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By Poornima Agoramurthy

Entitled
Electric Field Analysis of Human Breast Tumors for Treatment by Electroporation

For the degree of Master of Science

Is approved by the final examining committee:

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ELECTRIC FIELD ANALYSIS OF HUMAN BREAST TUMORS FOR TREATMENT BY ELECTROPORATION

A Thesis

Submitted to the Faculty

of

Purdue University

by

Poornima Agoramurthy

In Partial Fulfillment of the

Requirements for the Degree

of

Master of Science

December 2011

Purdue University

West Lafayette, Indiana

To my family, for their boundless love and support.

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ABSTRACT

Agoramurthy, Poornima. M.S., Purdue University, December 2011. Electric Field Analysis of Human Breast Tumors for Treatment by Electroporation. Major Professor: Dr. Raji Sundararajan.

Breast cancer is a frequently diagnosed disease in women, second only to cancers of the skin. According to the American Cancer Society there were approximately 210,000 new cases of breast cancer estimated in 2010 in the US, 20 % of which resulted in death. With such a high rate of incidence, there is clearly a need for alternate treatments, especially for in-operable tumors and chemo- and radio-resistive patients. Electrochemotherapy, a method by which high intensity, short duration electrical pulses are used to temporarily open pores of cells to enhance uptake of drugs, is gaining popularity in drug delivery for cancer treatment.

Electric field distribution is critical for effective electroporation. This thesis aims at providing a model by which breast cancer tissues can be studied and analyzed for treatment by electroporation. Maxwell SV and 13,Ansoft software packages are used for simulation of electrodes and tumor tissues. Suitable electrode models are developed for treatment of invasive and in-situ breast cancer. Finite element analyses of these models demonstrate the electric field intensity and distribution in the tumors. These results will help in improving electrical pulse-mediated drug delivery techniques for cancer treatment.

CHAPTER 1. INTRODUCTION

1.1. Preview

Breast cancer is the cancer that originates in the tissues of the breast. There are mainly two types of breast cancer. Ductal carcinoma is the cancer occurring in the ducts of the breast. Lobular carcinoma, starting in the milk producing areas called the lobules.

Breast cancer is a frequently diagnosed disease in women, second only to cancers of the skin. According to the American Cancer Society there were approximately 210,000 new cases of breast cancer estimated in 2010 in the US, 20 % of which resulted in death (Facts and figures 2010, American Cancer Society). Common methods of treating cancer are surgery, chemotherapy, radiation therapy, immunotherapy, and monoclonal antibody therapy (Love and Linsey, 2005). Many powerful and promising drugs that have been developed to treat cancer have not been effective because of low efficiency, safety and side effects (Sundararajan, 2009). This necessitates novel alternate cancer treatment methods. Electroporation is a technique by which high intensity; short duration voltage pulses are applied to temporarily open up pores in the membrane of cells to allow transport of therapeutic materials including drugs, antibodies and genes [Heller et. al., 1996; Gehl and Geersten, 2000; Mir et. al., 1999]. Electrochemotherapy is the process when a chemo drug is injected followed by electroporation of the cell or tissue in order to absorb the injected drug. This technique was first investigated in the 1980's and 1990's,where high amplitude exponential and square pulses were used to improve the efficacy of *bleomycin*, an antitumor drug (Okino and Mohri, 1987; Mir et. al., 1991;

Belehradek et. al., 1991). Since then there is significant literature published on electrode configurations, dimensions and voltage values suitable for electroporation (Gothelf et. al., 2003). Recent clinical trials on a number of patients have shown that the treatment is highly efficient and has many advantages over traditional therapies (Campana et. al., 2009).

The efficiency of electroporation depends on a number of parameters such as applied voltage, electric field distribution, and electrode placement. Electric field distribution is the most dominant factor of all because it determines the response of cells and tissues to applied voltages. Hence in order to efficiently electroporate cells and tissues, it is important to understand the electric field magnitude and distribution that occur within body tissue. Finite element analysis is an efficient tool that can be used to study electric, magnetic field distributions and stresses in materials when subjected to an external stimulus. The present work aims at creating two and three-dimensional finite element models and studying the effect of applied voltages in breast tissues for a number of electrode configurations, such as parallel plate electrodes, and two and multi-needle electrode arrays. Various pulse parameters are investigated and the energy associated with electroporation is also analyzed. These results will help improve the understanding of electroporation and pulse mediated drug delivery techniques for cancers that are not receptive to conventional therapies.

1.2. Objectives

The overall goal of this research was to analyze the electric field distribution in normal and tumor human breast tissues and study the difference in the electrical

properties through finite element modeling and analysis. Towards this goal, the proposed work is to:

1. Develop suitable physical and electrical models for normal and tumor breast tissues.
2. Develop suitable electrodes to apply voltage to tissues.
3. Study electric field distribution in various tissues when external voltage is applied.
4. Find the best-suited electrode and tissue model for practical applications of electroporation.
5. Verify that electroporation is a non-thermal phenomenon (electrical and not thermal phenomenon).

1.3. Research Question

This thesis aims at answering the following research questions:

1. What is the electric field distribution in human breast tissues when an external voltage is applied to it?
2. How does the electric field distribution of tumor breast tissues differ from that of normal breast tissues?
3. Why are tumor tissues more susceptible to electroporation than normal tissues?
4. What type of electrodes is best suited for electroporation of human breast tissues?
5. How can electrodes be designed to treat large tumors?

6. Is electroporation an electrical or thermal phenomena?

1.4. Definitions

Electroporation – Also known as electropermeabilization, is the process of applying electric pulses to cells to temporarily open and create transient pores in the plasma membrane of cells ("Electroporation", n. d.).

Electrochemotherapy – Is when electroporation is used so that non-permeant particles such as drugs can pass through the cell membrane ("Electrochemotherapy", n. d.).

Electric field – The magnitude of the electric field at any given point is defined as the force exerted on a unit test charge of one coulomb at that point and the direction of the field is given by the direction of force ("Electric Field", n. d.).

Human Breast – The human breast is an organ, which is more developed and functional in females than males. Its main function is to produce milk after childbirth. The human breast may have up to 20 lobes and each of them has several lobules where milk is made. The lobes and lobules are connected by tubular structures called ducts, which carry milk to the nipple ("Breast", n. d.).

Lobular Carcinoma – Cancer originating in one of the lobules of the breast is called lobular carcinoma ("Lobular Carcinoma (Invasive and In Situ)", n. d.).

Ductal Carcinoma – Cancer originating in one of the ducts in the breast is known as ductal carcinoma ("Ductal Carcinoma In Situ (DCIS)", n. d.).

Finite Element Method – is a numerical technique used to find approximate solutions to partial differential equations and integral equations ("Finite Element Method", n. d.).

