ApOtEl: Development of a Software for Electroporation Based Therapy Planning

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Abstract

The objective of this paper is to describe the implementation of a software application, called *ApOtEl*, developed for needle electrodes positioning optimization for electrochemotherapy procedures in the treatment of cutaneous and subcutaneous tumors. The software was developed using MATLAB®, and it optimizes the needle-type electrodes positioning configurations, through the study of the analytical electric field, using Laplace equation in a homogeneous bi-dimensional environment. The optimization was based on requirements chosen to guarantee the tumor total coverage and to minimize healthy neighboring tissues damage. An optimization function was created to orientate the electrochemotherapy application, and the best option available in all configurations generated by the distance variations between electrodes and positioning orientations was determined. The software provides, by the entry of tumor dimensions, the optimized distances for positioning needle-type electrodes, as well as the representation of the electric field distribution and intensity. Representation of the electrodes positioning and instructions for the procedure to facilitate the procedure planning are provided.

Keywords

Electrochemotherapy • Software development
Electric field

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1 Introduction

Electrochemotherapy (ECT) is an effective and safe form of local antitumor treatment in which short and intense electrical pulses are applied to the target volume in conjunction with chemotherapeutic agents [1, 2]. Due to exposure to electrical pulses of sufficiently high intensity, the cell membrane becomes temporarily permeable, a process known as reversible electroporation, allowing large molecules, such as chemotherapeutics, to cross the cytoplasmic membrane barrier, potentializing its effects [3].

Studies on electroporation date back to the 1960s [1]. Over the years, several experiments, both in vitro and in vivo, have been performed. In 2002, the European Standard Operating Procedures for Electrochemotherapy and Electrogenetherapy (ESOPE) was created to define standard operating procedures for the technique. The study reported complete tumor regression in 73.7% of nodules treated with only one ECT application [1, 4]. Many other clinical studies have been performed, and the regression rate followed by a single ECT application is 60% (85% of objective response), although this percentage varies between tumor types [5].

Among the main ECT advantages, the technique has the ability to preserve tissues, functions and sensitive structures, as well as, to produce minimal and tolerable side effects. Moreover, ECT has the ability to treat tumors of any histology, it is a quick (taking only a few minutes) and a cost-effective treatment, that greatly improves the quality of life of the treated patients [4, 5].

The number of patients benefiting from ECT as a form of treatment has been increasing rapidly, with more than 1,500 patients treated in 2011, in more than 100 hospitals around the world [1]. By the end of 2015, approximately 13,000 cancer patients were treated with ECT and currently it is used routinely in about 140 European centers [5]. In Brazil, research with electroporation began in 2008 in a university veterinarian hospital. Currently, the treatment is part of the routine of this animal hospital [3].

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However, ECT success is highly dependent on the electric field distribution and parameters related with its distribution and intensity, such as type, quantity and electrodes positioning, whose incorrect choice may compromise the treatment.

The objective of this paper is to describe the implementation of a software application, developed for needle electrodes positioning optimization for ECT procedures in the treatment of cutaneous and subcutaneous tumors.

2 Methods

2.1 Electric Field

The distribution of the electric field is one of the fundamental aspects for the effectiveness of electroporation treatments. For a successful treatment, all tumor cells must be destroyed and it is extremely important that the electric field is as uniform as possible, covering the entire tumor with intensity that exceeds the electroporation threshold (E_{rev}), around 600 V/cm for most neoplasms [3]. In order to obtain the electric field intensity, some parameters such as type and configuration of electrodes, their positioning should be carefully chosen, since they have a great influence on the electric field intensity and distribution. If these parameters are not chosen appropriately, the electric field may be insufficient or inadequate, leading to an ineffective treatment and tumor resection due to the insufficient magnitude of the local electric field or to non-coverage of parts of the tumor.

The analytical solution for the electric field distribution has limitations, such as being only possible for regular geometries, usually confined to 2D and it assumes that the electrical properties of the tissues are uniform, which rarely occurs in practice. However, it is a quick and convenient way for analyzing the electric field distribution in the tumor, providing an overview of the treatment area, as well as its effectiveness.

For the development of this work, mathematical models and analytical calculations, based on Čorovič (2010), were incorporated in the software application to calculate the electric field between needle electrodes, positioned in the region of interest. According to this method, electric field intensity and distribution are estimated by Laplace equation, considering the electric potential as a sum of the multipoles of all electrodes, in a homogenous environment.

2.2 Electrode Positioning Optimization

The distribution of the electric field can be controlled by the applied voltage, number, electrodes distances and how they are placed in the target tissue. We sought an optimization of the main parameters that dictate the field distribution for different tumor sizes.

