Finite Element Modeling and Analysis of Human Breast Tissue for Electrochemotherapy

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Abstract- **Cancer is the second most common cause of death in the United States of America. It accounts for nearly 1 out of four deaths. Excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women. With such a high rate of incidence, there is clearly a need for additional complementary/supplementary, and alternate treatments, especially for in-operable tumors and chemo- and radio-resistive patients. Electrochemotherapy, the method by which high intensity, short duration electrical voltage pulses are used to temporarily open pores of cells to enhance the uptake of the chemodrug, is gaining popularity in drug delivery for cancer treatment. This paper aims at providing a model by which breast cancer tissues can be studied and analyzed for treatment by electroporation. Maxwell 13, an Ansoft software package is used for 2D simulation of electrodes and tumor tissues. Suitable electrode models are developed for treatment of invasive and in-situ breast cancer. Finite element analysis of these models demonstrate the electric field intensity and distribution in the tumors. Effects of various electrode types are studied. For large tumors, multi-electrode arrays are used to cover more area compared to currently existing needle arrays. These results will help in electrode design for clinical applications in the treatment of larger tumors using electrical pulse-mediated drug delivery techniques.**

I. INTRODUCTION

Worldwide, it is estimated that more than one million women are diagnosed with breast cancer each year and more than 410,000 will die from it [1]. In US, every 13 minutes, a woman dies due to breast cancer even in 2010, amounting to about 40,000 (1/10of the worldwide deaths) deaths per year.

Once a disease of the industrialized western world, now breast cancer is everywhere; in Asia, China, Africa and other countries [2]. The global burden of breast cancer measured by incidence, mortality, and economic costs is significant and is on the rise. In low and middle income countries, due to lack of resources and infrastructure for routine screening test (mammography) and monitoring, breast cancers are commonly diagnosed at late stages [1] and we need alternate, affordable treatment for pain relief and/or palliate care. Towards this end, electrochemotherapy (ECT), the electrical pulse-mediated enhanced chemo drug delivery [3-5] is a useful technique for in-operable, locally advanced [6], chemo-resistant breast cancers. So far, it has been applied only to chest wall breast carcinoma [4, 5], which occurs after the breast is removed and radio and chemotherapy have been administered. Fig. 1 shows a typical case treated successfully using ECT in Ireland [3]. In our research, we studied the electric field distribution of primary invasive and in-situ breast cancers using parallel plate electrodes and needle electrodes, as the efficacy of ECT depends, in addition to the right dose of drug present at the tumor site during the pulse application (hence the drug should have been administered a few minutes before the application of the pulses, either intratumorally or intravenously), the applied voltage (and hence the electric field) magnitude, the duration of pulse, the number of pulses, the interval between them, and the type of electrodes used. Both needle electrode arrays and parallel plate arrays have been used successfully for skin cancer ECT applications [7]. For deep tumors, needle electrodes are more effective [8].

Typically 4mm gap electrode geometries are used to obtain a uniform field of about 1200V/cm [5]. To treat larger tumor, multiple overlapping applications of pulses are administered. To treat large areas like, breast, this takes several applications of the pulses, which means the patients have to be sedated for a longer time, which could induce complexities for some. Hence another goal of our research is to study the efficacy of large area needle electrode arrays for breast cancer applications using their electric distribution.

(a) Pretreatment (b) 2 months post ECT-all lesions eliminated

Fig. 1. Chest wall recurrence of breast carcinoma in a 52-year-old woman 4 years after left mastectomy and auxiliary clearance and adjuvant chemotherapy. There was no response to systemic chemotherapy. Complete response to ECT was seen in 2 months treatment, without recurrence with the treated area at the 14 month follow-up [3]. All the 5 metastatic nodules were cured and no evidence of disease elsewhere in this patient..

II. SIMULATION

A. Software

Maxwell 13, software by Ansoft Corporation [9] which utilizes finite element analysis was found to be suitable for our research and is used to model tissues and electrodes and run simulations.

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B. Model

A two-dimension model consisting of the human breast, tumor tissue and electrodes was developed to study electric field distribution. As shown in Fig. 1, electrode 1(positive) and electrode 2(negative) are used to apply voltages. A voltage of 8400V was applied to obtain a 1200V/cm electric field intensity across the 7cm diameter of the breast. The various models studied include, the normal breast tissue (a), breast tissue with a tumor within (b). Parallel plate electrodes (a, b) are used to apply voltages externally whereas needle electrodes (c) are inserted directly into the tumor area. The dimensions of model components are listed in Table 1 and model parameters in Table 2.