1.5. Organization

The introduction to the thesis and the objectives of this research are covered in Chapter 1 of this document. Chapter 2 explains and summarizes work done by previous and contemporary researchers throughout the world in the area of electroporation and finite element modeling of biological tissues and in particular human breast tissues. Chapter 3 deals with the framework and methodology of the research. The models created and parameters used for various models are explained under this section. Results, discussion and analysis are explained in detail in Chapter 4. Electric field distributions of various tissue models, comparisons and plots help understand nature of tumor tissues and their susceptibility to electroporation. Chapter 5 summarizes the research and lists recommendations for future work.

CHAPTER 2. LITERATURE REVIEW

This chapter summarizes research done in the field of electroporation and finite element modeling for breast cancer. A literature review in this area provides a background for the research thesis.

2.1. Breast Cancer

Breast cancer is the uncontrolled growth of cells in the breast, mostly occurring in women. The American Cancer Society estimated that the number of new breast cancer cases in the United States in 2010 was approximately 210,000 and the number for 2011 was estimated to be 230,480. Excluding cancers of the skin, breast cancer is the most frequently diagnosed cancer in women. Over the last few decades, breast cancer incidence has been increasing steadily. Breast cancer ranks second, after lung cancer, as a cause of cancer death in women. Approximately 40,000 deaths were estimated in both 2010 and 2011 due to breast cancer only (Cancer Facts and Figures, 2010, Cancer Facts and Figures, 2011; American Cancer Society). For most breast cancers, the etiology is not known but risk factors have been identified. Female gender, age, early menarche, late menopause, family history, genetic mutations and older age at first childbirth are the most common causes. Most of the breast cancers are invasive and are not confined to the region where they originated. Common methods of treating cancer are chemotherapy,

surgery, radiation therapy, immunotherapy, and monoclonal antibody therapy (Love and Linsey, 2005). Since there are not many strong modifiable risk factors for breast cancer, there is not much that can be done to prevent its incidence. However, effective treatment methods can help cure patients and reduce death rate due to breast cancer. Current treatment methods have many side effects and patient-response to the treatment cannot be predicted or guaranteed due to the nature of the treatment. This necessitates a new alternate treatment method with reduced side effects and more efficacies.

2.2. Electroporation

Electroporation is the phenomenon by which transient pores are created in the membrane of cells due to an increase in its conductance under the influence of an external electric field. The use of electric fields at certain parameters cause temporary permeabilization of cell membranes, allowing them to return to their normal state afterwards. The purpose of creating transient pores in the membranes is to allow foreign particles that would normally not pass through, to penetrate through it and enter the cell. These foreign particles could be genes, drugs, dyes and proteins (Gehl, 2003). The process is illustrated in Figure 2.1 where hydrophilic particles that normally do not pass through the cell membrane are allowed to enter the cell when a trans-membrane voltage,$V_m$causes creation of pores (Mechanism of Injury. Retrieved March 2011). As a result, reversible electroporation has a variety of clinical applications, such as introduction of drugs into cells, electrochemotherapy, gene delivery to tissues, and transdermal delivery of drugs and genes (Mir et. al., 2003). Electrochemotherapy is the

process when a drug is injected followed by electroporation of the cell or tissue in order to absorb the injected drug (Okino and Mohri, 1987; Mir et. al., 1991; Belehradek et. al., 1991, Gothelf et. al., 2003). This is a promising technique and can be an effective treatment for breast cancers that are not responsive to traditional treatment methods.

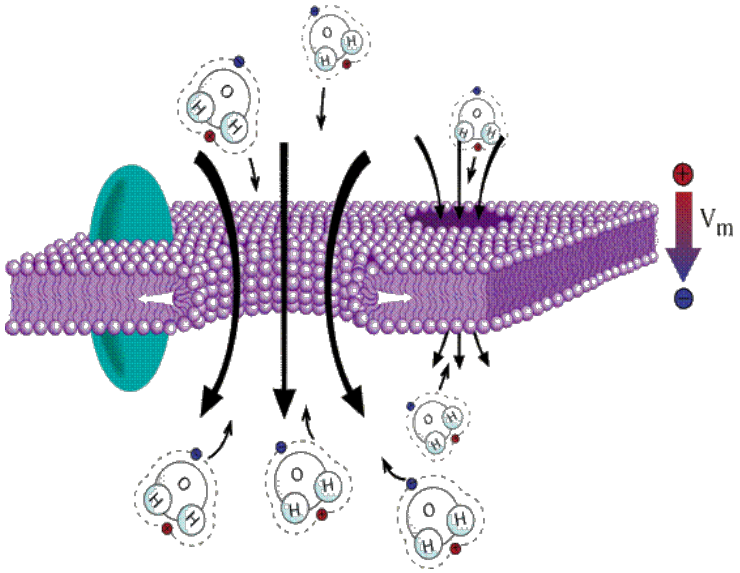


Figure 2.1. Pores created in cell membrane by electric pulses. (Mechanism of Injury. Retrieved March,2011)

2.3. Concept of Electric Field

In order to understand the phenomenon of electroporation, it is very essential to know the fundamentals of the electric field and its distribution in cells and tissues. The force exerted on a unit of positive charge is termed electric field. Electric field intensity in V/m is more commonly used to express the strength of an electric field and the direction of field is in the direction of the force. The electric field in a region can be computed by using Maxwell's equations of electrostatics as shown in equation (2.1) and (2.2):

$$\nabla \cdot E = \frac{\rho}{\epsilon_0} \qquad (2.1)$$

$$\nabla \times E = 0 \qquad (2.2)$$

where E is the electric field in V/m, ρ is the charge density and ϵ_0 is the permittivity of air.

The electric potential (in volts) defined as the work done in bringing a unit of positive charge from infinity to that point, can be derived from Maxwell's equation and is related to the electric field as shown in equation (2.3).

$$-\nabla \varphi = E \qquad (2.3)$$

where φ is the electric potential in volts.

2.4. Electrical Properties of Cells

As Steve Haltiwanger mentions in his work *Electrical Properties of Cancer Cells,* the ion concentrations on either side of the cell membrane are different causing a voltage difference across the membrane. The cell membrane is composed of a bilayer of lipids which acts an insulator and restricts movement of ions in and out of the cell. Sodium and potassium ions are maintained at different concentrations on either side of the membrane due to the selective permeability of the membrane, thus causing a membrane potential difference. The membrane potential difference helps in maintaining cell membrane permeability to a large variety of nutrients and controls energy production and synthesis of macromolecules. The membrane potential difference creates a strong electric field around the cell membrane (Haltiwanger, 2003). A healthy living cell has a membrane

potential of -60 to -100mV [Cure, 1991]. The electric field in a healthy cell can be as high as 10,000,000 to 20,000,000 V/m (Reilly, 1998; Brown, 1999).

