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Tissue heating during tumor ablation with irreversible electroporation

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Abstract. Exposing biological cells to sufficiently strong external electric fields causes electroporation of cell membranes, i.e. occurrence of transient or permanent permeable pathways between the interior and exterior of the cell. Electroporation can be used to introduce various molecules into cells (reversible electroporation) or to kill cells (irreversible electroporation), which can in turn be used for tissue ablation. The main advantages of irreversible electroporation over other ablation techniques are its non-thermal nature and consequently fast tissue regeneration. For efficient tissue ablation that utilizes its non-thermal nature it is therefore crucial that an adequate electric field distribution is achieved in the target tissue and that the temperature inside the tissue stays below the thermal damage thresholds. This can be achieved by careful positioning of the electrodes with respect to the target tissue and an appropriate choice of the number, duration and amplitude of electric pulses applied during the treatment. We present a treatment planning procedure for planning irreversible electroporation for cancer ablation that uses a sequential model of electroporation and a genetic algorithm-based optimization procedure. We show that it is possible to reduce tissue heating during the optimization procedure by penalizing higher temperatures in the objective function. We also show that optimization of electroporation parameters takes too much time when an accurate calculation of the temperature distribution is performed for each set of parameters. Instead, we propose that heating during electric pulse delivery is only conservatively estimated in the optimization procedure, while an accurate calculation is performed only when the conservative estimate implies the possibility of thermal damage.

Keywords: irreversible electroporation, ablation, numerical modeling, optimization, cancer

1 INTRODUCTION

If a biological cell is exposed to an external electric field of a sufficient magnitude, structural changes occur in the cell membrane and enable transport of otherwise impermeable molecules through the membrane. Electroporation, as the phenomenon is called, can be controlled by an appropriate choice of electric pulse parameters [1]. Electric pulses of a lower amplitude only transiently electroporate the cells; the membrane reseals and the cell retains its normal function [2]. This is called reversible electroporation and is mostly used to transport molecules into and out of the cells [3-5]. Electric pulses of higher amplitudes, on the other hand, cause irreversible electroporation that leads to cell death [6]. Recently, researchers have started utilizing irreversible electroporation as a method for tissue ablation [7]. Its main advantage over other ablation methods is its non-thermal mode of inducing cell death, thus preserving the proteins of the extracellular matrix and accelerating tissue regeneration [6].

To successfully ablate the target tissue with irreversible electroporation, a local electric field of a sufficient magnitude has to be induced around all target cells. This can be achieved by using numerical treatment planning before the procedure, as we showed before in cases of deep-seated tumor treatment with electrochemotherapy [8,9]. By using a combination of medical image analysis, building an anatomically realistic geometry of the target tissues, numerical calculations of the electric field distribution and optimization algorithms it is possible to determine the optimal positions of individual electrodes used to deliver the pulses and the voltages used between the electrodes that would lead to successful electroporation (reversible or irreversible). Nevertheless, when using irreversible electroporation for tissue ablation, it is also necessary to keep in mind that the electric field causes heating of the exposed tissue and that the main advantages of irreversible electroporation are lost if the temperature in the tissue denaturizes the extracellular matrix proteins. Therefore, we upgraded the numerical models used for electrochemotherapy treatment planning [8,9] to include also the calculations of the temperature increase because of the electric pulses. The aims of this study were to determine whether the pulses currently used in clinical trials of ablation with irreversible electroporation cause thermal damage and

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also to determine the time needed to produce a treatment plan for ablation with irreversible electroporation with current algorithms.

2 METHODS

Our calculations were made on the basis of a subcutaneous tumor geometry and needle electrodes inserted around it (Fig. 1) [10]. In the vicinity of the tumor we put a spherical object to represent a critical tissue, which must not be harmed during irreversible electroporation, i.e. the electric field threshold for irreversible electroporation must not be exceeded and the temperature has to remain below the thermal damage threshold [11]. In a clinical setting such a critical tissue could be e.g., important vessels, nerves or heart.

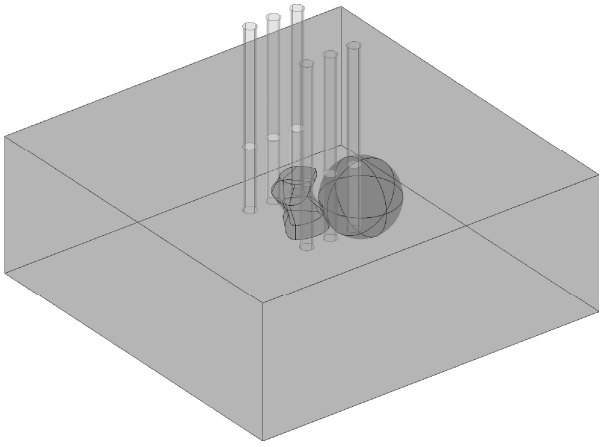

Figure 1: Tissue geometry used in the optimization of irreversible electroporation: six electrodes positioned in two rows around a centrally located tumor. On the right side of the tumor, there is a critical tissue where the electric field may not exceed the threshold of irreversible electroporation.

