ORIGINAL ARTICLE

Finite Element Analysis of Cell Killing Probability in Electroporation with Single Bipolar Electrode

Amir Khorasani *

Department of Medical Physics, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

*Corresponding Author: Amir Khorasani
Email: amir69k@yahoo.com

Received: 04 November 2020 / Accepted: 10 December 2020

Abstract

Purpose: In the electroporation we can use different electrode types such as needle and plate electrode with different arrangements. One of the new electrode types is single bipolar electrode that the anode and cathode components are in the same needle for decreasing the invasiveness of electroporation procedure.

Materials and Methods: For treatment planning purposes we can use different cell killing probability models such as Peleg-Fermi model. The aim of this study is to investigate the impact of geometric electrode parameters such as conductive pole length, insulated pole length and pulse voltage in bipolar electrode on the cell killing probability distribution in electroporation by COMSOL Multiphysics.

Results: The target tissue volume with cell killing probability of >80% was increased with conductive pole length, and voltage and decreased with insulated pole length.

Conclusion: This paper has highlighted the importance of conductive and insulated pole length and voltage in bipolar electrode on the cell killing probability distribution and electroporated volume in the EP.

Keywords: Bipolar Electrode; Cell Killing Probability; Finite Element Analysis; Irreversible Electroporation.

DOI: https://doi.org/10.18502/fbt.v8i1.5854

1. Introduction

Electroporation (EP) is a new technique of increasing the cell membrane permeability by application of minuscules and high-intensity pulsed electric field [1]. Pore formation on the cell membrane is the main cause of cell membrane permeability increase [2]. A useful feature of pore creation on cell membrane is permitting the entry of substance like the anticancer agent, and macromolecules (such as DNA and proteins) that otherwise could not enter the cytoplasm [3, 4]. The combination of pore creation and chemotherapy drugs is Electrochemotherapy (ECT) which is used for cancer treatment [3, 4]. In the ECT, EP introduces chemotherapy drugs into the tumor cells and drugs action kills the tumor cells (Figure 1).

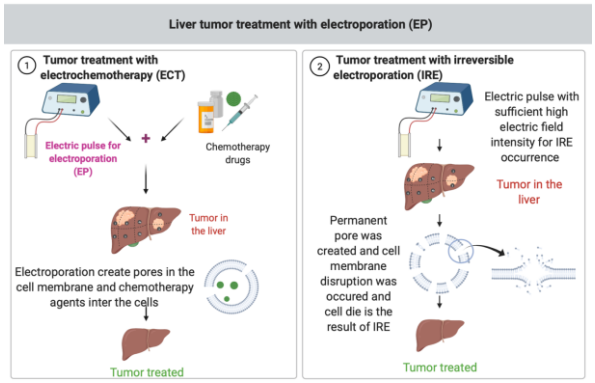

Figure 1. liver tumor treatment with electroporation. 1) electrochemotherapy 2) irreversible electroporation

If the electric field intensity increased to above the reversible EP threshold, Irreversible Electroporation (IRE) is occurred [5]. IRE is a non-thermal and minimal invasive ablation technique for cell killing and tumor treatment [6] (Figure 1).

In EP different electrode types were used, such as plate and needle electrodes with different arrangement [7, 8] (Figure 2). Electrode types and arrangement set to become a vital factor in EP process because they determine the shape of electric field distribution in the tissue [8]. Previous work has been limited to study EP with conventional needle and plate electrode for calculating the cell killing probability inside the target tissue for treatment planning proposes [9, 10]. The use of these conventional needle and plate electrodes in EP requires exact placement of needles, invasive procedure, time consuming for treatment planning [7, 8]. Recent developments in EP have led to introduce a single bipolar electrode [11–13]. The anode and cathode components

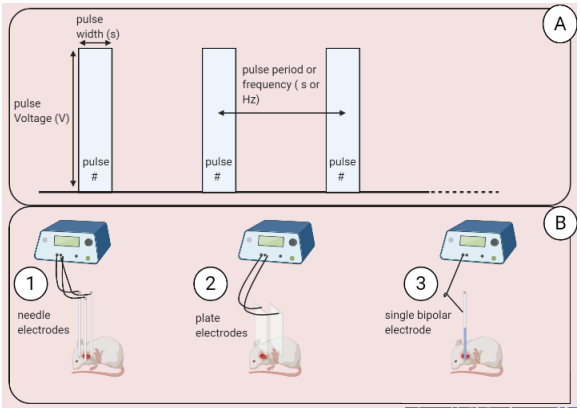

Figure 2. A) Electric pulse and their parameters B) different electrode 1- needle electrode 2-plate electrode 3-bipolar electrode

in bipolar electrode are held in the same needle. Through the use of bipolar electrode in EP, we were able to save treatment planning time, minimize EP invasiveness, simplify the electrode placement procedure and reduce the number of needles required to be inserted.

