COMBINATION OF SQUARE AND NEEDLE ELECTRODES FOR BETTER ELECTRIC FIELD DISTRIBUTION IN CANCER TREATMENT TECHNIQUES

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Abstract. The success of electrochemotherapy, electroendocytosis, iontophoresis and electrogene transfer techniques depend on the electric field distribution inside and outside the target area. Electrode configuration is a major factor that affects the intensity, homogeneity of electric field distribution. The aim of the present work is to examine different electrode configurations either square electrodes or combination of square and needle electrodes from the point of the electric field intensity and homogeneity. These parameters were studied practically using Ehrlich tumors. The results indicated that the four square electrodes + one needle electrode configuration gives the highest electric field intensity, while the two square electrodes + one needle electrode configuration gives the highest homogeneity. Combination on needle electrode with square electrodes gives better electric field intensity and homogeneity in the target area than using square electrodes only. The results show the electric characters of different electrode configurations which can help in the electrode selection according to the required treatment.

Key words: Electrode configurations, electric field distribution, cancer treatment techniques.

INTRODUCTION

Electrochemotherapy, irreversible electroporation, electroendocytosis, iontophoresis and electrogene-transfer are new methods used mainly in cancer treatment. These techniques depend to a great extent on the electrical distribution inside and outside the target region.

Electrochemotherapy (ECT) is a combination of high voltage electric pulses and an anticancer drug. It is a highly effective method for local treatment of tumors. It has achieved great results in the treatment of cutaneous and subcutaneous tumors. In order to be able to use ECT also for treatment of internal tumors appropriate and effective electroporative electric pulses to the whole tumor mass should be provided, and these pulses should allow the reversible close of the

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cell pores after the entrance of the drug into the cells [10, 17, 14]. Various studies have looked into the effects of varying the electrode configuration for reversible electroporation applications [3, 19, 26].

A new modality of cancer therapy is the exposure of cells to trains of low electric fields (in the range of 20–100 V/cm) which leads to efficient uptake of macromolecules with molecular weight in the range of 300–2,000,000 into cells. The uptake of macromolecules does not proceed through electroporation, but through an endocytotic-like mechanism. Therefore, this electrically induced endocytosis in combination with intratumoral injection of chemotherapy can be used to effectively incorporate antineoplastic drugs into the cells of the solid tumor [18].

Electroporation is widely used for gene transfection *in vitro* and has been shown lately to hold promises for *in vivo* gene transfection [4, 16]. As it is increasingly accepted that *in vivo* gene transfer will be the future direction for cancer therapy as well as for other human diseases [19, 24], the use of *in vivo* electroporation is gaining even wider interest.

The effectiveness of irreversible electroporation is also highly dependent upon the distribution of the electric field in the tissue to be more than the lethal threshold of the cells [12, 22], which in turn is dependent upon the configuration of electrodes and the amplitude of voltage applied. It was demonstrated that tumor coverage with an adequate electric field is important for the effectiveness of the therapy [2].

The efficacy and the sensation during skin electroporation can to some extent be controlled not only by using appropriate electric protocols, but also by using electrodes designed for the purpose of either electrogene transfection of the skin, or transdermal drug delivery. These techniques were performed with plate electrodes for superficial tumor nodules and with needle electrodes or hexagonal needle electrodes for deeper seated tumor nodules [11].

Previous studies have indicated differences in electric field magnitude and homogeneity for parallel plate or square and needle electrodes for specific external voltages applied [9]. To increase the probability of complete tumor eradication, the electrodes have to be accurately positioned, first to provide an adequate extent of electroporation of all tumor cells and second to prevent or minimize the damage induced in critical healthy tissues or organs in the vicinity of the treatment area [13].

Some authors study needle electrodes for their flexibility in placement and ability to treat both surface and deep-tissue tumors. Needle electrodes produce higher electric field intensity, but lower homogeneity than plate (square) electrodes [3, 5]. Others study plate (square) electrodes because they are one of the simplest electrode designs for the delivery of pulses to the skin or through the skin to the tissues [16, 20] and generate a more uniform electric field between the plates than the surface or the needle versions according to some authors [6, 7].