When cancer arises, all regular mechanisms occurring in cells are interrupted. The electrical properties of a cancer cell are much different than of a healthy adult cell. Some of the characteristics of cancerous cells that affect its electrical activity are:

- Cell energy production is greatly reduced. Cancer cells are not efficient in energy production (Haltiwanger, 2003).
- Cell membranes of cancer cells have different electrochemical properties than that of a normal cell. Charge distribution also is totally different (Cure, 1991, 1995).
- Lipid and sterol content is different in cancer cells (Revici, 1961).
- Membrane potential and membrane permeability are altered in cancer cells. Sodium and water move into the cell and potassium, calcium and magnesium are transported out of the cell (Seeger and Wolz, 1990).
- Cancer cells have higher water and sodium content and lower potassium concentrations than a normal cell (Cone, 1970, 1975; Cope, 1978).

Due to the several changes that occur in a cancer cell, the electrical properties of a cancer cell are altered. The electrical conductivity and permittivity of cancer cells were found to be greater than normal tissues (Foster and Schepps, 1981). The change in electrical properties of cancer cells makes them more susceptible to external electric fields. Thus, electroporation, a phenomenon based on electric fields can be effectively used to treat cancer cells while normal cells remain less or un-affected. The trans-

membrane voltage induced when an external field is applied is given by equation (2.4) also known as steady state Schwan's equation (Schwan, 1957).

$$\Delta\psi_m = 1.5ERcos\theta \qquad (2.4)$$

where ψ_m is the voltage induced, *E* is the electric field, *R* is the radius of the cell and θ is the angle measured from the center of the cell with respect to the electric field. This is the voltage induced much after the onset of the electric field. The transient behavior in the initial few microseconds can be described by first-order Schwan's equation (Pauly and Schwan, 1959) as given in equation (2.5).

$$\Delta\psi_m = 1.5ERcos\theta\ (1 - e^{\frac{-t}{\tau_m}}) \qquad (2.5)$$

where τ_m is the time constant of membrane charging and is given by equation (2.6).

$$\tau_m = \frac{R\varepsilon_m}{2d\sigma_i\sigma_e/(\sigma_i+2\sigma_e+R\sigma_m)} \qquad (2.6)$$

where σ_i, σ_m and σ_e are the conductivities of the cytoplasm, cell membrane, and extracellular medium, $\varepsilon_m$is the dielectric permittivity of the membrane, *d* isthe membrane thickness, and *R* is the cell radius.

2.5. Pre-clinical and Clinical Applications of Electroporation

Since electroporation facilitates drug transport through the cell membrane, hydrophilic molecules that do not pass through the membrane normally are identified for electrochemotherapy. Two drugs have been identified to be effective when coupled with electroporation. Bleomycin, which is hydrophilic, could be potentiated 1000 times with electroporation (Cemazar et. al., 1998; Gehl et. al., 1998). Cisplatin, another drug with

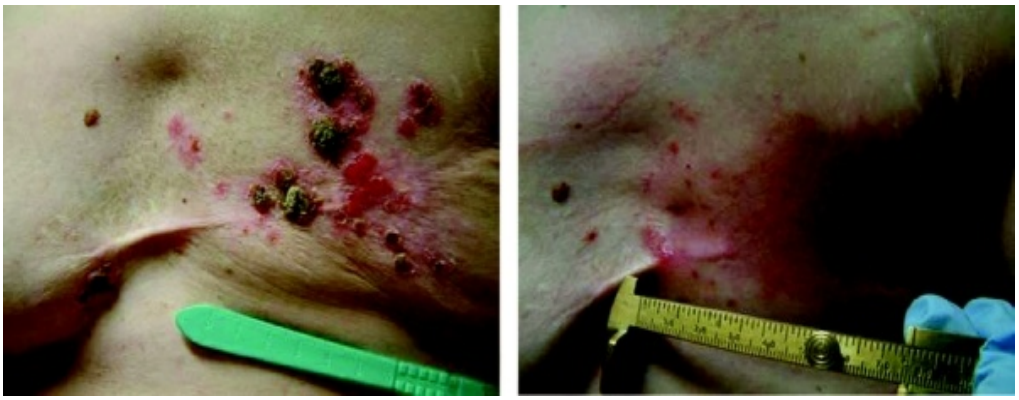
limited transport through cell membrane showed an80-fold increase in cytotoxity with electroporation (Sersa et. al., 1995).

Both drugs, bleomycin and cisplatin, have been tested in vivo and their effectiveness has been demonstrated in tumors. Electrochemotherapy has been successful in several animal models including mice, rats, rabbits, cats, dogs, horses and guinea pigs. Solid tumors in muscle, liver and brain were treated (Rols et. al., 2002; Mir et. al., 1995; Sersa 1995).

The first clinical study was done by Mir et. al. on tumors in head and neck of patients using bleomycin (Mir et. al., 1991). Over the past few years, several clinical trials have been performed on patients and have been proven successful (Gehl et. al., 2000; Belehradek et. al., 1993; Domenge et. al., 1996; Heller et. al., 1996; Rudolf et. al., 1995; Mir et. al., 1991).Belehradeket. al. treated 40 tumors in the head and neck of eight patients and observed about 57 % complete response (Belehradek et. al., 1993). Heller et.al. treated 18 tumors in six different patients. The tumors were malignant melanoma, basil cell carcinoma and one case of breast cancer. They could achieve 33 % complete response to electrochemotherapy (Heller et. al., 1996). Domengeet. al. treated 53 different tumors in seven patients and could achieve 11 % response. The tumors were in different locations: lung, head, neck, breast, salivary gland and cutaneous and sub-cutaneous metastatis (Domenge et. al., 1996). Gehlet.al. treated nine malignant melanoma tumors and achieved 100 % complete response to treatment (Gehl et. al., 2000).