The simplifications assumed include the analytical calculations for 2D representations of superficial cutaneous tumors measuring 1 cm × 1 cm to 15 cm × 15 cm, including tumors with elliptical shapes. The area of interest is represented as a 2D plane of the tumor in 3D space. This assumption is that the electric field is homogeneous along the electrode's axis of insertion, perpendicular to 2 D plane of the tumor.

The electric field is calculated by assuming 1 V between electrodes, allowing the use of several E_{rev} thresholds in the optimization, with electroporation occurring at 1 V/cm. However, in order to guarantee a greater safety, it is assumed that the area where the electroporation occurs is equal or greater than 1.20 V/cm, to provide a 20% safety margin. This safety margin is justified by model simplifications and tumors irregularity.

Electric field distribution is analyzed for 1, 2 and 3 pairs of electrodes positioned parallel in line with the configuration center, coincident with tumor center. Such linear arrangements are commonly used in ECT for minimizing the inhomogeneity of the electric field distributions generated by needle electrodes. The possibilities of distance between the electrodes (starting in a distance of 1 cm and using steps of 0.1 cm) and two orientations lead to a total of 1360 configurations available. It is important to mention that a previous evaluation was carried out to eliminate redundant configurations.

For the electrodes positioning optimization some requirements are chosen, such as the electric field with an intensity superior or equal to E_{rev} must cover the entire tumor; neighboring healthy tissue should not be exposed to an excessively high field, being as small as possible; and as few applications as possible should be carried out.

Considering these requirements, an "optimization" function was developed to evaluate the available electrode configurations, appropriate for each tumor size, which takes into account the tumor coverage by the electric field for electroporation and the conformation of the electric field to the tumor shape.

First the tumor coverage fraction by the electric field configurations is evaluated through the calculating of the coverage fraction (CF), given by Eq. (1):

$$CF = \frac{AC}{AT} \tag{1}$$

where AC refers to the total area covered by the setting within the criterion of intensity greater than or equal to E_{rev}, and AT is the total area of the tumor. CF values below 1 indicate that the area of the tumor covered by the electric field threshold that generates electroporation is less than necessary; if CF is greater than 1, electroporation occurs in a

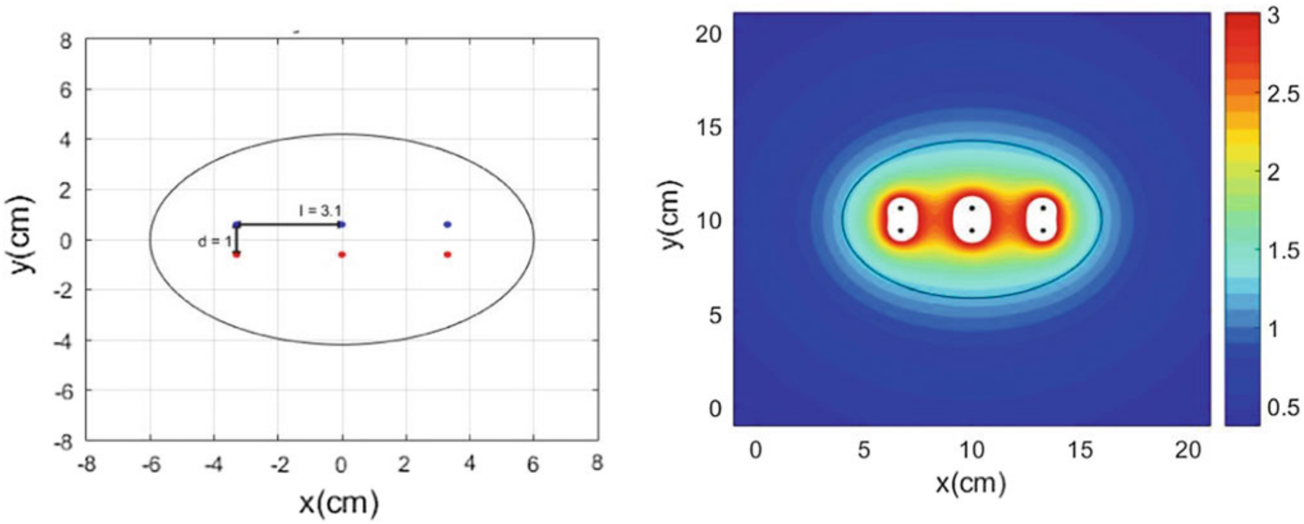

Fig. 1 (Left) Representation of electrodes positioning for a 12 cm × 8.4 cm tumor. (Right) Electric field distribution for the optimized configuration for a 12 cm × 8.4 cm tumor

region larger than the tumor area, reaching the healthy neighborhood.