We studied in previous work the electric field intensities and homogeneity in different needle electrode configurations theoretically and practically [23]. The present work aims to study the electric field distribution in square electrodes alone or in combination with needle electrodes to achieve the best electrode configuration in tumor treatment techniques.

MATERIALS AND METHODS

ELECTRODE CONFIGURATIONS

Four electrode configurations (Fig. 1) were tested to give the highest intensity and the most homogeneous electric field using Ehrlich tumors as a model:

a. Two square electrodes (stainless steel, square shape (2 mm × 2 mm, 2 mm length, and the two electrodes were kept at 10 mm distance) one positive and the other negative arranged opposite to each other at the edges of the tumor.

b. Three electrodes (two square and one needle electrode) arranged in straight line that the needle electrode (stainless steel, 2 mm length, 2 mm diameter) was placed in the middle (at 5 mm distance from the plate electrode) acted as a cathode and the two square electrodes (acted as anodes) on the opposite sides of the cathode.

c. Four square electrodes (two positives, and two negatives), arranged at the edges of a square (10 mm side length), enclose the tumor.

d. Four square electrodes (positive), arranged at the edges of a square form (10 mm side length), and a needle electrode (negative) at the centre of the tumor.

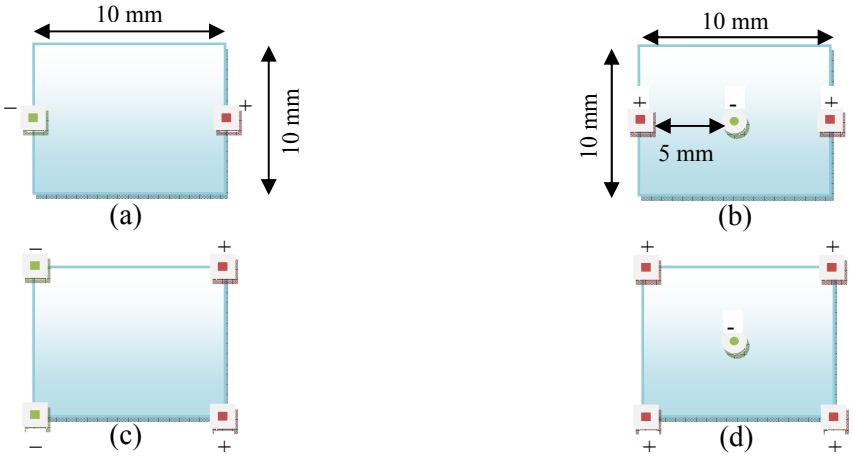

Fig. 1. Different electrode configurations used in the experiment.

MAPPING OF THE ELECTRIC FIELD INSIDE A TUMOR SAMPLE (*IN VITRO*)

Sample preparation

A total of 25 male albino mice, aged 8–10 weeks and weighing between 20–25 g, were obtained for use from the animal house, faculty of medicine, Alexandria University, Egypt. Induction of Ehrlich tumor (subcutaneous tumor) was developed by injection of 2 millions tumor ascites (purchased from the National Oncology Institute, Cairo University, Egypt) in 100 mL saline of phosphate buffer saline subcutaneously in the upper right limb of each mouse [25]. The tumor dimensions were measured by vernier caliper. When the tumor volume reached about 2000–2500 mm^3, each mouse was anesthetized and sacrificed and the tumor mass was excised, approximately 20 mm in length, 20 mm in width, and 5 mm in thickness. So 25 tumor samples were obtained of approximately equal volumes. Experiments were conducted within 90 min from animal sacrifice with the tissue stored in 0.9% NaCl at room temperature until use. The results are the average of six cases.