In our numerical modeling we used Comsol Multiphysics 3.5a (COMSOL AB, Sweden), a package for solving partial differential equations with the finite element method. We used the Laplace equation to determine the electric potential distribution:

$$\nabla \cdot (\sigma \cdot \nabla V) = 0\,, \tag{1}$$

where σ is the tissue electrical conductivity and V the electric potential. The following boundary conditions were used in the calculations: 1) a constant electric potential on all active electrodes

$$V = k \tag{2}$$

and 2) electrical insulation

$$n \cdot (J_1 - J_2) = 0 \tag{3}$$

on all external boundaries.

We chose the sequential mathematical description of electroporation that takes into account changes in electrical conductivity during exposure to the electric field; the electric conductivity is thus a function of the electric field [12,13]:

$$\sigma(E) = \frac{\sigma_2 - \sigma_1}{E_{irr} - E_{rev}} \cdot E + \sigma_1\,, \tag{4}$$

where σ_1 and σ_2 are electrical conductivities before electroporation and after irreversible electroporation, respectively, and E_{rev} and E_{irr} are the reversible and irreversible thresholds of electroporation, respectively.

Exposing the biological tissue to electric pulses results in its heating, which we described by using the Pennes bioheat equation [14]:

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) - \rho_b c_b w_b (T - T_b) + Q_m + Q\,, \tag{5}$$

where T is the temperature, ρ the tissue density, c the heat capacity, ρ_b, c_b, w_b and T_b the density, heat capacity, flow and temperature of blood, respectively, k the heat conductivity, Q_m the metabolically generated heat and Q the heat resulting from external sources, in our case the Joule losses because of exposure to an external electric field. The values of these parameters were taken from literature and can be found in Table 1[12, 15].

Table 1. Parameters used in calculation of the electric field and temperature distribution with Eqs. (1), (4) and (5) during delivery of electric pulses for irreversible electroporation. The thermal parameters were considered equal for all tissues, while for the electroporation parameters, different values were used for the tumor and other tissues.

Parameter	Value
σ_1^{tumor}	0.2 S/m
σ_2^{tumor}	0.8 S/m
σ_1^{tissue}	0.1 S/m
σ_2^{tissue}	0.4 S/m
E_{rev}^{tumor}	400 V/cm
E_{irr}^{tumor}	900 V/cm
E_{rev}^{tissue}	200 V/cm
E_{irr}^{tissue}	800 V/cm
ρ	1050 kg/m^3
c	3600 J/(kg·K)
k	0.51 W/(m·K)
ρ_b	1060 kg/m^3
c_b	3600 J/(kg·K)
w_b	0.0044 s^{-1}
T_b	37 °C
Q_m	420 W/m^3

Fig. 2 shows the temperature distribution after applying 50×100 µs electric pulses of 500 V, as calculated with Eq. (5).

To perform a less time-consuming evaluation of temperature distribution, we used Eq. (6), for disregarding heat conduction and dissipation due to the blood flow and also for disregarding the heat generated by metabolism :

$$\Delta T = \frac{\sigma E^2 N t}{\rho c}, \tag{6}$$

where N is the number of electric pulses, t duration of a pulse, σ, ρ and c already defined in Eq. (5). As, in our case, Eq. (6) gives higher temperatures than Eq. 5, it is possible to use Eq. (6) as a conservative estimate of heating during irreversible electroporation.

Fig. 3 shows the temperature distribution after applying 50×100 µs electric pulses of 500 V, as calculated with Eq. (6).