The aim of this study is to determine the impact of geometric parameters in bipolar electrode, and pulse voltage on the cell killing probability distribution during EP. This paper is divided into the two sections. The first section gives a brief overview of electrode design and electrode parameters. The second section analyzed the finite element model by COMSOL Multiphysics software.

2. Materials and Methods

2.1. Electrode Design and Parameters

To design a stainless-steel bipolar electrode, positive (P1) and negative (P2) poles which are separated by an insulting (S) part on the same needle was intended (Figure 3). Electrode properties of these parts are listed in Table 1. To determine the impact of

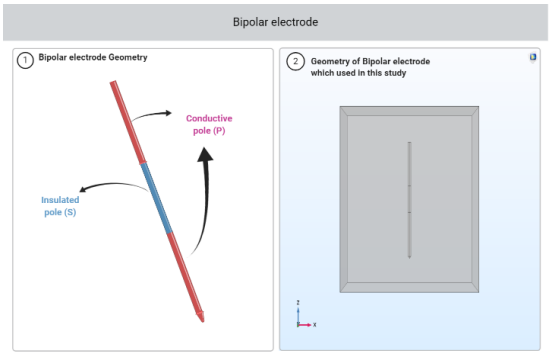

Figure 3. Bipolar electrode

Table 1. Electrode properties [13]

Properties	Conductive Pole	Insulated Pole
Density[kg/m^3]	7850	1300
Thermal Conductivity[W/mK]	44.5	0.15
Specific heat [J/kgK]	475	1100
Electric Conductivity[S/m]	4.032×10^{6}	10^{-10}
Thermal Coefficient[K^{-1}]	12.3×10^{-6}	-
Relative Permittivity	1	4

electrode geometry properties (conductive pole lengths and insulated pole length) and voltage on cell killing probability distribution, in this study different P and S and Voltage (V) were used (Table 2). The electric pulses are designed as 8 pulses with 1 Hz frequency and 100 µs pulse width and different V (Figure 2A). A rectangular with 30*30*50 mm was used as a tumoral tissue. In this study, triangular meshing model which contained 68,957 mesh nodes were used.

2.2. Finite Element Analysis

The data and finite element model of this paper were obtained using COMSOL Multiphysics 5.4 software. To calculate the cell killing probability distribution in each geometrical configuration, Peleg-Fermi model was used. The Peleg-Fermi model was based on experimental data [14–16]. This model was chosen because it is one of the most practical ways of the calculation of cell killing probability during EP.

The Peleg-Fermi model (Equation 1-3) is a mathematical model to calculate the cell killing probability due to IRE and given by:

$$S(E,N)=\frac{N}{N_0}=\frac{1}{1+e^{\left(\frac{E-E_c(N)}{A(N)}\right)}} \quad (1)$$

$$E_c(N)=E_0e^{-k_1n} \quad (2)$$

$$A(N)=A_0e^{k_2n} \quad (3)$$

$$P_{kill}=100(1-S) \quad (4)$$

Where S is the surviving fraction of cells, N is the number of surviving cells, N_0 is the number first cells before the treatment, E is the electric field, $E_c(N)$ is

Table 2. Variable which used in this study

Test Session	Changed Variable	Conductive Pole Length P (mm)	Insulated Pole Length S (mm)	Voltage (V)
1	Voltage	5	3	500
		5	3	600
		5	3	700
		5	3	800
		5	3	900
		5	3	1000
		5	3	1100
		5	3	1200
		5	3	1300
		5	3	1400
		5	3	1500
2	Conductive Pole Length	5	5	1000
		10	5	1000
		15	5	1000
3	Insulated Pole Length	10	2	1000
		10	3	1000
		10	4	1000
		10	5	1000
		10	6	1000
		10	7	1000
		10	8	1000
		10	9	1000
		10	10	1000

the electric field intensity for killing 50% of the cells, n is the number of pulses and A(N) is a function of the pulse number, P_{kill} is a percentage cell kill.

Other constants in these equations are, $E_0 = 399{,}600\ V/m$, $A_0 = 144{,}100\ V/m$, $k_1 = 0.03$, and $k_2 = 0.06$ [14].