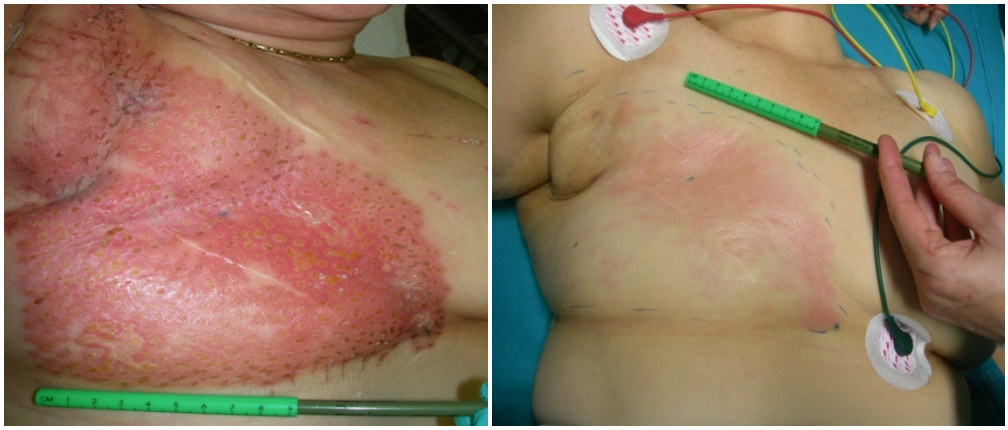
Electrochemotherapy has also been proven to be effective for breast cancer. Larkin et. al. used electroporation to treat 111 tumors in 30 patients and achieved 60 % complete regression. Figure 2.2 shows the image of a 52-year old woman being treated

for chest wall carcinoma four years after mastectomy. She did not respond to chemotherapy. Complete response was observed to electrochemotherapy after 2 months and there was no recurrence (Larkin et. al., 2007). Figure 2.3 shows another image of a woman recently treated for breast wall carcinoma in Italy by Dr. L. Campana. The figure shows the tumor before electrochemotherapy and its disappearance a few weeks after treatment. Campana et. al. treated 608 tumors in 52 patients out of which 174 were breast tumors. An outstanding success rate of 96 % was achieved by the group (Campana et. al., 2009).



Before After

*Figure 2.2.*Electrochemotherapy of chest wall carcinoma of a 52-year old woman(Larkin et. al., 2007).



Before After

*Figure 2.3.*Electrochemotherapy of chest wall carcinoma performed by Dr. Campana.

2.6. Electrodes and Pulse Parameters Used in Electrochemotherapy

2.6.1. Electrodes

Different types of electrodes have been identified for use in electrochemotherapy. The most common electrodes are parallel plate and needle electrodes. Parallel plate electrodes were the first electrodes introduced for tumor treatment but proved to be disadvantageous due to its limited use. They can be used only for cutaneous tumors and cannot reach deeper sites. Several configurations of needle electrodes were compared by Gilbert et. al. Figure 2.4 shows the different types of electrodes that were compared. They found that a circular array with six needle electrodes as shown in (E) and pulses delivered with 2x2 needles was the most efficient. Gehl et. al. developed an electrode configuration of a 2x4 needle electrode array with an inter-electrode distance of 4mm. They found that

this configuration yielded a homogenous electric field and the applied voltage could be reduced (Gothelf et. al., 2003).

Cliniporator is a commercially available electroporator used by around 100 doctors and researchers for electroporation. The various electrode types that are currently used along with the cliniporator are shown in Figure 2.5. Parallel plate electrodes (a) are 30mm in length with a 4mm gap. The 2×4 linear needle electrode array (b) and circular array (c) is available in three different lengths – 10mm, 20mm and 30mm and can be chosen according to the depth of the tumor. Finger configurations with orthogonal (d) and longitudinal (e) needles are available in 5mm and 10mm lengths (Cliniporator Technical Sheet, IGEA, March 2010).

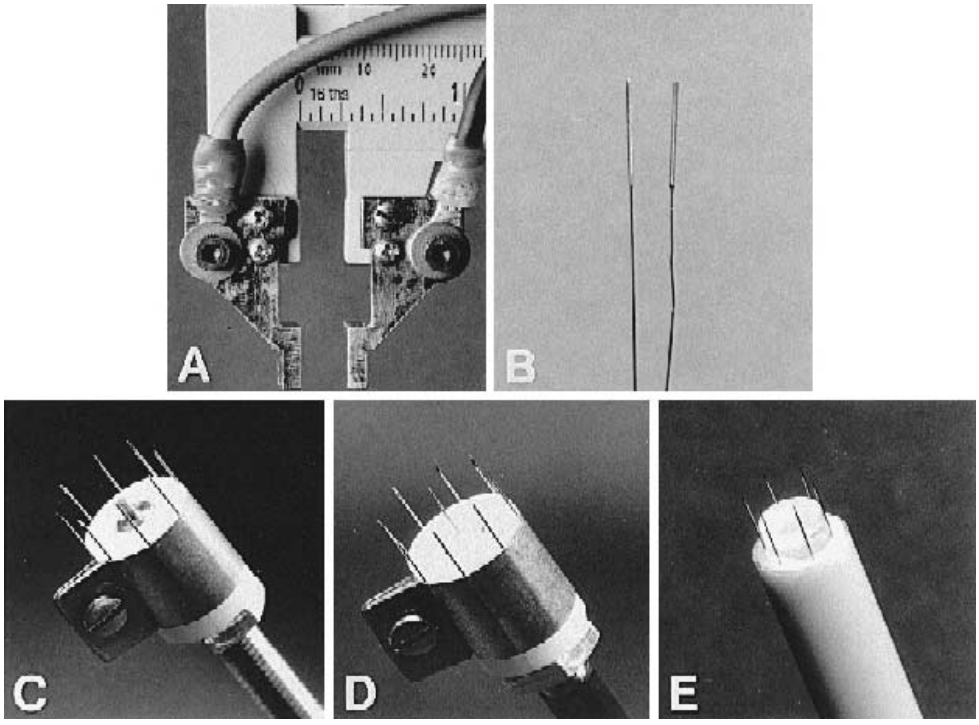


Figure 2.4. Electrode configurations used for electrochemotherapy treatment: parallel plate electrodes (A), needle pair electrodes (B), 8+1 solid electrode (C), 8+1 needle electrode (D),3×3 and 2×2 arrays (E) (Gilbert et. al., 1997).

