ORIGINAL ARTICLE

The Effect of Conductivity Changes on Temperature Rise during Irreversible Electroporation

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Abstract

Purpose: Irreversible electroporation is a physical process which is used for killing the cancer cells. The process that leads to cell death in this method is a unique process. Thermal damage does not exist in this process. However, the temperature of the tissue also increases during the electroporation. In this study, we aim to investigate the effect of conductivity changes on tissue temperature increase during the irreversible electroporation process.

Materials and Methods: To perform simulations and solve equations, COMSOL MultiPhysics has been used. Standard electroporation pulse sequence (8 pulses with different electric field intensities) was used as a pulse sequence in the simulation.

Results: During the electroporation process, the electrical conductivity and the temperature of the tissue were increased. Changes in the tissue temperature in the simulation with variable electrical conductivity are more than in the simulation with constant electrical conductivity during the electroporation process. This difference for pulses with more vigorous electric field intensity and points closer to the electrodes has been achieved more.

Conclusion: To more accurately estimate and calculate the temperature and thermal damage inside the tissue during the irreversible electroporation process, it is suggested to consider the effect of conductivity changes during this process.

Keywords: Temperature; Irreversible Electroporation; Finite Element; Electrical Conductivity.

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Frontiers in BIOMEDICAL TECHNOLOGIES

1. Introduction

In the electroporation process, we used electric pulses. During this process, pores are made in the cell membrane due to the presence of a strong electric field. Depending on the intensity of the electric field in the cell membrane, these pores will be either temporary or permanent. Temporary pores on the cell membrane can be closed after the sending of electrical pulses. The result of this process will be reversible electroporation. However, in irreversible electroporation, these pores form permanently on the cell membrane, destroying cell stability, and eventually leading to cell death [1]. Therefore, irreversible electroporation can be used to kill malignant cells as a new treatment modality for tumor treatment.

Reversible electroporation can be used to transfer macromolecules and genes into the cell. Chemotherapy drugs with reversible electroporation can be used, which is called electrochemotherapy. In comparison, irreversible electroporation can be used for killing the undesirable cells and tumor treatment as a new ablation technique without Joule heating [2].

Irreversible electroporation is a process with threshold, and the intensity of the electric field threshold at the desired point must be at least 580 V/cm [3]. Therefore, the intensity of the electric field and distribution within the target tissue will be critical. Many factors affect the distribution of electric field intensity and magnitude, such as pulse voltage, pulse shape, type of electrodes, geometric arrangement and spatial properties of electrodes, type of target tissue, conductivity of target tissue, etc. [4–6]. Therefore, setting these parameters will be very important for successful electroporation treatment. Numerical and finite element simulations must be used to obtain the shape of the electric field distribution and its magnitude within the target tissue.

Previous studies have shown that during electroporation, due to the electric current inside the tissues, heat is generated, and the temperature of the tissue will be increased [7–9]. A number of these studies have calculated this temperature raise using finite element simulations [7, 8]. Studies have shown that rising tissue temperatures can lead to undesirable thermal damage to the tissue [10]. Therefore, measuring and calculation of temperature during electroporation will be a necessary quantity.

Changes in tissue temperature during electroporation are affected by several parameters such as the intensity of the electric field at the desired point, the type of electrodes and their geometric arrangement, the distance of the tissue and the desired position from the electrode, frequency and width of the pulse used, etc. In previous studies, constant electrical conductivity was used for the target tissue to measure temperature changes during electroporation [7]. However, studies have shown that during electroporation, the electrical conductivity of the target tissue changes, and electroporation will increase the conductivity of the tissue [11–17]. This increase in electrical conductivity for irreversible electroporation will be higher than the rise in irreversible electroporation [16]. In our previous studies, the effect of conductivity change in the electroporation process on the electric field distribution and the cell kill probability have been investigated [12, 18]. The aim of this study was to examine the effect of conductivity changes during irreversible electroporation on temperature changes in the target tissue. For this purpose, in this study, numerical and finite element methods have been used.

2. Materials and Methods

2.1. Model Geometry and Characteristics of Electric Pulses

In this study, needle electrodes, which are commonly used in clinics, were used. Liver tissue has been simulated as target tissue in this study. The electrodes are also made of surgical stainless steel. The physical properties of these materials are taken from the previous study [19, 20] and are given in Table 1. The dimensions and geometry of the electrodes can be seen in Figure 1.

In this study, eight electrical pulses with a frequency of 1 Hz and different electric field intensities and time periods of 100 microseconds were used. The pulses parameters are given in Table 2.