In this paper based on the previous recommendation for calculation of accurate electric field distribution [17], Equation 5 has been used for calculating the electric conductivity during EP.

$$\sigma = \sigma_0 * \Big(1 + flc2hs\big(E - E_{delta}, E_{range}\big) + \alpha * (T - T_0)\Big) \quad (5)$$

See our previous articles for more information and details about Equation 5 and their parameters and usage [18, 19].

3. Results

3.1. Impact of Voltage

The first set of analyses investigated the impact of pulse voltage on cell killing distribution in the target tissue, while the conductive and insulated pole length were not changed. As the voltage increased, the tissue volume which have cell killing probability of >80% was also increased. Increasing the voltage from 500 to 1500 V increased 381.9 % of tissue volume with cell killing probability of >80% (Figure 4).

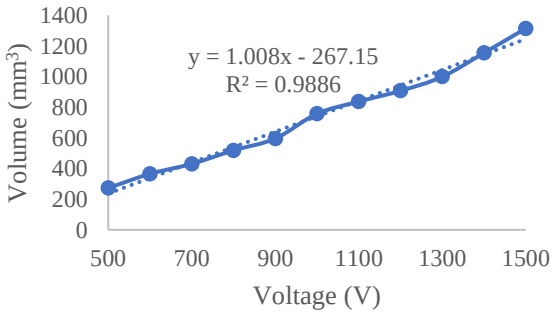

Figure 4. Effect of pulse voltage on tissue volume with cell killing probability >80%

3.2. Impact of Conductive Pole Length

The second test session analyzed how the change in the conductive pole length influences the cell killing distribution around the electrode, while other parameters such as pulse voltage and insulated pole length were not changed. According to Figure 5, there was a positive correlation between conductive pole length and tissue volume with cell killing probability of >80%.

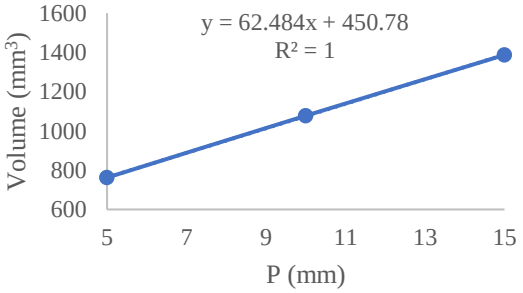

Figure 5. Effect of conductive pole length on tissue volume with cell killing probability >80%

3.3. Impact of Insulated Pole Length

The last test session examined the effect of insulated pole length on the cell killing distribution in the single bipolar electrode while voltage and the length of the conductive poles were remained unchanged. As the insulated pole length increased from 2 to 10 mm, the decrease of 44.62% in the tissue volume with cell killing probability of >80% was detected (Figure 6).

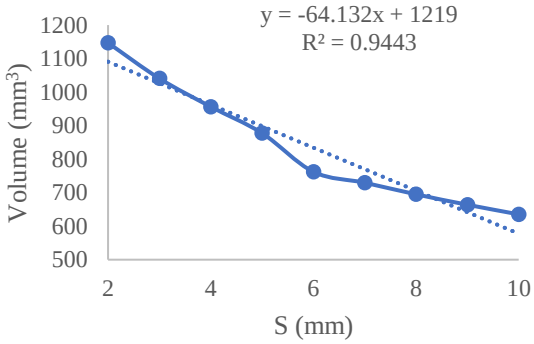

Figure 6. Effect of insulated pole length on tissue volume with cell killing probability >80%

In Figure 7, we can see the impact of voltage, conductive pole length (P), and insulated pole length (S) for bipolar electrode on the cell killing probability distribution around the electrode graphically.

4. Discussion

IRE and EP are a new cancer treatment and macromolecule delivery system. In this method, plate and needle electrodes were used for electric pulse