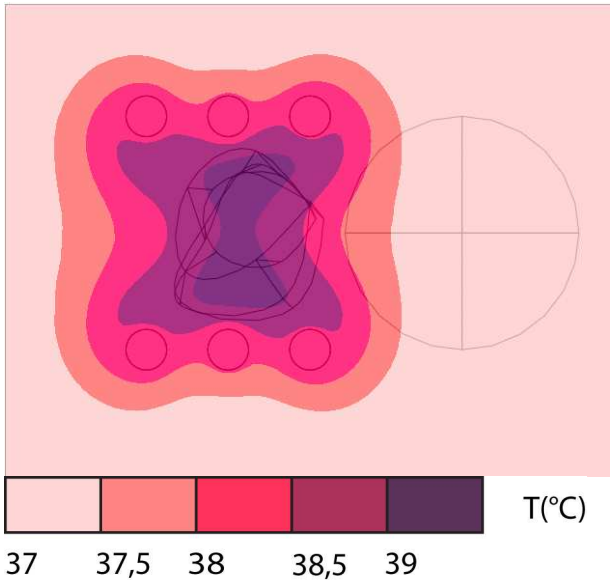

Fig. 2. Temperature distribution after 50×100 µs electric pulses of 500 V, as calculated with Eq. (5). The maximum calculated temperature in the vicinity of the electrodes was 38.1 °C (311.1 K). In the center of the tumor, the temperature reached 39.3 °C (312.3 K).

To optimize the electrode positions and voltages between the electrodes, we used the genetic algorithm [16]. The input of the used objective function was the electric field distribution in the tissue. It returned a scalar value of the solution quality as the output. The initial population was chosen randomly by taking into account the following constraints: acceptable distances between two rows of electrodes, acceptable depths of insertion of the electrodes and permissible voltage between the electrodes. Solutions were chosen for reproduction in each generation with probabilities proportional to their objective function values:

$$F = \sum a_i E_{irr}^i - \sum b_j E_{irr}^j - \sum c_j E_{rev}^j - \sum d_{ij} T^{ij}, \tag{7}$$

where a_i, b_j, c_j and d_{ij} are the weights representing the importance of individual factors for efficient irreversible electroporation of the tissue. These factor are the target tissue (^{i}) and other tissue (^{j}) coverage with an electric field above reversible E_{rev} and irreversible E_{irr} electroporation threshold and temperature T in the tissue.

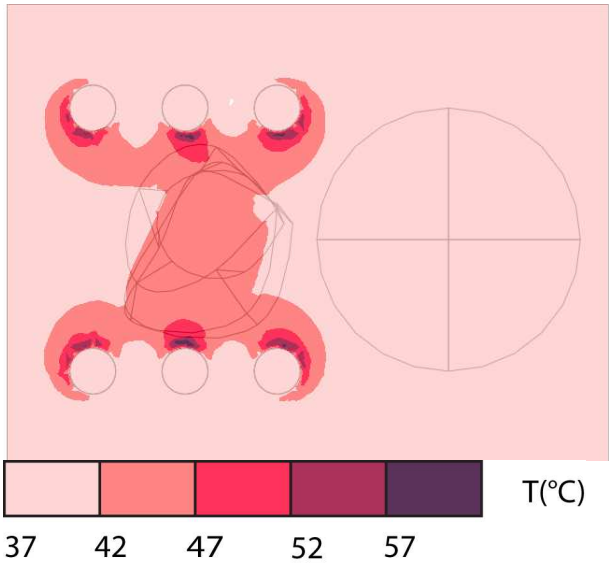

Fig. 3. Temperature distribution after 50×100 µs electric pulses of 500 V, as calculated with Eq. (6). The maximum calculated temperature in the vicinity of the electrodes was 67.3 °C (340.3 K). In the center of the tumor, the temperature reached 43.2 °C (316.2 K).

The next generation of the solution was obtained from the previous generation with mathematical operations crossing (Eq. (8)) and mutation (Eq. (9)), chosen with probabilities given in Table 2, P_{mut} and P_{cross}:

$$z_{i+1} = e_i \cdot x_i + (1 - e_i) \cdot y_i; \quad e_i \in [0,1] \tag{8}$$

$$z_{i+1} = x_i + f_i \cdot x_i; \quad f_i \in [-p, p], \tag{9}$$

where z_{i+1} are the next generation solutions, x_i and y_i are the previous generation solutions and e_i and f_i are randomly chosen values from the above intervals. Table 2 shows parameters of the genetic algorithm used in the study.

Table 2. Parameters used in the genetic algorithm and its objective function.

Parameter	Value
a_i	100
b_j	20
c_j	2
d_{ij}	10
p	0.25
P_{mut}	0.4
P_{cross}	0.6

3 RESULTS

In the first part of ourstudy we made several calculations of the temperature increase during irreversible electroporation by using Eq. (5). As an individual calculation takes several minutes and at least a thousand calculations are needed in the optimization procedure [8], we estimated that the whole optimization procedure would take several days or even weeks (in fact it took 11 days as we determined later). This is not acceptable in the clinical environment, where the treatment plan has to be prepared in a few days maximally. Therefore, we decided to use Eq. (6) at least in some parts of the optimization procedure.