Measuring circuit

To measure the electric field at any point within the tumor area, a versatile printed circuit was constructed as shown in Fig. 2, to resemble the position of the electrode geometries, in which a part of the tumor on exact size to cover the electrode area were placed. Electric field intensity of 20 V/cm was applied (which is in the range of electroendocytosis), since the distance between anode and cathode

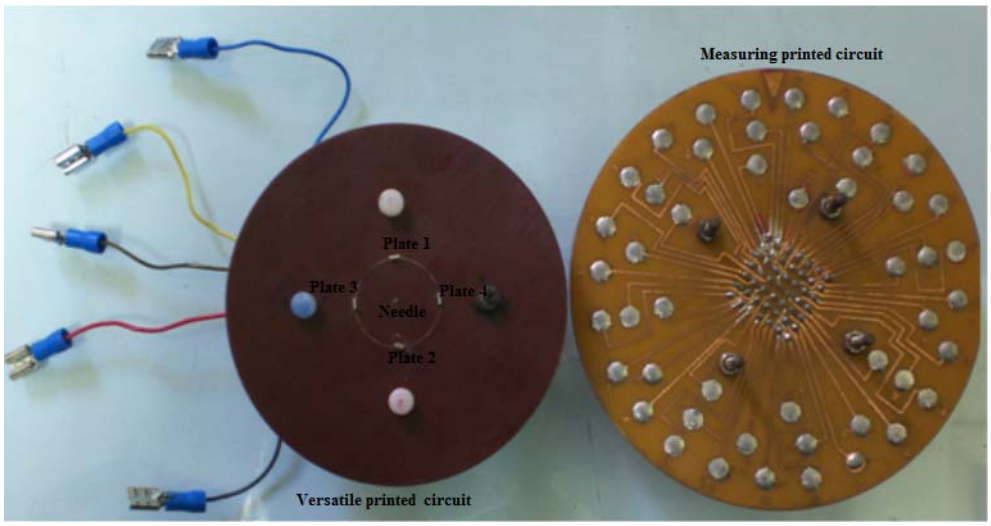

Fig. 2. Electric field mapping circuits.

is different from one configuration to another, different voltages were applied to ensure electric field intensity is 20 V/cm for all the four electrode configurations (20 V for two parallel square electrodes and four parallel square electrodes, 10 V for two parallel square electrodes + one needle electrode, and 14 V for four parallel square electrodes + one needle electrode).

Another printed circuit was constructed to act as a measuring platform, shown in Fig. 2. This printed circuit consisted of 49 stainless steel electrodes with 5 mm length, placed in seven rows with a fixed distance 2 mm between each other.

The potential difference in volts is measured between pair of electrodes, then divided on the distance between them in cm to get the electric field strength in V/cm. The measurements were taken place between the adjacent electrodes (neighbouring pads) only so 49 measurements were taken.

RESULTS AND DISCUSSION

In this study, we quantified and compared the local electric field intensity produced by different electrode configurations in Ehrlich tumor model. The comparison was done by means of two parameters: the electric field intensity (averages) and the homogeneity (standard deviations) of the fields inside the tumor zone.

Figures 3–6 show the electric field intensity (V/cm) inside the tumor for two parallel square electrodes, two parallel square electrodes and one needle electrode in the centre between them, four parallel plate electrodes, and four parallel square electrodes and one needle electrode in the centre between them respectively. Table 1 shows averages and standard deviations (homogeneity) of the electric field intensity (V/cm) inside the tumor for the previously mentioned electrode configurations while Table 2 shows the statistical analysis of the results.

The results indicated that the four square electrodes + one needle electrode configuration gives the highest significant electric field intensity inside the target area , followed by the two square electrodes + one needle electrode configuration. There is no significant difference between the two square electrodes + one needle electrode configuration and four square electrodes configuration. Also there is no significant difference between two square electrodes and four square electrodes configurations according to Table 2.

