on the basis of practical experiences. In reversible electroporation, the cell membrane pores will close again after the electrical pulse collapse within a certain time. Electrical energy in the form of electrical impulses that are too large or too long can result in damage to the cells by damaging the cell membrane (irreversible electroporation). Therefore, application of PEF requires careful, systematic, measured procedures. While the acknowledgement of the impact of the PEF is necessary, in the in vivo application, it is hard to do so. Not only because of difficulty of measurement device installation but also lack of readable phenomenon due to very short and temporary impact. The problem that arises is how to determine the success of electroporation application [3].

A research by Pliquett and Schoenbach [4] suggests that electrical properties of mammalian cells are affected by PEF. The electrical conductivity of the cells increase by the intensity of electrical pulse. The conductivity changes temporarily. This impact also applies on plant tissue or cell [5].

Measurement of tissue conductivity can be done indirectly using impedance meter [6]. Small signal source e.g. sinusoidal excitation is flown to the tissue and the current and voltage can be obtained. The fraction of voltage and current in frequency basis give the complex impedance. The real part is resistance and imaginary part is reactance. The conductance is then derived from the real part i.e. the reciprocating of resistance. The conductivity is the conductance per unit distance. Measuring impedance during PEF with ordinary impedance meter (LCR) is

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difficult because the present of high current and voltage. This may impact not only the unreadable metering but also safety of the metering tool.

An impedance measurement method during pulse train by [7] suggest that measurement can be done by taking impedance signals between pulses using frequency excitation signals. Some varied frequency can also be applied. They show the frequency spectrum from 5 kHz to 1.3 MHz. The PEF is of 8 pulses, 100 µs, 1 Hz with three different electric field intensities (400, 800 and 1200 V/cm). The result give a model that convenient to circuital circuit model rather than the classical Cole model.

A measurement is important but sometimes un-applicable or unreadable, therefore it is necessary to support research on electroporation process in detail through numerical computational simulation. PEF modeling at the cellular level by FEM has been presented by Smith et al. [8] with model of biological cells as a layered model. The model shows the structure and dielectric properties of the cell and its membrane. The simulation has not emphase on the level of a biological tissue exposed to an electric field that most occurrence of electroporation application.

Most study assume that the biological tissue as homogeneous materials. Most studies reveal that the biological tissue are considered to be conductive. The object of biological tissue electroporation, especially in the case of drug delivery and DNA vaccines generally is muscle tissue. In that case the temperature and external environmental influences are ignored [9].

The relationship between the decrease of conductivity and increase of electric field intensity is linear. In the other hand, finite element method models the conductivity as a constant. So it is necessary to modify the model. Needle electrode produce non uniform electric field, so it would also affect the distribution of the field. It will further affect the conductivity changing. This research aim are firstly to show the non uniform PEF exposure on the tissue due to using needle electrodes and secondly to illustrate the distribution of conductivity in the tissue. The distribution of instanteneous conductivity during PEF can be used as a way to predict the effective location of electroporation application. The result may aid the electroporation application design and procedure.

A Fourier transform based analysis is mostly used to calculate the complex impedance. An impulse can be represented by some sinusoidal signals [10].

II. MATERIALS AND METHODS

The research material is a biological tissue conductivity model under exposed by PEF. The tissue model is a three dimensional tissue block. The pulsed electric field deliver through two needle electrodes. An electrode is assigned as positive and the other as negative potential. The pulse potential comes from a capacitor discharging pulse generator circuit. The generator consists of high voltage variable power supply, capacitor, and switch. The generator works in two stages, the first stage is the charge and the second stage is the capacitor discharges to the load through the electrodes. A digital storage oscilloscope is used to record the impulse voltage and current. Direction of the electric field perpendicularly to that the muscle fibers.

Before pulse conducts, the tissue is modeled as homoge- neous conductivity media. Simulation validated by ex vivo resistance measurements on a sample of muscle slices of lamb, which sliced thin sheets with a thickness of 2 mm with a rectangular area of 2 cm × 2 cm. The pulsed electric field delivers through two 0.45 mm diameter 1 cm distance needle electrodes. The model is shown in fig. 1.