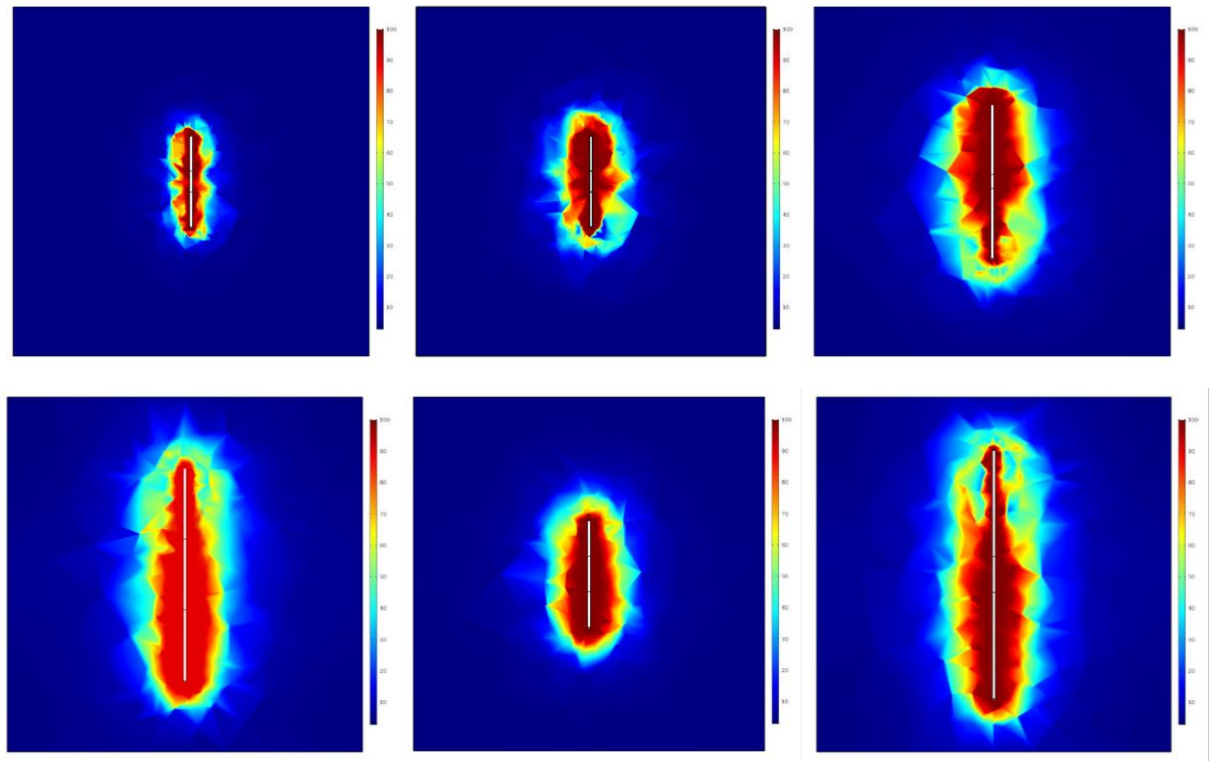

Figure 7. Impact of voltage, conductive pole length (P), and insulated pole length (S) on cell killing probability distribution inside the tissue. a- (P=5 mm, S=3 mm, V=700 V) b- (P=5 mm, S=3 mm, V=1500 V) c- (P=10 mm, S=2 mm, V=1000 V) d- (P=10 mm, S=10 mm, V=1000 V) e-(P=5 mm, S=5 mm, V=1000 V) f- (P=15 mm, S=5 mm, V=1000 V)

delivery to the target tissue. To reduce the invasiveness and the number of electrode insertion in EP, a single-insertion bipolar electrode has been introduced. In the bipolar electrode, the conductive poles (anode and cathode) are holed on a single needle electrode.

The simulation results revealed that with increasing the pulse voltage, the tissue volume with cell killing probability of >80% also increased due to increase in the electric field intensity in the target tissue. This is in good agreement with Merola *et al.* [13] who used a single bipolar electrode and concluded that the ablation volume in electroporation process with single bipolar electrode is mainly influenced by pulse voltage. In [11] the authors investigated the effect of injection of hypertonic fluid during the electroporation with single bipolar electrode on the ablation volume. They concluded that, the ablation volume increased with pulse voltage, pulse width, and frequency. It is important to note that, the cell killing probability is linked with electric field intensity. These values correlated fairly well with [11,13].

The tissue volume with cell killing probability of >80% increased with conductive pole length because of increasing the electrode surface contact with target tissue. As indicated by [13], electroporated volume, which indicated by electric field threshold method, increased with conductive pole length. The inverse relationship between insulated pole length and tissue volume with cell killing probability of >80%, which obtained in this study, are in line with previous results [13].

This paper has investigated the use of cell killing probability model (Peleg-Fermi) with single bipolar electrode. This paper has highlighted the importance of geometric parameters (S and P) and voltage in bipolar electrode on the cell killing probability distribution in the EP. For tumor with different size and shapes, we can use different single bipolar electrode geometries setup (P,S) and voltage for sufficient cell killing probability coverages of tumor for successful treatment.