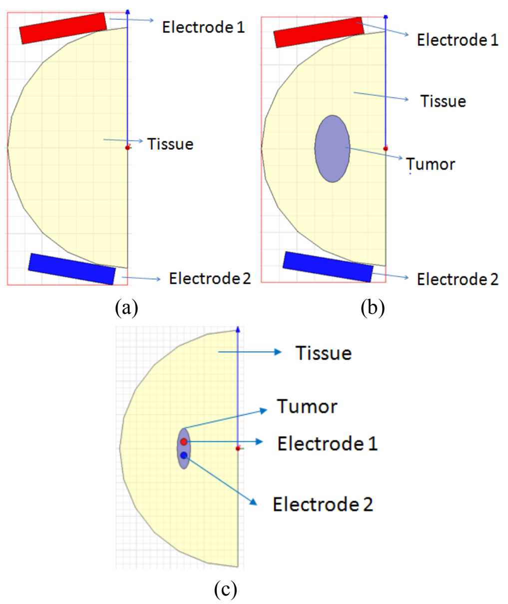

Fig. 2. Finite element model of normal breast tissue with parallel plate electrodes (a), tumor within breast tissue with parallel plate electrodes (b) and tumor within breast tissue with needle electrodes (c).

TABLE I
DIMENSIONS OF MODEL COMPONENTS

Model Component	LengthxBreadth (cmxcm)	Diameter (cm)
Parallel plate electrode	2.5x0.5	-
Needle electrode	-	0.2
4x2 Needle Electrode array	1,4x0.6	-
4x2 Electrode array	1.4x1.4	-
Breast Tissue	-	7
Tumor	1x0.4 (ellipse)	-
Large Tumor - 1	2x1 (ellipse)	-
Large tumor - 2	-	2

TABLE II
MODEL PARAMETERS [10, 11]

No.	Material	Properties
1	Tissue	$E_r = 200$, $\sigma = 0.4S/m$
2	Tumor	$E_r = 1000$, $\sigma = 2S/m$

III. RESULTS AND ANALYSIS

A. Effect of Tumor on the Electric Field Distribution of Breast Tissue using parallel plate electrodes

The voltage distribution of breast tissue with 8400V applied across the 7cm diameter using parallel plate electrodes is shown in Fig. 3. The voltage is maximum near the positive electrode and reduces gradually towards the negative electrode. The voltage distribution is the same for the breast tissue with or without tumor.

The electric field distributions of normal breast tissue and tissue with tumor inside is shown in Figs. 4a and b. A voltage of 8400V causes an electric field of magnitude between 350 – 500V/cm in the normal breast tissue (Fig. 4a). A similar model with a rectangular block of tissue showed that the field was 1150V/cm, close to the calculated value (data not shown). This reduction in electric field in case of breast tissue could be due to the shape of the tissue and the difficulty in placing plate electrodes exactly parallel to the tissue (due to the limitation of the software and exploiting its features). The electric field in the tumor is about 146V/cm (Fig. 4b), which 60% lower than that of the electric field in the normal tissue. The difference in the electric fields in the normal tissue surrounding the tumor and the tumor could be due to changes in the electrical properties of malignant cell compared to normal cells [12] and this desirable aspect is exploited in the electrochemotherapy treatment [3-5].

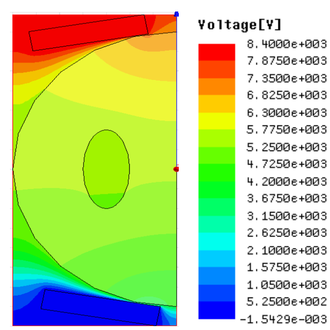

Fig. 3. Voltage distribution of breast tissue with parallel plate electrodes.

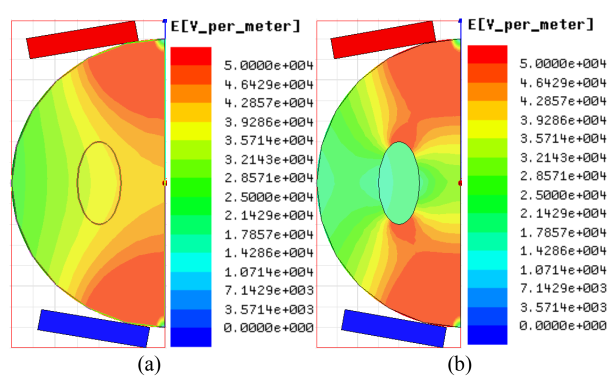

Fig. 4. Electric field distribution of normal breast tissue (a) and tumor within breast tissue (b).

B. Parallel Plate versus Needle Electrodes

Cancers are 'in-situ' when they are in their initial stages and are restricted to a small area. The model of a tumor in a breast tissue is a representation of in-situ breast cancers. Depending upon the thickness of the tumor, either parallel plate electrodes or needle electrodes could be used. For deeply seated tumors, needle electrodes are more suitable than plate electrodes.