Several candidate points have been selected to investigate temperature and conductivity changes within the tissue. These points include the tip point of the electrodes, the point between the electrodes (point 1), the point between the electrodes (point 2), and the point at the edge of the electrode (point 3) that can be seen in Figure 1. Two simulation groups have been used to investigate the effect of conductivity changes on temperature rise in the electroporation process. The first group consists of simulations in which the tissue conductivity in the electroporation process changes. In the other group, the tissue conductivity is considered constant during electroporation, and the results obtained from these two groups are compared with each other.

Table 1. Basic parameters used in simulation

Variable	Variable value	Reference
σ_0	0.067 [S/m]	[19], [20]
E_{delta}	580 [V/cm]	[19], [20]
E_{range}	(-120, +120) [V/cm]	[19], [20]
α	0.015 $°C^{-1}$	[19], [20]
T_0	37 [°C]	[19], [20]

Table 2. Characteristics of electrical pulses used in this study

Electric Field Intensity (V/cm)	Duration (µs)	Frequency (Hz)	Number of Pulses
1000	100	1	8
1500	100	1	8
2000	100	1	8
2500	100	1	8
3000	100	1	8

We used COMSOL 5 software as a finite element simulation to solve the equations during this process. The simulated model is shown in Figures 1 and 2. The model contains 56, 242 mesh nodes, which can be seen in Figure 2.

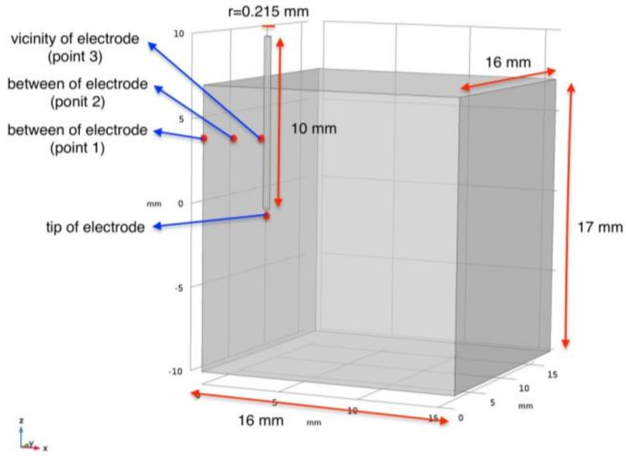

Figure 1. Geometry and candidate points used in this study

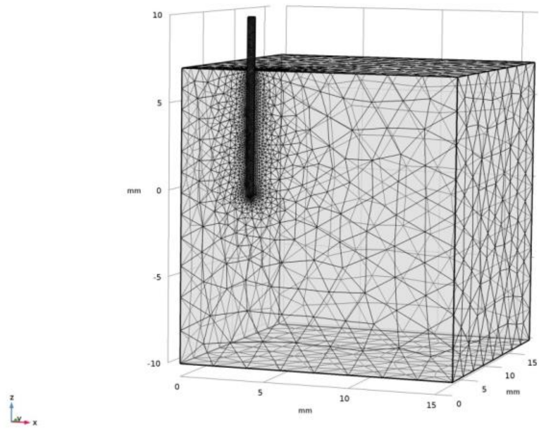

Figure 2. Geometry with the mesh

By solving the Laplace equation (Equation 1), the distribution of the electric field inside the tissue is calculated:

$$\vec{\nabla}.(\sigma.\vec{\nabla}\varphi) = 0 \quad (1)$$

In this equation, σ is the tissue conductivity, and φ is the electrical potential at any point in the tissue.

Boundary conditions are also considered, where the surfaces of one of the electrodes are considered in potential φ = V (t), and the surface of the other electrode is equal to φ = 0. V (t) is equal to the electrical pulse as a function of time. Other surfaces that are not in contact with the electrode are assumed to be electrically insulated.

Temperature changes during the electroporation process are obtained from the Bio-Penes equation, which is defined as follows:

$$\nabla.(k\nabla T) + \sigma|\nabla\varphi|^2 + q''' - W_b c_b T = \rho c_p \frac{\partial T}{\partial t} \quad (2)$$

In Equation 2, φ is the electric potential, T is the temperature, σ is the conductivity, q''' is the heat generated by the metabolism and $W_b c_b T$ is the heat generated by the bloodstream, ρ is the density, and c_p is the specific heat of the tissue. In this study, the ambient temperature is considered as 25 ° C.