First we tested a "screening" procedure, in which we used Eq. (6) to calculate temperature distribution for each proposed solution. We used Eq. (5), when calculation made with Eq. (6) implied that thermal damage would be possible (when the maximum temepreture reached 50 °C). Thus, Eq. (5) was only used in 12 % of all the calculations in the optimization procedure. The optimization time was decreased down to 29 hours that is on the borderline of acceptability in the clinical environment. After the treatment plan had been complete, we verified it by performing one more calculation with Eq. (5). This time this was done with a very fine meshing. A comparison of the treatment plans obtained with and without screening showed no significant differences (Table 3).

Table 3. Comparison of the treatment planning results obtained with the basic and screening procedure: the volume of irreversibly electroporated tumor (^{i}) and critical tissue (^{j}) and maximum temperature achieved in the tissue are compared.

Procedure	$E_{irr}(^{i})$ [%]	$E_{irr}(^{j})$ [%]	T_{max} [°C]
Basic	100	0,05	39,3
»Screening«	100	0,09	39,3

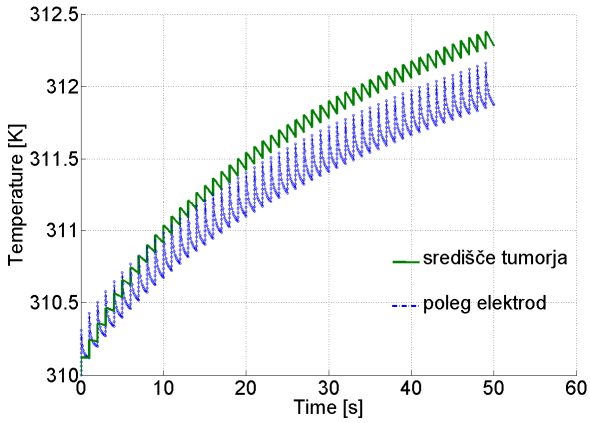

Fig. 4. Temperature in the center of the tumor and in the vicinity of the electrodes when applying 50x100 µs electric pulses of 500 V, as calculated using Eq. (5). The maximum calculated temperature in the vicinity of the electrodes was 39.1 °C (312.1 K), while in the center of the tumor the temperature reached 39.3 °C (312.3 K).

Fig. 4 shows the time course of temperature near the electrodes and in the center of the tumor, when applying 50 electric pulses of 500 V (calculated with Eq. (5)). The treatment obtained with the screening optimization procedure was used for the calculation. Temperature time course depicted in Fig. 4 shows the effect of the electrode high heat conductivity. As the electrodes function as a heat sink, the temperature near the electrodes decreases significantly between the pulses and the decrease is much smaller in the center of the tumor. It is thus not surprising that after the last pulse, the temperature in the center of the tumor is higher than near the electrodes.

4 DISCUSSION

One of the most important advantages of irreversible electroporation used as a tissue ablation method is its non-thermal way of killing cells. We, therefore, calculated temperature distribution during electroporation to add functionality to our previously developed treatment planning procedure of electrochemotherapy [8].

As optimization together with accurate temperature increase calculations (Eq. (5)) takes too much time for the clinical environment, we replaced Eq. (5) with a less accurate but faster Eq. (6). As seen from the results, the use of the "screening" procedure did not significantly affect the quality of the obtained treatment plan, however it did reduce the time it took for the planning to complete - from 11 days to 29 hours. This brings us to the conclusion that calculating the temperature distribution during optimization of irreversible electroporation is not necessary with the electric pulse

parameters currently used; however, if the repetition frequency or the number of pulses is increased, the temperature increase is expected to be much higher and the inclusion of the temperature calculation into the numerical treatment planning procedure would become a necessity.

In previous studies an effort was taken to calculate the temperature increase during tissue ablation with irreversible electroporation [17,18]. Safe electric pulse parameters that do not cause excessive heating were determined. However, these studies did not take into account the changes in tissue conductivity during electroporation. These changes can significantly increase the electric current through the tissue and thus increase temperature more than previously thought [19]. Using the sequential model of electroporation enabled us to take the changes in conductivity into account. Our results confirm that the electric pulses currently used in clinical trials (50×100 µs electric pulses, with a repetition frequency of 1 Hz and voltage to distance ration of approximately 2000 V/cm) [20] do not thermally damage the ablated tissue.

The presented procedure to be used in numerical treatment planning of tumor ablation with irreversible electroporation is the first in the series of numerical treatment planning aimed at providing support in clinical irreversible electroporation. In the future the obtained results will be experimentally validated in *in vivo* studies of irreversible electroporation and adapted to the needs of a specific application in clinical setting.