In this study, the needle electrode effects are studied. For this purpose, they were directly inserted into the tumor and this resulted in different electric field magnitudes compared to parallel plate electrodes. The voltage distribution of the tumor in the breast model using needle electrodes with 4mm gap is shown in Fig. 5. The maximum voltage is concentrated in the tumor region and did not affect the surrounding normal tissue, a desirable outcome.

The electric field distribution and magnitudes are shown in Fig. 6, for an electrode gap of 4mm. In this case, the electric field intensity varies from 2100 to 2500V/cm, compared to the 350 to 500V/cm obtained using parallel plate electrodes, for the same applied voltage of 480V to give the required electric field intensity of 1200V/cm (480V/0.4cm) as in the case of parallel plate electrodes. However, it is interesting to note that all the electric field is concentrated in between the electrodes, which happens to be the tumor and there is very little field affecting the surrounding normal tissue, again a desirable outcome, as we don't want the surrounding normal tissue to be affected much.

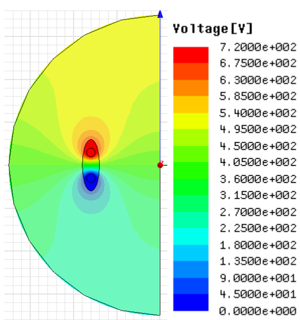

Fig. 5. Voltage distribution of breast tissue with needle electrodes.

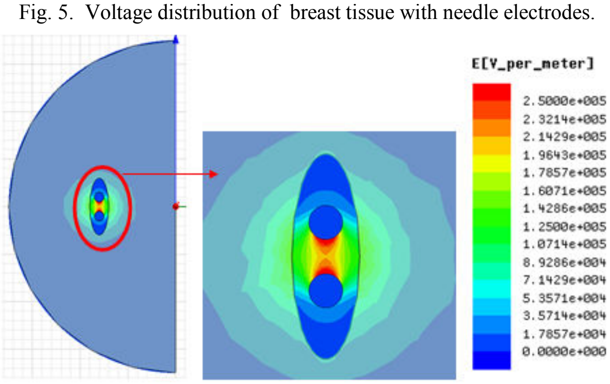

Fig. 6. Electric field distribution of tumor in breast tissue with needle electrodes.

C. Effect of Source Type: DC versus AC

The above simulations were also performed for ax voltages and Fig. 7 shows the comparison of electric field values in the tumor region for DC and AC sources in various cases. In the case of DC, a constant voltage to produce an electric field intensity of 1200V/cm is applied and the electric field distribution is studied. In the case of AC, the same magnitude of voltage was applied with zero degree phase angle at 1 Hz (as one second is the interval between the pulses applied for the human clinical trial [5]).

As shown in Fig. 7, the electric field in the case of AC source is lower than DC for all the various cases studied. The reduction is greater in the case of normal tissue (31%) and much lower in the case of tumor tissues (22% and 7% respectively for parallel and needle plates respectively). The reduction in the electric field with ac compared to DC could be due to the reduced accumulation of charges due to the biphasic nature of the ac field.

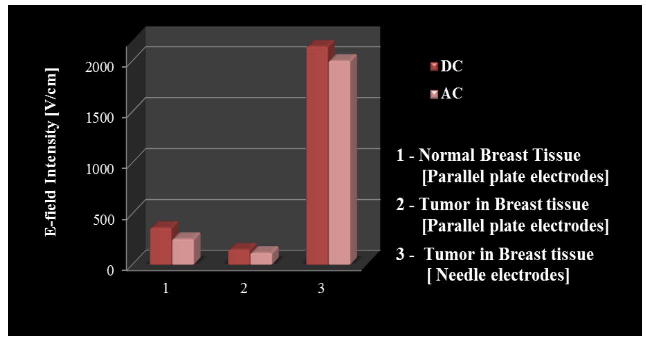

Fig. 7. Comparison of Electric field distribution in tumor with DC and AC sources.

D. Electric field distribution in inter-electrode gap of tumor

In order to study the electric field distribution in various gap lengths, the inter-electrode gap was varied with needle electrodes inserted in the tumor region of the breast tissue. The diameter of the needle electrode is 2 mm, and the gap is varied from 4mm to 8mm, with increments of 2mm. The electric field distribution for the three gaps is plotted in Fig. 8. The electric field distribution is highly non-linear, which could be due to the size and shape of electrodes used. The field in the case of 4mm gap is maximum (>2000V/cm) and is almost uniform. The field magnitudes reduced with increase in gap and the variation in the gap increases. Hence a small gap is most suited for such treatments.