Equation 3 is used to calculate conductivity changes during the electroporation process:

$$\sigma = \sigma_0 * (1 + flc2hs(E - E_{delta}, E_{range}) + \alpha * (T - T_0)) \quad (3)$$

In this equation, σ_0 is the initial conductivity of liver tissue (baseline), E is the intensity of the electric field at the desired point, E_{delta} is the value of the electroporation threshold, E_{range} is the interval of electric field intensity, α is a constant, T is temperature and T_0 is the initial temperature. Flc2hs is a predefined function in COMSOL and values and weighs between one and zero at any point in terms of the parameters E_{range}, E_{delta}, and E. The values of the parameters used in this research are shown in Table 1 [21].

3. Results

3.1. Conductivity Change

Tissue conductivity increases during pulse transmission in the electroporation process. This conductivity increase depends on the intensity of the electric field, and increased with electric field intensity of the pulses (Table 3). For example, the figure of conductivity changes per unit time for eight pulses with an electric field strength of 2500 V/cm and a frequency of 1 Hz and a pulse duration of 100 µs at the tip point of the electrodes and between the electrodes is shown in Figure 3. The electrical conductivity of the liver tissue at the time of the last pulse (8th pulse) for pulses with different electric field intensities is given in Table 3.

3.2. Temperature Changes

In order to study the temperature changes during the transmission of electric pulse, four candidate points that can be seen in Figure 1 have been used.

Table 3. Conductivity changes at the end of the pulses at the tip of the electrode and the point between the electrodes for electrical pulses of different intensities

Electric Field Intensity (V/cm)	1000	1500	3000
Conductivity at the tip of the Electrode(S/m)	0.144	0.175	0.242
Conductivity at between of Electrode Point1(S/m)	0.135	0.135	0.135

Figures 4 and 5 show temperature changes over time for these candidate points and eight pulses with an electric field strength of 2000 V/cm and a frequency of 1 Hz and a pulse duration of 100 µs. Figures 6 and 7 show the temperature changes over time for eight pulses with an electric field strength of 3000 V/cm and a frequency of 1 Hz and a pulse duration of 100 µs, and the tip point of the electrodes and the point between the electrodes (point 1) in two conditions, constant and variable conductivity during the electroporation. As can be seen, the temperature changes during the electroporation process under variable conductivity conditions are higher than the constant conductivity conditions. Numerical values of temperature at different points and at the time of sending the last electrical pulse for different electrical pulses are given in Table 4.

4. Discussion

The purpose of irreversible electroporation is to destroy undesirable cells. The killing cells in electroporation is a unique process in which there is no heat killing process due to the increase in temperature and Joule heating. However, it has been shown that the tissue temperature raised during the electroporation process [7].

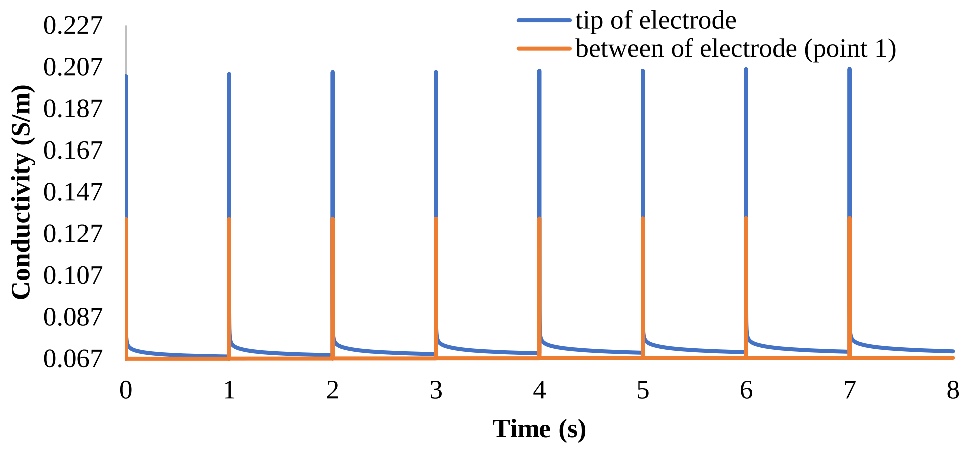

Figure 3. Conductivity changes per unit time for the electrode tip points and the point between the electrodes (point 1) for a pulse of 2500 V/cm