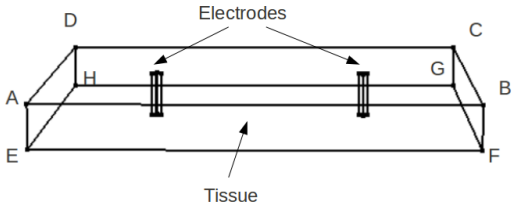

Fig. 1: Schematic of the 3D FEM model showing the tissue and electrodes, and symmetry plane defined by points ABCD

Three main electrical parameters in the interaction between an electric field and material are permittivity, conductivity and permeability, but the most important in the study of electroporation is the conductivity. The conductivity σ (S/cm) indicates the number of conduction current density caused by a number of electric field. In modeling the initial conductivity is 2.2885×10^{-4} S/cm refer to [11].

Formulation of PEF can be derived from Maxwell's electromagnetic equations with E is the electric field strength. Research conducted by Phillips et al. [12] considers that the capacitive properties of biological tissues are less dominant, so ignored. A partial differential equation solving methods is often used e.g the finite element method (FEM) [13]. Studies electroporation is generally considered that when the magnetic field is ignored, and φ is a scalar potential, then the Laplace equation becomes:

$$\nabla (\sigma \nabla \varphi) = 0 \qquad (1)$$

Which is an electrostatic partial differential equations that represent characteristics of biological tissue under electric potential. The basic principle of FEM is to divide the material into elements in large number of elements and finite. Firstly, FEM is forming mesh. At each point of the triangle coordinate is calculated the amount of voltage and

electric field strength, with a potential boundary condition on the positive electrode φ_1 is +V and negative electrodes φ_2 is -V. In this experiment, voltage is a charge voltage of 250 V maximum.

According to the Schwan equation [14] that corresponds between the electric field E with the transmembrane voltage φ_T on assuming spherical cell is $\varphi_T = -Er\cos\theta$. Where r is the cell radius and θ is the angle at any point in the cell membrane that is formed between the field lines in the middle of the cell and the field lines through these points. Because transmembrane voltage is linear the conductivity thus E linearly correlated to conductivity as from [15]:

$$\sigma = kE \tag{2}$$

For a while linear constant k is unknown but can be calculated through measured equivalent resistance R_{eq}. The next step is to measure the resistance R_{eq} between electrodes obtained by calculating the ratio of the instantaneous voltage and current of the pulse. The measurement uses tetrapolar electrode configuration as in [16]. In this case as initial consideration only instantaneous resistance during peak are used. The value of resistance after the peak impulse may not linear and its effect will be discussed later. It is due to the effects of the recovery cell membrane pores are relatively slow. The resistance R is essentially the sum of elementary series resistance along the line formed between the two electrodes, l, as:

$$R = \int_a^b \frac{\rho}{A} dl \tag{3}$$

With resistivity, ρ in Ω·cm and area, A in cm^2, a is lower bound at first electrode and b is upper bound at the second electrode. Resistivity is reciprocational of conductivity so $\rho = IkE$ and the constant k is calculated as follow [17]:

$$k = \int_a^b \frac{1}{AER} dl \tag{4}$$

Which is integral over finite interval from first electrode to second electrode. The final conductivity for each point in the medium that be approached and calculated using eq. 2 above can then be rewritten in matrix form as $\sigma = kE$. The equivalent resistance of homogeneous medium when measure across the model by thin electrode as in fig. 5.

The above model can be solved using finite element method. We choose Gmsh as geometry formation and meshing and GetDP as PDE solver. Gmsh is an open-source three- dimensional finite element grid generator with a build-in CAD engine and post-processor. Equipped with meshing tool with parametric input and visualization capabilities. It has default PDE solver GetDP [18].

III. RESULTS AND DISCUSSION

A. Initial Electric field distribution

Mesh of the model as shown in fig. 2. Potensial across the model (V) obtained which applied just after initial time to start pulse at t0+ is shown in fig. 6. Electric field (E) obtained which applied just after initial time to start pulse at t0+ is shown in fig. 7.

It can be seen from the fig. 7 that the electric field intensity distribution is not homogeneous. Section near the electrodes to get a greater impact, especially in a straight deal with the other electrode. When the straight line drawn from one electrode to electrode 2 then along these lines have such electric field profile on fig. 8.