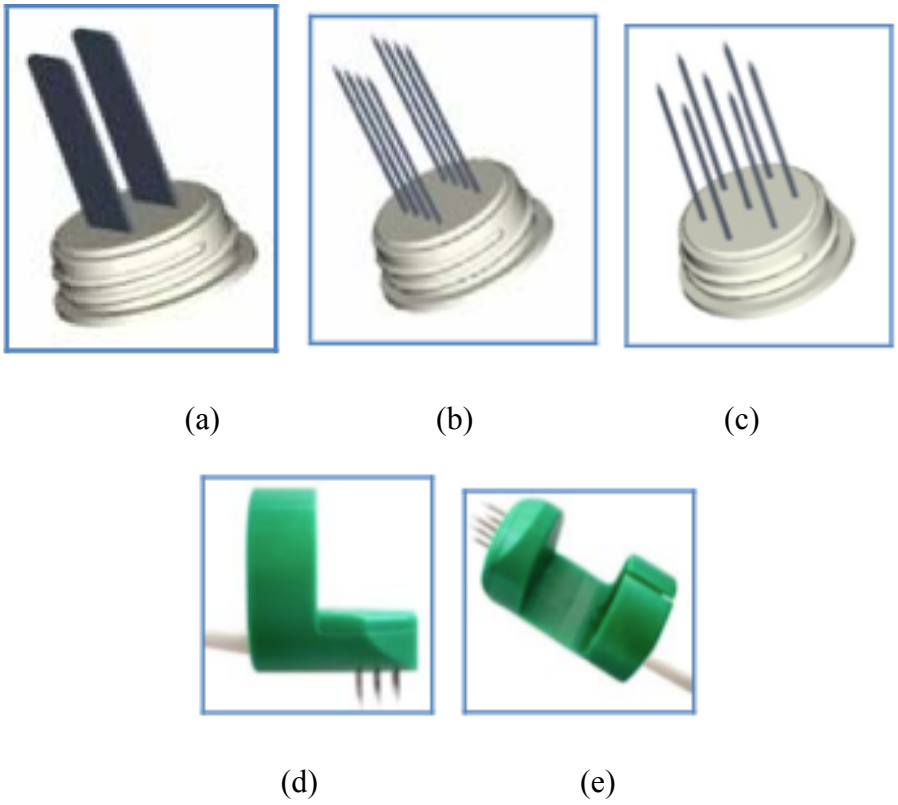


Figure 2.5. Electrode types available for commercial use – parallel plate (a), 2x4 needle electrode array (b), circular array (c), orthogonal electrodes (d) and (e). (Cliniporator Technical Sheet, IGEA, March 2010).

2.6.2. Pulse Parameters

The electric field in the tissue depends on the voltage applied, inter-electrode gap and the electrode configuration. The field strengths that have been used in actual clinical trials vary between 800 – 1300 V/cm depending on the type of electrodes. Square wave voltage pulses with duration of 100μs and 1Hz frequency are typically used. The number of pulses is 4,6 or 8 for every run (Mir et. al., 1991; Gehl et. al., 2000; Campana et. al., 2009; Larkin et. al., 2007; Belehradek et. al., 1993; Domenge et. al., 1996; Heller et. al., 1996; Rudolf et. al., 1995).

2.7. Advantages of Electrochemotherapy

Several in vitro, in vivo and clinical studies that have been performed suggest that electrochemotherapy can be an effective treatment for breast cancer. Moreover, electrochemotherapy has many advantages over conventional therapies. They can be summarized as (Sersa et. al., 2003, Gehl et. al., 2000; Mir et. al., 1991; Belehradek et. al., 1993):

- Quick, easy, inexpensive technique.
- No side effects.
- Can be performed on an outpatient basis.
- One time treatment.
- No post-treatment medication.
- No special dressing required.
- Treatment can be performed in any part of the body.
- Several types of cancers all over the body have been treated.

2.8. Thermal Effects of Electroporation

Electroporation techniques primarily focus on optimizing pulse parameters so that maximum area of tissue is electroporated and minimum damage occurs to surrounding tissues (Miklavcic et. al., 2000). While electroporating tissues and designing protocols, secondary effects arising from electrical currents need to be considered. One of the most important effects to be avoided is Joule heating. (Davalos et. al., 2003). Joule heating is the process by which passing current through a conductor releases heat. For

electroporation applications, a temperature rise below 50 degree centigrade in the tissue is considered not harmful. The equation for determining temperature rise due to Joule heating is given in equation (2.7) (Miller et. al., 2005).

$$\Delta T = \frac{tE^2}{r\rho c_p} \qquad (2.7)$$

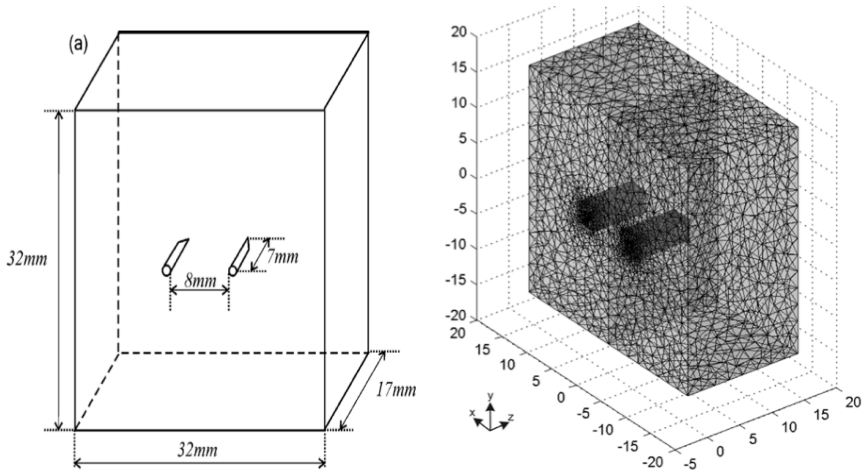
where ΔT is the temperature rise in degree centigrade, *t* is the pulse length that causes the temperature rise, *E* is the electroporation voltage gradient, *r* is the resistivity of the medium, ρ is the density and c_p is the specific heat of the medium.

2.9. Finite Element Modeling

A real system can be represented using a mathematical model and defined using a set of variables and equations. The aim of such a model is to understand the given system, explain some of the phenomenon associated with it and help in designing the system itself. Numerical methods are often used to model biological systems because of their complex and intricate nature. Finite element modeling is one such numerical method, which has been a powerful tool to explain the complex processes in biological systems (Rubinsky, 2010). Previous studies have indicated that numerical models of cell and tissue electroporation have been useful to describe the processes that occur in them and for evaluation and optimization of various parameters. Modeling has been used to improve electrode design and placement and in the planning of treatment. (Semrov and Miklavcic, 1998; Brandisky and Daskalov, 1999; Miklavcic et. al., 2000; Dev et. al., 2003; Miklavcic et. al., 2006). The effect of tissue characteristics and electrical parameters on electrical field distribution have also been studied and analyzed. New

experiments can be designed and planned at lower costs since experimental conditions can be evaluated by modeling (Semrov and Miklavcic, 2000).

Figure 2.6shows a finite element model created by Sel et. al. for their electric field studies on liver tissues. Two needle electrodes are inserted for the application of voltage in a block of tissue. Figure 2.6a shows the model developed. The software, in this case FEMLAB, generates a mesh in the entire model in order to compute the required parameters for the entire region as shown in Figure 2.6b (Sel et. al., 2005).