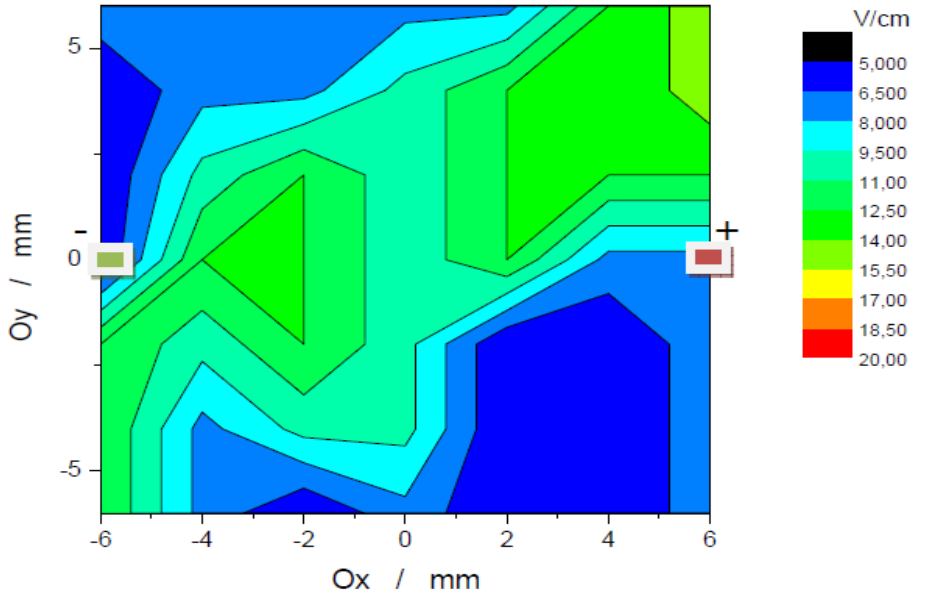

Fig. 3. Electric field intensity (V/cm) inside the tumor for two parallel square electrodes.

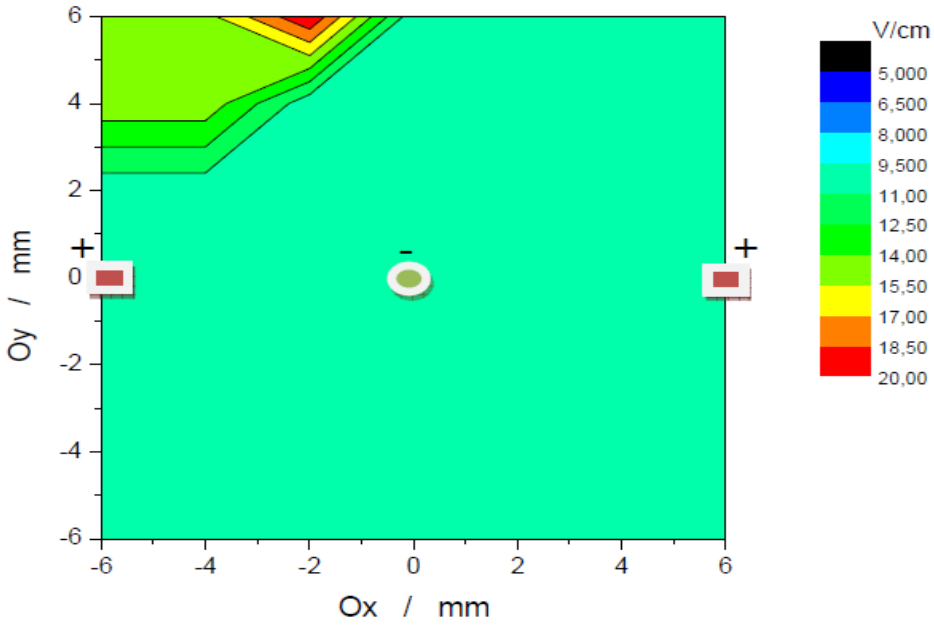

Fig. 4. Electric field intensity (V/cm) inside the tumor for two parallel square electrodes and one needle electrode in the centre between them.