References

1- B. Rubinsky, “Irreversible electroporation in medicine,” *Technol. Cancer Res. Treat.*, vol. 6, no. 4, pp. 255–259, 2007.

2- L. F. Cima and L. M. Mir, “Macroscopic characterization of cell electroporation in biological tissue based on

electrical measurements," *Appl. Phys. Lett.*, vol. 85, no. 19, pp. 4520–4522, 2004.

3- C. Y. Calvet and L. M. Mir, "The promising alliance of anti-cancer electrochemotherapy with immunotherapy," *Cancer Metastasis Rev.*, vol. 35, no. 2, pp. 165–177, 2016.

4- D. O. H. Suzuki, C. M. G. Marques, and M. M. M. Rangel, "Conductive gel increases the small tumor treatment with electrochemotherapy using needle electrodes," Artif. Organs, vol. 40, no. 7, pp. 705–711, 2016.

5- B. Rubinsky, G. Onik, and P. Mikus, "Irreversible electroporation: a new ablation modality—clinical implications," *Technol. Cancer Res. Treat.*, vol. 6, no. 1, pp. 37–48, 2007.

6- H. J. Scheffer *et al.*, "Irreversible electroporation for nonthermal tumor ablation in the clinical setting: a systematic review of safety and efficacy," *J. Vasc. Interv. Radiol.*, vol. 25, no. 7, pp. 997–1011, 2014.

7- O. Adeyanju, H. Al-Angari, and A. Sahakian, "The optimization of needle electrode number and placement for irreversible electroporation of hepatocellular carcinoma," *Radiol. Oncol.,* vol. 46, no. 2, pp. 126–135, 2012.

8- S. Čorović, M. Pavlin, and D. Miklavčič, "Analytical and numerical quantification and comparison of the local electric field in the tissue for different electrode configurations," *Biomed. Eng*. Online, vol. 6, no. 1, p. 37, 2007.

9- A. Khorasani, "A numerical study on the effect of conductivity change in cell kill distribution in irreversible electroporation," *Polish J. Med. Phys. Eng.*, vol. 26, no. 2, pp. 69–76, 2020.

10- P. A. Garcia, B. Kos, J. H. Rossmeisl Jr, D. Pavliha, D. Miklavčič, and R. V Davalos, "Predictive therapeutic planning for irreversible electroporation treatment of spontaneous malignant glioma," *Med. Phys.*, vol. 44, no. 9, pp. 4968–4980, 2017.

11- A. Wandel *et al.*, "Optimizing irreversible electroporation ablation with a bipolar electrode," *J. Vasc. Interv. Radiol.*, vol. 27, no. 9, pp. 1441–1450, 2016.

12- F. Pedersoli *et al.*, "Single-needle electroporation and interstitial electrochemotherapy: in vivo safety and efficacy evaluation of a new system," *Eur. Radiol.*, vol. 29, no. 11, pp. 6300–6308, 2019.

13- G. Merola, "Design and characterization of a minimally invasive bipolar electrode for electroporation," *Politecnico di Torino*, 2020.

14- A. Golberg and B. Rubinsky, "A statistical model for multidimensional irreversible electroporation cell death in tissue," *Biomed. Eng*. Online, vol. 9, no. 1, p. 13, 2010.

15- J. Dermol and D. Miklavčič, "Predicting electroporation of cells in an inhomogeneous electric field based on mathematical modeling and experimental CHO-cell permeabilization to propidium iodide determination," *Bioelectrochemistry*, vol. 100, pp. 52–61, 2014.

16- P. A. Garcia, R. V Davalos, and D. Miklavcic, "A numerical investigation of the electric and thermal cell kill distributions in electroporation-based therapies in tissue," *PLoS One*, vol. 9, no. 8, p. e103083, 2014.

17- A. Khorasani, S. M. Firoozabadi, and Z. Shankayi, "Conductivity Changes of Liver Tissue during Irreversible Electroporation and Calculation of the Electric Field Distribution," *Modares J. Biotechnol.*, vol. 9, no. 2, pp. 227–232, 2018.

18- A. Khorasani, S. M. Firoozabadi, and Z. Shankayi, "Conductivity change with needle electrode during high frequency irreversible electroporation: a finite element study," *Polish J. Med. Phys. Eng.*, vol. 25, no. 4, pp. 237–242, 2019.

19- S. M. Firoozabadi, "Finite Element Analysis of Tissue Conductivity during High-frequency and Low-voltage Irreversible Electroporation," *Iran. J. Med. Phys.*, vol. 14, no. 3, pp. 135–140, 2017.