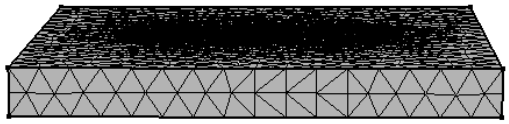

Fig. 2: Schematic of the 3D FEM model a representative mesh case

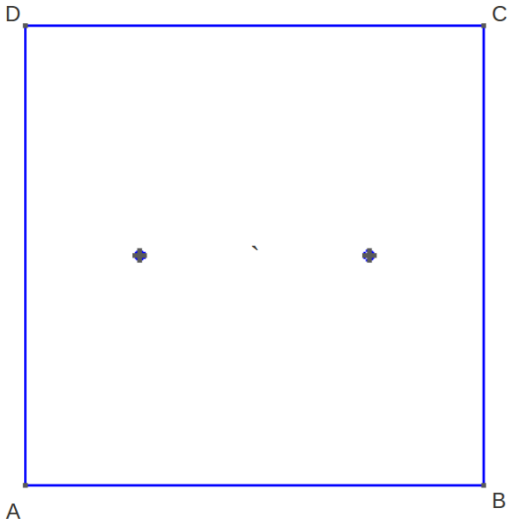

Fig. 3: Schematic of the FEM model showing the tissue and electrodes from top view of tissue regions

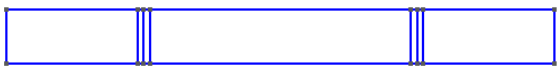

Fig. 4: Schematic of the FEM model showing the tissue and two electrodes cross-section view along the center line of the tissue

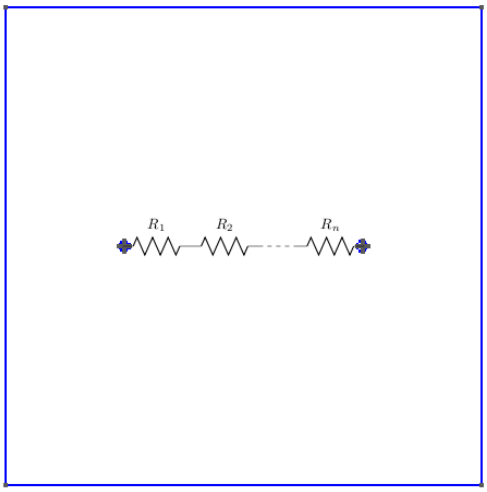

Fig. 5: Equivalent resistance in the biological tissue is series resistance from point of contour

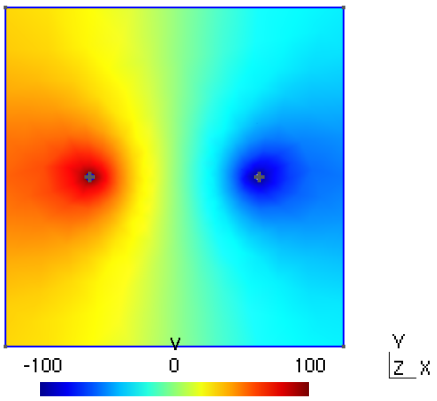

Fig. 6: Top view of the distribution of potential (V) in Volt (color and contour) in the biological tissue. Left circle is a positive impulse voltage source of 250 V and left cicle is 0 volt. Horisontal and vertical axis is two dimension in cm unit.

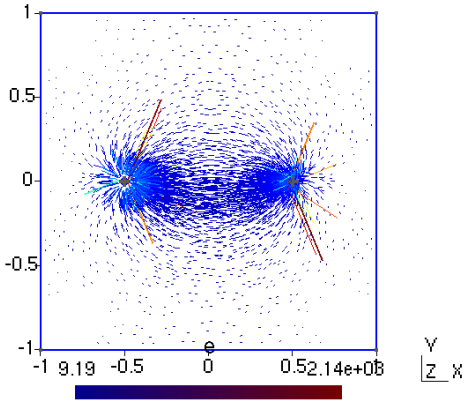

Fig. 7: Top view of the distribution of the electric field (E) in V/cm (color and contour) in the biological tissue. Left circle is a positive impulse voltage source of 250 V and left cicle is 0 volt. Horisontal and vertical axis is two dimension in cm unit.

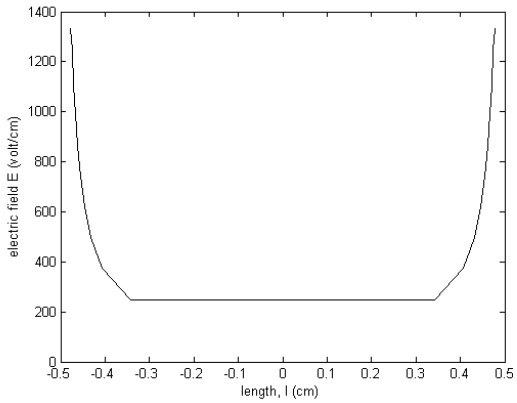

Fig. 8: Electric field profile along the reference line.