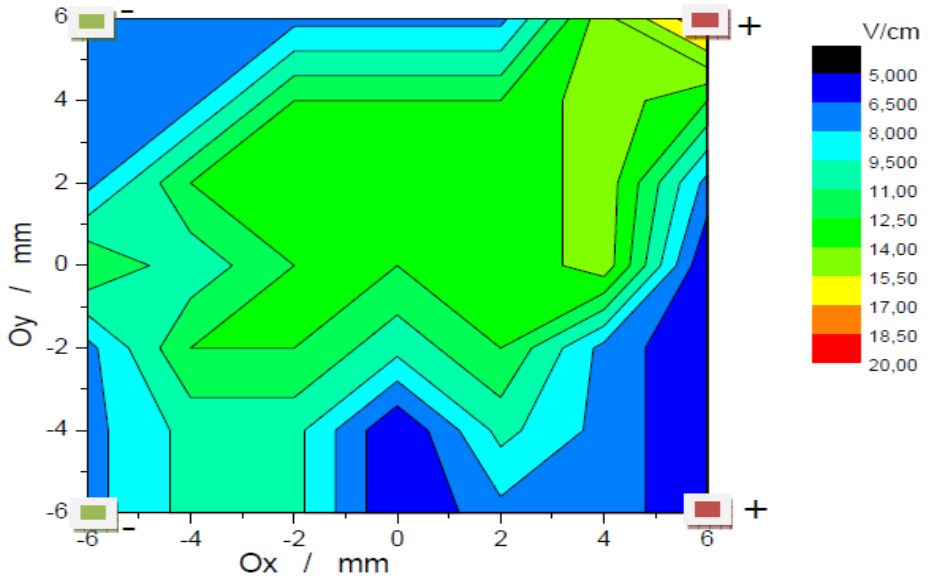

Fig. 5. Electric field intensity (V/cm) inside the tumor for four parallel square electrodes.

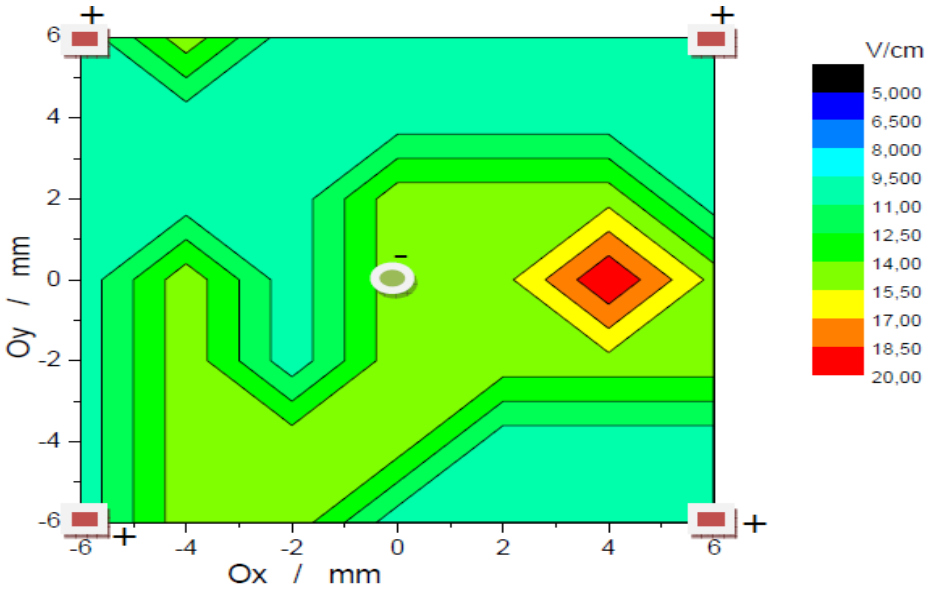

Fig. 6. Electric field intensity (V/cm) inside the tumor for four parallel square electrodes and one needle electrode in the centre between them.