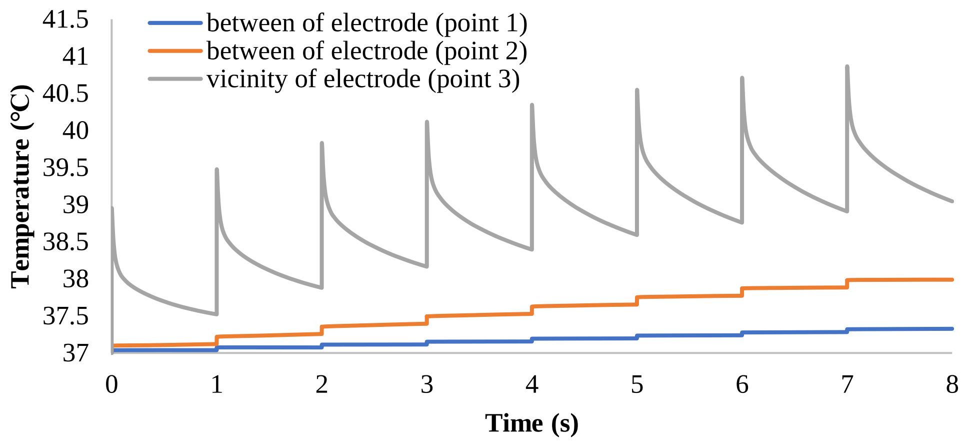

Figure 4. Temperature changes for candidate points (between electrodes, electrode margin, and the point between electrodes 2) per unit time for a pulse of 2000 V/cm with variable conductivity

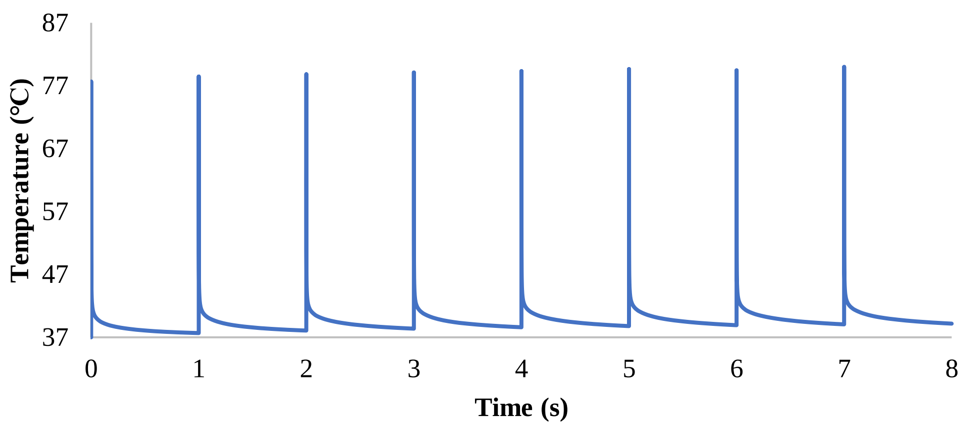

Figure 5. Temperature variations for electrode tip points per unit time for 2000 V/cm pulses using variable conductivity

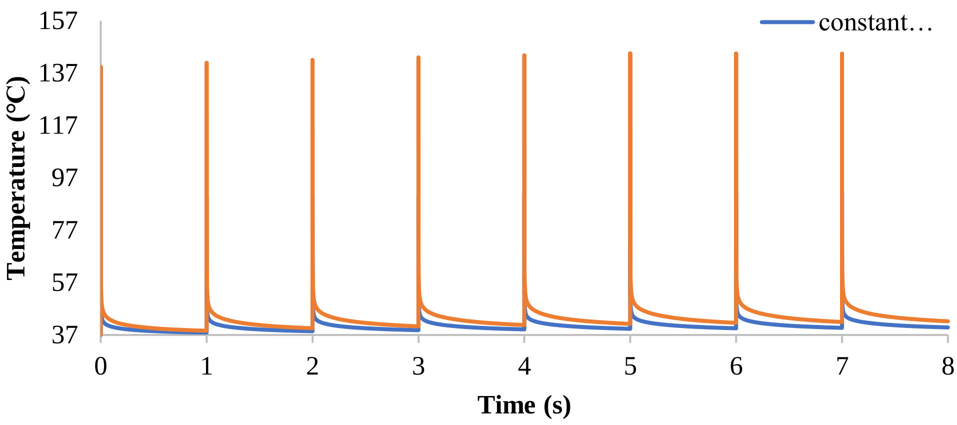

Figure 6. Temperature variations for electrode tip points per unit time for a pulse of 3000 V/cm using variable conductivity and constant conductivity