B. Conductivity distribution

The results of experiment by using impulse voltage and current signals will give minimum equivalent resistance, R_{eq} , when both variables at its peak. at peak voltage of 250 V and current of 0.3041 A give equivalent resistance R_{eq} of 822 Ω. By using measured R_{eq} and numerical integration of (4), k can be calculated. In this study we get $k = 4.8662 \times 10^{-6}$ and σ distribution when voltage is 250 volts in the media as shown in fig. 9.

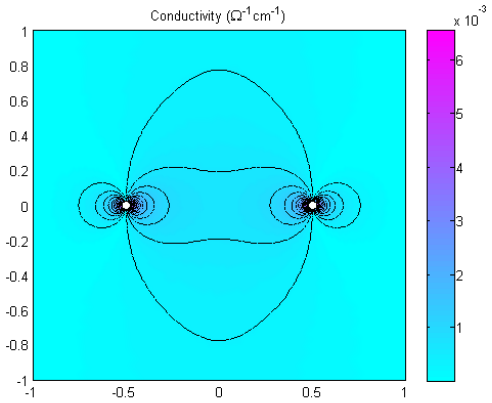

Fig. 9: Conductivity distribution in biological tissue (color) and (contour).

Application of the FEM for calculation of electrical conductivity in the tissue is given in Fig. 9. The graphics can be explained as follows: two electrode needles, injected by impulse voltage difference in of 250 V give changes of conductivity. The distributions shows the conductivity in color and contour lines. Contour lines stated location points where the same conductivity. Gradient color is also used to indicate the magnitude of conductivity around the surface of the media. Colors tend to be red indicates

high conductivity while blue indicates low conductivity.

It appears that the greatest conductivity occurs in the biological tissue which has the closest distance to electrodes. There is significant drop of the average resistance of 3547.8 Ω become 822 Ω,from originally be 4369.75 Ω during the peak of the impulse or drop 81%. This is equivalent to an average equivalent conductance of 2.2885×10^{-4} S up to 1.216×10^{-3} S. The conductivity value spread between 2.2885×10^{-4} to 6.5876×10^{-3} S/cm. This is because most cells between the electrodes are experiencing electroporation for the formation of pores that increase conductivity.

Distribution of σ is linear to the distribution of E. The results of the σ distribution may indicate a region where the biological tissue most affected and which parts are less affected. It can be assumed that the greater the conductivity the larger the pores. Furthermore selective placement drug can be applied to areas of high conductivity regions that pores open larger. The dose of medication can also be optimized as needed. In connection with previous research has shown the recent study predicted unhomogenous conduc- tivity distribution when the impulse occurs which previously considered that the conductivity change uniformly.

IV. CONCLUSION

Simulating exposure of pulsed electric field into biological tissue can produce a description of the tissue conductivity. Based on the physical properties of cells in tissues exposed to an electric field and measurement of equivalent resistance, the conductivity at any point on the medium can be calculated and mapped. A muscle tissue with volume of 0.8 cm^2 ($2 \times 2 \times 0.2$ cm), when exposed to the pulse voltage of 250 V peak through two needle electrodes of 0.45 mm diameter and 1 cm distance, result a changing conductivity. Average conductivity increase to 81% with the lowest value of 2.2885×10^{-4} S/cm at locations away from both electrodes and up to 6.5876^{-3} S/cm around the electrodes. A significant change occurred at locations around the electrodes with an increase up to 29 fold. From the result it can be assumed at any locations that the more conductivity increases the more electroporation intenses.

It is also shown that the intensity of the field is higher in the location near electrode and smaller in remote location. Then, electrical conductivity, derived from electric field exposure is then can be computed. It is shown that needle electrodes exibit inhomogeneous conductivity distribution. A large increase of conductivity occurs surrounding both electrodes and much smaller increase on other location. A larger conductivity change means more number and size of pores are produced. In practical aspect, the result can be further developed for designing in-vivo pulsed electric field applications. In the case using two needle electrode the effective electroporation locations are around the electrodes. Therefore it would be more effective if the agent, gen, drug or subtances is injected around both electrodes, especially the side that face each other.

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