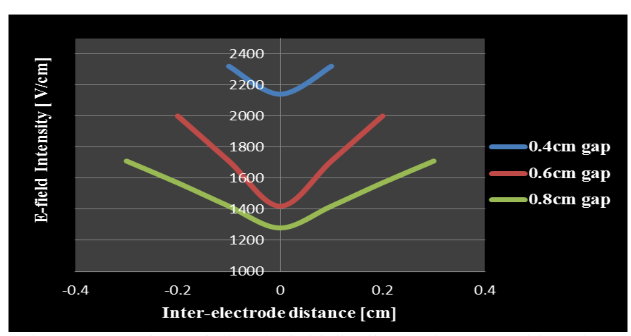

Fig. 8. Comparison of Electric field distribution in tumor with various inter-electrode gaps.

E. Multi-needle electrodes for larger tumors

Most breast cancers are invasive, which means that they spread fast into the surrounding normal tissues. Therefore in case of invasive cancers, tumor sizes can be bigger, such as >2cm. Inserting a single pair of 0.4cm needle electrodes to treat the entire tumor region would need several attempts making it more time consuming and thus the patient has to be sedated for longer durations and the treatment time also increases for the oncological surgeon. Hence, a novel, larger, multi-needle electrode array which would cover larger areas would be more efficient and convenient.

Fig. 9 shows an electrode array with 8 needle electrodes inserted in the tumor region of a breast tissue. The electric field distribution reveals that the electric field magnitude is the same as that of a single pair of needle electrodes with 4 mm gap (2100 to 2500V/cm) and is duplicated across each of the 4-pairs of electrodes. Fig. 10 shows a larger tumor area with 16 needle electrodes. The electric field is again duplicated across the electrode array and the same magnitude is maintained. This shows that designing an electrode array with multiple electrodes would help fast and effiecient treatment of invasive cancers using electrical pulses.

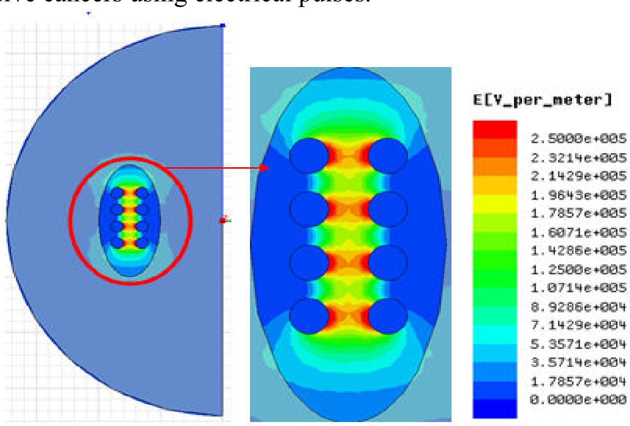

Fig. 9. Electric field distribution of tumor with 8-needle electrodes.

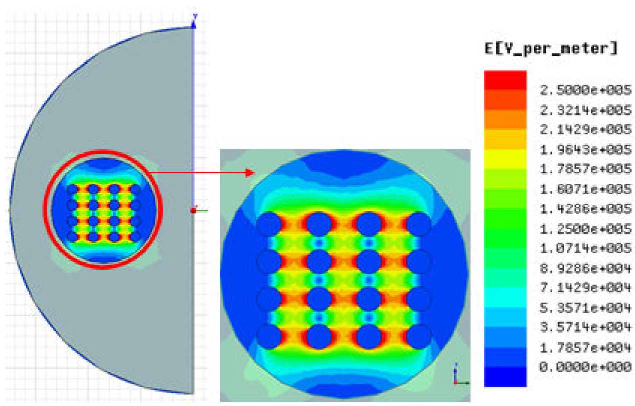

Fig. 10. Electric field distribution of tumor with 16-needle electrodes.

IV. Conclusion

In situ and invasive (80% of occurrence) breast cancers are the most commonly occurring primary breast cancer types. For in-operable, recurrent, and chemo-resistant tumors, which are unresponsive to current modalities of treatments, there is a critical need for alternate, physical treatments due to the problems with chemo (chemical) drugs.

ECT is a viable technique, whose efficacy depends on the electric field distribution and the magnitude. In this research, we explored the efficacy of needle and parallel plate electrode geometries for both normal and tumor breast models.

Our results indicate that the electric field intensity in the tumor (146V/cm) is less than that of the normal tissue (350-500V/cm), indicating the different electrical characteristics of the malignant and normal tissues and hence their susceptibility for electrochemotherapy.

The needle electrodes showed higher electric field intensities than the plate electrodes due to the shape and size of the electrodes used. They were also nonlinear for increased gap lengths.

The ac electric field intensities are lower (7-30%) than dc for the same voltage. This could be due to the reduction in charge accumulation due to the bipolar nature of the ac voltage applied.

Novel, large needle electrode arrays showed uniform field distribution as desired. These are more suitable for treating larger tumors, using reduced number of applications for a given tumor size, thus reducing treatment time and hence the patient sedation dose and time.

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