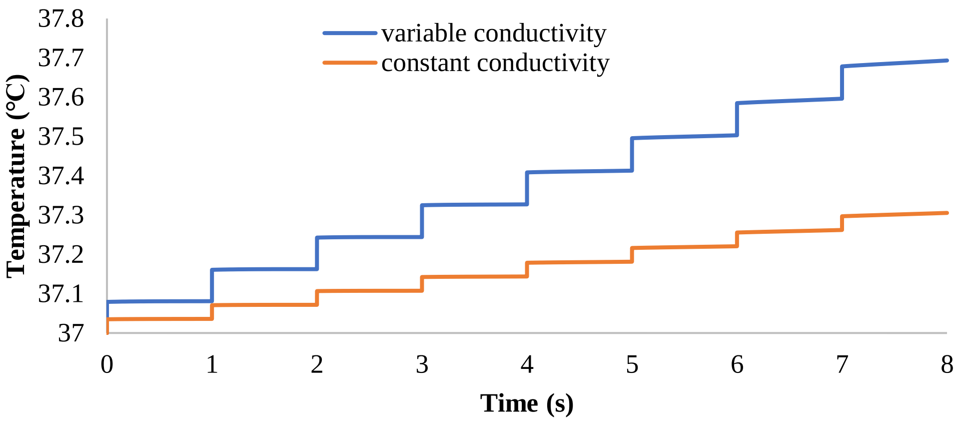

Figure 7. Temperature changes for points between electrodes (point 1) per unit time for a pulse of 3000 V/cm using variable conductivity and constant conductivity

Table 4. Temperature at the end of the 8th pulse at candidate points for electrical pulses of different intensities

Variable Conductivity				Constant Conductivity				Electric Field Intensity (V/cm)
Vicinity of the Electrode (point 3)	Between of Electrode (point 2)	Between of Electrode (point 1)	Tip of electrode	Vicinity of the Electrode (point 3)	Between of Electrode (point 2)	Between of Electrode (point 1)	Tip of Electrode	
37.82	37.23	37.13	46.12	37.54	37.12	37.03	43.03	1000
39.07	37.54	37.19	59.33	38.22	37.28	37.07	50.58	1500
40.82	38	37.32	79.97	39.20	37.51	37.13	61.16	2000
43.23	38.55	37.48	108.21	40.44	37.81	37.20	74.92	2500
46.07	39.25	37.68	144.34	41.96	38.16	37.29	91.35	3000

In order to accurately estimate the increase in temperature in the electroporation, some factors must be considered. One of these factors is the electrical conductivity of the tissue. In previous studies, tissue electrical conductivity was considered constant in order to measure temperature during electroporation simulations [7]. However, previous studies, as well as the present study, have shown that the electrical conductivity of tissue increases during electroporation [11–13,18]. And to more accurate estimation of the temperature in electroporation, the effect of conductivity changes must be considered.

As can be seen from Figures 5 and 6 and Table 4, the temperature changes at the tip of the electrodes were greater than the other candidate points in this study, which was in line with the results of previous studies [7]. The reason can be attributed to the greater electric field intensity at the tip of the electrodes. The electric field intensity decreases with increasing distance from the electrodes. Therefore, as you move away from the electrodes, the temperature rise decreases during electroporation. At the time of pulse transmission, the temperature rises at any point in the tissue, and at the time interval between the two pulses, the temperature begins to decrease (Figures 4-7). But the time interval between two pulses is not large enough that the tissue temperature returns to its original value. During the tissue temperature reduction process, the next pulse is sent, and the tissue temperature rises again. This process will lead to an increase in tissue temperature ascending. These results are in assent with previous studies [7].

In order to investigate the effect of conductivity changes during irreversible electroporation on tissue temperature change, two categories of simulations have been used in this study. One group with constant conductivity and another group with variable conductivity. Finally, the results of these two simulation categories are compared with each other (Figures 5, 6 and Table 4). As can be seen, considering the changes in conductivity in increasing the temperature of the candidate points in the simulation, the temperature is higher than the simulation with constant conductivity. This increase in temperature due to conductivity changes was observed in all study points, but its effect was greater at the tip of the electrodes and the periphery of the electrode.

At the tip of the electrode, due to the higher density of the electric current, the conductivity changes are much greater than at other points. Previous studies also confirm the findings of this study [11–13]. These more significant changes in electrical conductivity at the electrode tip will result in a higher temperature change in comparison with constant conductivity conditions. As can be seen from Table 4, considering conduction changes in temperature calculation during electroporation becomes more critical for pulses with larger electric field intensities.

5. Conclusion

Finally, it can be concluded that in order to measure temperature more accurately during irreversible electroporation, conductivity changes must be considered. The significance of the effect of conductivity changes in electroporation on temperature is much greater in electric pulses with larger electric field intensities and points closer to the electrodes.

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