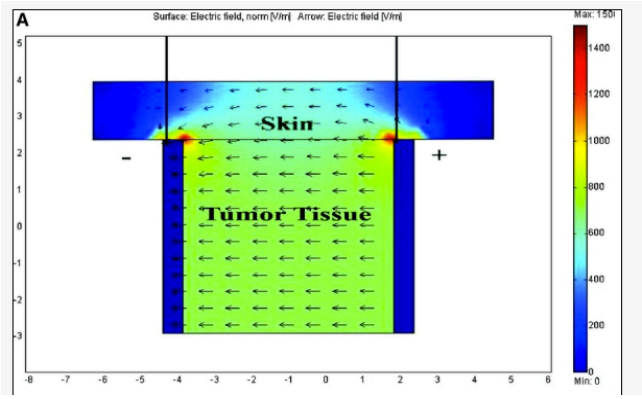


(a) (b)

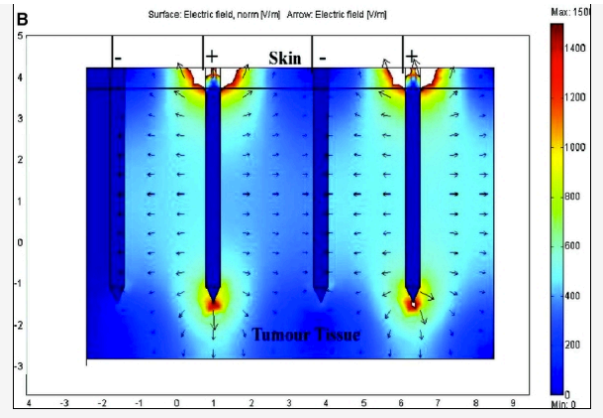
*Figure 2.6.*Finite element model (a) and mesh generated (b) for block of liver tissue with electrodes (Sel et. al., 2005).

The same software was used by Larkin et. al. to study electric field distribution in tumor tissues. They compared electric fields in tissues for different electrode types, namely parallel plate and needle electrodes. Figure 2.7a shows the electric field distribution obtained in case of parallel plate electrodes. Figure 2.7b shows the electric field in case of needle electrodes when a voltage of 1400 V/cm is applied. Plate

electrodes generated a homogenous electric field where as needle electrodes show a marked reduction in field away from the tips (Larkin et. al., 2007).



(a)



(b)

Figure 2.7. Electric field distribution of tumor tissue with parallel plate electrodes (a) and needle electrodes (b) (Larkin et. al., 2007).

Research on electroporation techniques and numerical methods reveal that finite element analysis is an effective tool to study electric field distribution in tumor tissues and explore the area of electrochemotherapy. Various softwares are available to develop models and carry out simulation studies. Modeling and simulation makes experimentation more effective and reliable.

2.10. Summary

Recent statistics suggest that breast cancer rates are high and there is a need for alternate anti-tumor treatments. Electroporation has proven to be an efficient technique for cancer treatment and has evolved in the past few years. Recently, clinical trials of electrochemotherapy materialized and researchers have been seeing positive results. Most of the cancers that have been electroporated have been cancers of the skin, head or neck. Electrochemotherapy can be a good alternative treatment for breast cancer in patients not responsive to conventional therapies. Since electroporation specifically for breast tissues have not been explored, this thesis aims at studying electric field distribution of breast tissues so that treatment methods for breast cancer can be improved.

The concept of electric field and electrical properties of cells are discussed to explain their characteristics that are favorable for electroporation. Various studies indicate that tumor tissues have characteristics different from normal tissues, which make them susceptible to electrochemotherapy. However, no research has been done to compare tissues of the breast in particular and how breast lobules and ducts respond to external voltages. This thesis deals with breast lobules and whole breast tissues and their response to DC and AC voltages for different electrode configurations. Numerical methods have been used as an effective tool to model and study biological tissues. Since electrochemotherapy for breast cancer is still evolving, finite element modeling of breast tissues will help in designing electrodes and planning treatment.

Patients who have been affected with breast cancer have to remove their breast in most cases when the cancer has spread to large areas. Even after breast removal, chest wall carcinoma occurs. To avoid spreading of breast cancer and chest wall carcinoma,

electroporation can be implemented as a treatment in early stages of breast cancer. Results from this thesis will help in understanding of electric field distributions in breast tissues so that electrochemotherapy can become a feasible and wide-spread method of treatment.

CHAPTER 3. FRAMEWORK AND METHODOLOGY

For the purpose of this research, various models were developed to study electric field distribution of normal and tumor breast tissues. Maxwell Student Version and version 13, commercially available software was used for finite element modeling and analysis. This chapter introduces the framework adopted for Finite element analysis, software details and the steps involved in developing the model and running simulations. The tasks involved in the research and the various models and parameters used are discussed under methodology.

3.1. Framework

3.1.1. Finite Element Method

The finite element method is an effective numerical technique used to find approximate solutions to partial differential equations. In this method, the entire region consists of a complex system of points called nodes, which connect together to form a grid. The grid, called the mesh has defined properties. The mesh is created according to the anticipated stress in the materials. Higher stress regions will have a higher number of nodes and a compact mesh. The mesh is generated automatically by the software used.

Finite element analysis has proven to be beneficial in computation of electric field inside biological systems (Semrov et. al., 1997; Miklavcic et. al., 1997). In this research, a finite element model of the human breast tissue along with electrodes was developed and electric field distribution was plotted for various models, varying different parameters. The entire model was treated as a domain, which is divided into segments. A mesh was created and the electric field plotted for the entire region. The voltage and electric field plots were obtained after solving a set of partial differential equations. The partial differential equations governing this model are given below.

The electric potential is computed by the partial differential equation,

$$\nabla . \varepsilon_r \varepsilon_0 \nabla \phi(x, y) = -\rho(x, y) \qquad (3.1)$$

where, ϕ (*x, y*) is the electric potential;ε_r is the relative permittivity, and can be different for each material, ε_o is the permittivity of free space, 8.854 x 10^{-12}F/m and ρ (*x,y*) is the charge density.

After the solution for the potential is generated, the system automatically computes the E-field using the relation,

$$E = -\nabla \phi \qquad (3.2)$$

where, *E* is the electric field and ϕ (x, y) is the electric potential.

3.1.2. Software

Maxwell Student Version (SV), Version 3.1.04, freely available software by Ansoft Corporation was used to create models and run two-dimensional simulations. Maxwell 13, the improved and complete version of the software, was used for further

two-dimensional analysis and also used for three-dimensional modeling and analysis. All simulations were run on Windows 7 on a 32-bit, 3GHz, Intel Dual core processor. Simulation time was about 5 minutes for each electrostatic analysis. Mesh generation was automatic, with every model consisting of approximately 5000 elements. The mesh was generated in such a way that curved and higher stress regions have more nodes than other low stress areas.