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REFERENCES

[1] I.P. Sugar, E. Neumann. Stochastic model for electric field-induced membrane pores electroporation. *Biophysical Chemistry* 19: 211-225, 1984.

[2] E. Neumann, M. Schaefer-Ridder, Y. Wang, P.H. Hofschneider. Gene transfer into mouse lyoma cells by electroporation in high electric fields. *EMBO Journal* 1: 841-845, 1982.

[3] L.M. Mir, S. Orlowski, J. Belehradek, C. Paoletti. Electrochemotherapy potentiation of antitumor effect of bleomycin by local electric pulses. *European Journal of Cancer* 27: 68-72, 1991.

[4] L.C. Heller, R. Heller. In vivo electroporation for gene therapy. *Human Gene Therapy* 17: 890-897, 2006.

[5] G. Serša, D. Miklavčič. Electrochemotherapy of tumours (Video article). *Journal of Visual Experiments* 22: 1038, 2008.

[6] B. Rubinsky, G. Onik, P. Mikus. Irreversible electroporation: A new ablation modality - Clinical implications. *Technology in Cancer Research and Treatment* 6: 37–48, 2007.

[7] R. Davalos, L.M. Mir, B. Rubinsky. Tissue ablation with irreversible electroporation. *Annals of Biomedical Engineering* 33:223-231, 2005.

[8] A. Županič, S. Čorović, D. Miklavčič. Optimization of electrode position and electric pulse amplitude in electrochemotherapy. *Radiology and Oncology* 42: 93-101, 2008.

[9] D. Miklavčič, M. Snoj, A. Županič, B. Kos, M. Čemažar, M. Kropivnik, M. Bračko, T. Pečnik, E. Gadžijev, G. Serša. Towards treatment planning and treatment of deep-seated solid tumors by electrochemotherapy. *Biomedical Engineering Online* 9: 10, 2010.

[10] D. Šel, A. Maček-Lebar, D. Miklavčič. Feasibility of employing model-based optimization of pulse amplitude and electrode distance for effective tumor electropermeabilization. *IEEE Transactions on Biomedical Engineering*, 54: 773-781, 2007.

[11] A. Županič, D. Miklavčič. Optimization and numerical modeling in irreversible electroporation treatment planning. V: B. Rubinsky (urednik), Irreversible electroporation, Berlin, Springer Verlag, 203-222, 2010.

[12] D. Šel, D. Cukjati, D. Batiuskaite, T. Slivnik, L.M. Mir, D. Miklavčič. Sequential finite element model of tissue electropermeabilization. *IEEE Transactions on Biomedical Engineering* 52: 816-827, 2005.

[13] N. Pavšelj, Z. Bregar, D. Cukjati, D. Batiuskaite, L.M. Mir, D. Miklavčič. The course of tissue permeabilization studied on a mathematical model of a subcutaneous tumor in small animals. *IEEE Transactions on Biomedical Engineering* 52: 1373-1381, 2005.

[14] H.H. Pennes. Analysis of tissue and arterial blood temperature in the resting human forearm. *Journal of Applied Physiology* 85: 5-34, 1948.

[15] I. Lacković, R. Magjarević, D. Miklavčič. Three-dimensional finite-element analysis of joule heating in electrochemotherapy and in vivo gene electrotransfer. *IEEE Transactions on Dielectrics and Electrical Insulation*, 15: 1338-1347, 2009.

[16] J.H. Holland. Adaptation in natural and artificial systems: an introductory analysis with applications to biology, control, and artificial intelligence. Cambridge, MIT Press, 1992.

[17] R.V. Davalos, B. Rubinsky. Temperature considerations during irreversible electroporation. *International Journal of Heat and Mass Transfer* 51: 5617-5622, 2008.

[18] H. Shafiee, P.A. Garcia, R.V. Davalos. A preliminary study to delineate irreversible electroporation from thermal damage using the Arrhenius equation. *Journal of Biomechanical Engineering* 131: 074509, 2009.

[19] A.T. Esser, K.C. Smith, T.R. Gowrishankar, J.C. Weaver. Towards solid tumor treatment by irreversible electroporation: intrinsic redistribution of fields and currents in tissue. *Technology in Cancer Research and Treatment* 6: 261-273, 2007.

[20] J. Rubinsky, G. Onik, P. Mikus, B. Rubinsky. Optimal parameters for the destruction of prostate cancer using irreversible electroporation. *Journal of Urology* 180: 2668-2674, 2008.

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