Table 1

Summary of the electric field intensity means and standard deviations inside the tumor by practical application for different electrode configurations

Electrode configuration	**Mean (V/cm)**	**Standard deviation (V/cm)**
Two square electrodes	9.13	3.04
Two square electrodes + one needle electrode	10.61	1.95
Four square electrodes	9.95	3.37
Four square electrodes + one needle electrode	12.04	2.66

Table 2

Statistical analysis of means and standard deviations of electric field intensities produced by different electrode configurations

Electrode configurations	***p*-value**	**Significance**
(Two square electrodes) compared to (Two square electrodes + one needle electrode)	$p = 0.00508$	Significant
(Two square electrodes) compared to (Four square electrodes)	$p = 0.2109$	Not significant
(Two square electrodes) compared to (Four square electrodes+one needle electrode)	$p = 2.4E{-}6$	Very highly significant
(Two square electrodes + one needle electrode) compared to (Four square electrodes)	$p = 0.23525$	Not significant
(Two square electrodes + one needle electrode) compared to (Four square electrodes + one needle electrode)	$p = 0.00327$	Very highly significant
(Four square electrodes) compared to (Four square electrodes + one needle electrode)	$p = 0.00098$	Very highly significant

This increase in the electric field intensity inside target area when using combination of square (plate) and needle electrodes may be because the needle tip which represents a radius curvature different from plain electrodes which in turn have charge density higher than plain electrodes such as plate electrodes according to Neuman [15]. On the other hand, using higher number of needle electrodes leads to higher invasive pain, so using combination of both is better.

If we considered the increase in the electric field standard deviations represents the decrease in electric field homogeneity in the target area, the good homogeneity arrangements are two square electrodes + one needle electrode, four square electrodes + one needle electrode, two square electrodes, then four square electrodes respectively, according to Table 1.

These results are completing the work of Agoramurthy *et al*. [1], who used different needle and plate electrodes configurations on tumors, and they stated that needle electrodes can be inserted right into the region where a tumor is present (intra-tumorally) so that a high field is produced only in the region around it, keeping the surrounding tissue unaffected, which makes it more beneficial than

parallel plate electrodes alone (square in my case). A pair of needle electrodes results in a highly non-uniform concentrated electric field which is undesirable. The voltage is evenly distributed between the positive and negative electrodes in case of parallel plate electrodes whereas needle electrodes result in uneven distribution of voltage in the entire tissue area. The voltage is maximum in the region near the electrodes and reduces drastically as the distance from electrodes increases. Hence the position where needles are placed is important when inserted inside the tumor and tissue area.

Sersa *et al*., stated that electrode configuration used in some previous studies were not the most appropriate for efficient electrochemotherapy [21]: many tumors re-grew in the areas where the intensity of the electric field was presumably below threshold. A search for better ways of electric field application was thus initiated [8, 14]. The data on use of different electrodes further substantiated the need to approach this problem more systematically. In fact, electrode geometry and configuration used and tested so far were determined empirically. The application of this paper can be modulated by choosing electric field intensity of the range of electroporation; it is now in the range of electroendocytosis which uses low electric field intensity for treating tumors.

In order to analyze possible effects of tissue inhomogeneities on the electric field distribution, additional models should be made where target tissue has increased conductivity which is based on the fact that the tumor tissue has in general higher conductivity than its surrounding tissue [3].

Each bio-electrical application requires certain conditions in the electric field distribution; electric field intensity inside the target zone and homogeneity of electric field inside the target zone. These results can help in selecting an electrode configuration for certain purpose according to the application needs.

CONCLUSION

Combination of plate and needle electrodes can be a solution of some problems facing electric field dependent cancer treatment techniques to select the proper electric field characteristics produced by certain electrode configuration according to the demands of the technique. The results indicate that both the electric field intensity and homogeneity are better in case of combining needle electrodes with plate electrodes than using plate electrode configuration only.

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