3.1.3. Process

The systematic approach used in order to develop models and simulate them is described in the form of a flowchart as shown in Figure 3.1. The structure of the human breast tissue is to be well understood before creating an electrical model. Hence, a study on the anatomy of the breast was done as the first step. Once the size and shape of tissues are known, basic two-dimensional models were developed to represent breast lobules and electrodes. From previous literature, electrical parameters of normal and tumor tissues weredetermined. The dimensions of tissues and electrical parameters used for all models are listed later in this chapter. With the model and parameters entered in the software, boundary conditions were set. Neuman and Dirichlet conditions were used for electrostatic simulations in Maxwell. Automatic meshing was available for all the models created. A region of interest, which encloses the entire model, was marked. The analysis was set up specifying the error margin to 5 %. The above stated steps were verified and simulations were run. Once the simulation is complete, voltage distribution and electric field distribution were plotted for the model. Values of the electric field at specific points

of interest were recorded. Tumor models were developed in a similar way. The basic model shape remains the same, but electrical parameters vary since their electrical characteristics are different from normal tissues. Simulation and analysis were run for normal and tumor tissues and compared. Once breast lobules were compared and analyzed, the full breast is designed. When tissue design was completed, the focus was on design of electrodes. Electric fields for different electrode shapes and sizes were compared and the best electrode design was sought for, from a practical perspective. Graphs were plotted where necessary to illustrate the difference in characteristics.

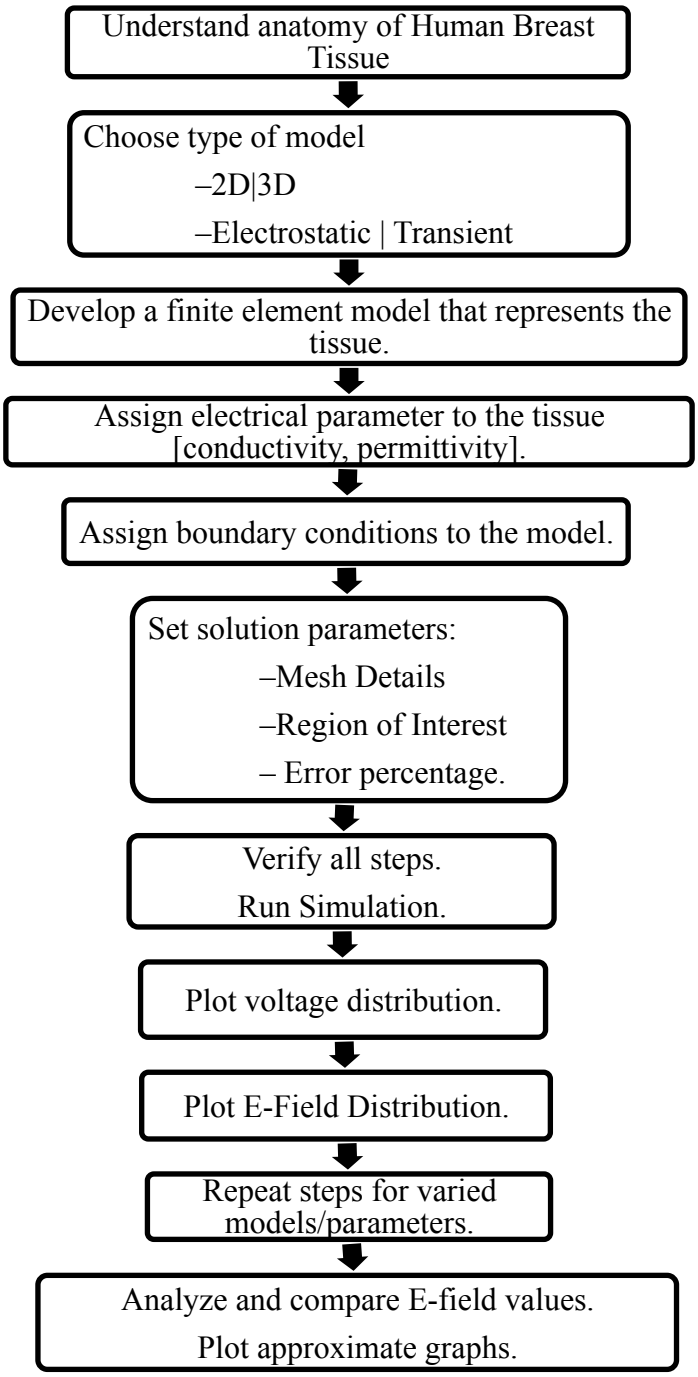


Figure 3.1. Flowchart illustrating process of finite element analyses of tissues.

3.2. Methodology

The research project was broken down into several tasks, each of which discusses an aspect of electroporation. The effect of tissue shape, electrode type and position, type of source, layers of fat and skin were illustrated with simulation results and analysis. The tasks that outline the research project are listed in this section.

3.2.1. Modeling of Breast Lobule and Duct

The human breast is made up of several lobules and ducts. Cancer can originate in any region and spread fast to neighboring tissues. Since lobules have a curved structure, the electric field distribution was anticipated to be different in them than usual. This section involved electric field analysis in the lobules of human breast. Results obtained will benefit treatment planning for lobular carcinoma.

Task 1: Developing a 2-dimenional model of the lobule and duct in a human breast. Comparison of electric field distribution of normal and tumor lobules.

- As the first step in the project, this task helps identify the difference between a normal and tumor tissue. The reason why electroporation is possible is because of the difference in characteristics between normal and malignant tissues.

Task 2: Introduction of fat and skin layers to the lobule to observe effect of surrounding tissues on electric field distribution.

- Considering real life scenario, breast tissues are surrounded by fat and have a layer of skin over it. Though we are concerned about the breast tissue mainly, this

step helps identify the effect of the surrounding tissues while we electroporate breast tissues.

Task 3: Study difference in DC and AC pulses on lobule field distribution.

- The electric field in the tissue depends on the type of voltage source. This step helps identify the difference in electric field in tissues due to DC and AC sources.

3.2.2. Modeling of Human Breast

Though modeling of lobules and ducts helps study electric field in specific regions of the breast, it is necessary to understand the electric field distribution in the breast as a whole. This section outlines the various tasks involved in analyzing electric field in breast tissues and the various factors it is dependent on.

Task 4: Developing a 2-dimensional model of a human breast as a whole. Study effect of electrode types – Parallel plate and Needle electrodes on breast tissue.

- A model of the entire breast helps see the tumor as a part of a bigger tissue. This model will benefit practical applications.

Task 5: Compare electric field distribution of normal and tumor breast tissues.

- This task compares a normal breast tissue to tumor tissues and analyze their electric field distributions.

Task 6: Study effect of electrode type and position

- This task compares external parallel plate to internal needle electrodes and studies their differences.

Task 7: Compare effect of DC and AC sources

- Effect of source type is analyzed in this step. Though the magnitude of voltage applied is same, the type of source makes a significant difference in electroporation.

Task 8: Study the effect of tumor shape, size and location.

- Tumors can be in any part of the breast and they can be of different sizes and shapes. A single size and shape is assumed for most of the studies. This task analysis the electric field distribution in different locations, sizes and shapes of tumors in the breast.