However, the comparison between areas is not enough to optimize the positioning, since some electrode configurations can generate asymmetric areas and tumors can be irregular. To solve this problem, the tumor maximum dimensions in vertical and horizontal directions and the electric fields thresholds generated by the configurations are determined. For optimization, a penalty is established if tumor dimensions are greater than the electric field distribution area with intensity superior or equal to E_{rev} of a given configuration, in any direction. The penalty is calculated as follows:

$$\begin{cases} P_x = W_T - W_E, \textit{if } W_T \le W_E \\ P_x = 100, \textit{if } W_T > W_E \end{cases} \quad (2)$$

$$\begin{cases} P_y = L_T - L_E, \textit{if } L_T \le L_E \\ P_y = 100, \textit{if } L_T > L_E \end{cases} \quad (3)$$

$$\mathrm{P} = \mathrm{Px} + \mathrm{Py} \quad (4)$$

P_x is the penalty applied to height, P_y is the penalty applied to width, P is the total penalty applied to the configuration, W_T is the tumor height, W_E is the height of the configuration, L_T is the tumor width and L_E is the configuration width.

Thus, the total optimization of the configuration is given by Eq. (5):

$$Op = CF + P \quad (5)$$

The closer the *Op* function value is to 1, better the criteria are met by the configuration. If the configuration for one application is not optimized for tumor size or shape, a larger number of applications optimized for different tumor areas should be performed.

The software application was developed using MATLAB® tools, language and compiler, which generated an executable for installation. The software application is restricted to Windows operational systems.

3 Results

The software application, called *ApOtEl*, which stands for Application for Optimization of Electrodes, can be installed through the executable (.EXE) provided by the authors.

Through the entry of tumor dimensions, optimized parameters for electrodes positioning are provided, with the electric field covering the entire tumor with intensity higher than E_{rev} threshold. In addition, *ApOtEl* provides an electric field distribution representation, and a brief explanation of the technique application procedure.

When starting the simulation panel, user should provide the 2D tumor dimensions (in cm). *ApOtEl* fills in the results —Tumor Dimensions, Procedure and Optimization.

ApOtEl will initiate the optimization process for the inserted tumor size. After optimizing or choosing the ideal parameters. Dimensions section presents tumor dimensions and electroporated volume; volume calculation is estimated, assuming the smaller dimension as the tumor depth. Procedure section provides instructions on how electrodes should be placed, the depth they should be inserted and whether more than one application will be needed. In Optimization section, ECT optimum parameters for the tumor are presented, such as number and distances between the electrodes. *ApOtEl* also generates an electric field distribution representation for the optimized parameters, and a representation of electrodes positioning in the tumor.

An example of *ApOtEl* in a hypothetical case study with a 12 cm × 8.4 cm tumor is presented (see Fig. 1). By informing the tumor dimensions, the system will optimize and provide the most appropriate parameters for a safe and efficient procedure.

For a total coverage of the tumor with an electric field with intensity above E_{rev} and with the minimum of healthy tissue affected, the system determined the use of six electrodes in two parallel lines with a distance of 1 cm between the electrodes of different polarity (d) and distance of 3.1 cm for the electrodes with the same polarity (l). Finally, the system provided a chart schematically showing where these electrodes should be positioned and the distribution of the electric field generated by them.

4 Conclusion

The main result of this work is the software application *ApOtEl*, desktop-installable, that provides the visualization of the optimized electric field distribution of needle electrodes for ECT.

The oncology professionals are not familiar with the concept of electric field distribution, which is the ECT base. Thus, the developed software will help these professionals to visualize what happens during ECT application, as well as providing an optimization of the treatment, seeking greater effectiveness. The visualization of the electric field distribution will give oncology professionals a better understanding of the physical phenomena involved in ECT, in addition to providing a greater "confidence" in the application of the technique.

This software application will contribute to the evaluation and planning of treatments involving ECT in a safe and efficient way, through studies using mathematical models (in silico studies). These analyzes may benefit in decision-making and planning of pre-application procedures.

The preliminary application of the developed software has been shown to be suitable for the planning of cancer treatment in animals. Further studies will integrate this software application with optical medical images for the evaluation of tumor dimensions and subsequent choice of the appropriate positioning for each situation.

Compliance with ethical standards

Conflicts of interest: The authors declare that they have no conflict of interest.

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