Task 9: Parametric studies

- The two main parameters that are significant in electric field models are conductivity and permittivity. This task identifies the effect of each of the parameters individually.

Task 10: Develop suitable multi-electrode array for large tumors.

- Tumor sizes can vary from a few millimeters to centimeters. This task is used to analyze electric fields in large tumors so that multi-electrode arrays can be introduced instead of single electrode – multiple treatments.

Task 11: Electrode polarity

- Verify the effect of changing polarity of electrodes on the electric field distribution of tissues.

3.2.3. Electrode Configurations

Task 12: Study electric field distribution of parallel plate and needle electrodes in 2D

- This step focuses on the electrode design more than the tissue. Tissue is a developed as a single block in the software and different electrode types are compared.

Task 13: Study electric field distribution of parallel plate and needle electrodes in 3D.

- Two-dimensional studies done in the previous step are re-done in three-dimension. Electrode dimensions in 3D will help obtain accurate field distribution in the entire tissue area.

Task 14: Develop multi-electrode array in 2D and 3D for treatment of large tumors.

- Multi electrode arrays and the electric field distribution in tissues are studied in two and three-dimensional models.

Task 15: Electrode polarity check

- Verify the effect of changing polarity of electrodes on the electric field distribution of tissues.

3.2.4. Thermal Calculations

Task 16: Thermal calculations are done based on heat transfer and energy balance equation to prove that electroporation is a non-thermal phenomenon.

3.3. Modeling in Maxwell

Various models were developed to study electric field distribution through finite element analysis. The shape of tissue and electrode is different for each study. The models developed for this project are listed in this section. For analysis of tumor tissues, two-dimensional models were used. For electrode design, two and three-dimensional analysis was carried out in the models.

3.3.1. Understanding Human Breast Anatomy

The breast lies between the second and sixth ribs of the human body and consists of 15-20 lobes that radiate from the nipple. Lobes are surrounded by fat and connective tissues. Each lobe further consists of several lobules, which are the milk producing regions. Lobules are the basic structural units of the breast and have a lining of epithelial cells. Milk is produced in the lobules and is carried to the nipple through ducts (Cancer Detection Programs: Every Woman Counts, 2010). The anatomy of the human breast is shown in Figure 3.2.

Many of the cancers in the breast first occur as non-invasive and then later become invasive. The most common types of breast cancer are:

- Non-invasive Breast Cancer
    - Ductal Carcinoma in situ (DCIS) – refers to uncontrolled growth of cells confined to breast ducts.
    - Lobular Carcinoma in situ (LCIS) – abnormal changes in the cells that line lobules or lobes.

- Invasive Breast Cancer
    - Invasive ductal carcinoma (IDC) – also called infiltrating ductal carcinoma, cancer cells penetrate through walls of ducts and spread in surrounding breast tissue
    - Invasive Lobular Carcinoma (ILC) – extends to surrounding adipose and connective tissues from the lobules. This type of cancer is very difficult to detect.

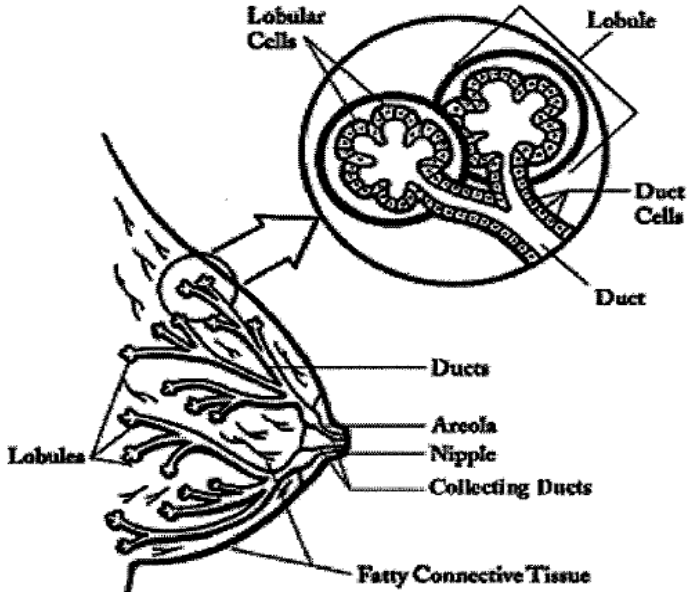


Figure 3.2. Human breast anatomy.
(Non invasive breast cancer (2011). *Saint Francis Breast Health Services.* Retrieved on July, 2011)

3.3.2. Modeling of Breast Lobule and Duct

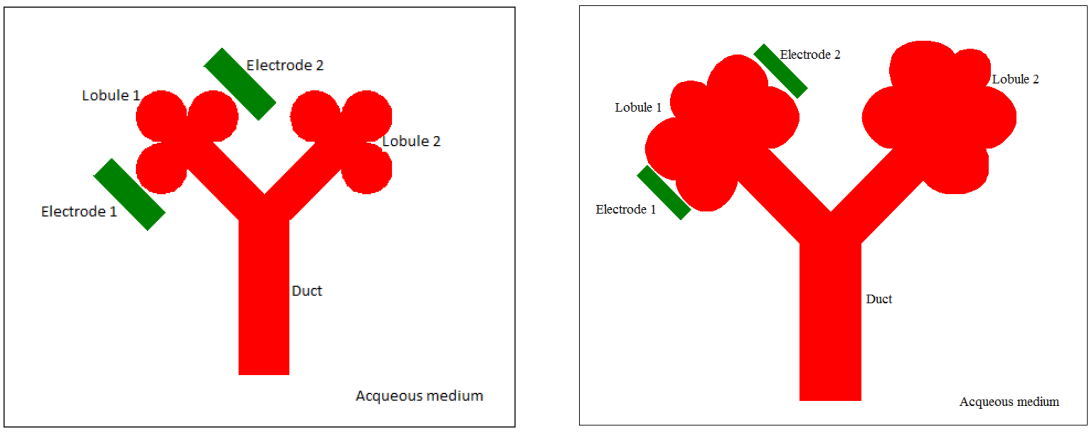
3.3.2.1. 3-segment Lobule

The 3-segment lobular model was developed in order to study cancers that originate in the lobules of the breast. The finite element model shown in Figure 3.3acan be viewed as a representation of in-situ and invasive lobular carcinoma. The figure shows two lobules, lobule 1 and lobule 2. For a cancer that originates at lobule 1, electrodes are placed on either side of the lobule and electric field distribution is studied after application of voltages at the electrodes. Electrode 1 is the positive terminal and electrode 2 is grounded. Dimensions of tissue and electrodes are given in Table 3.1. Layers of fat (20mm) and skin (2mm) are included in the model to make it closer to reality. The model with fat and skin layers included is shown in Figure 3.4a.

3.3.2.2. 5-segment Lobule

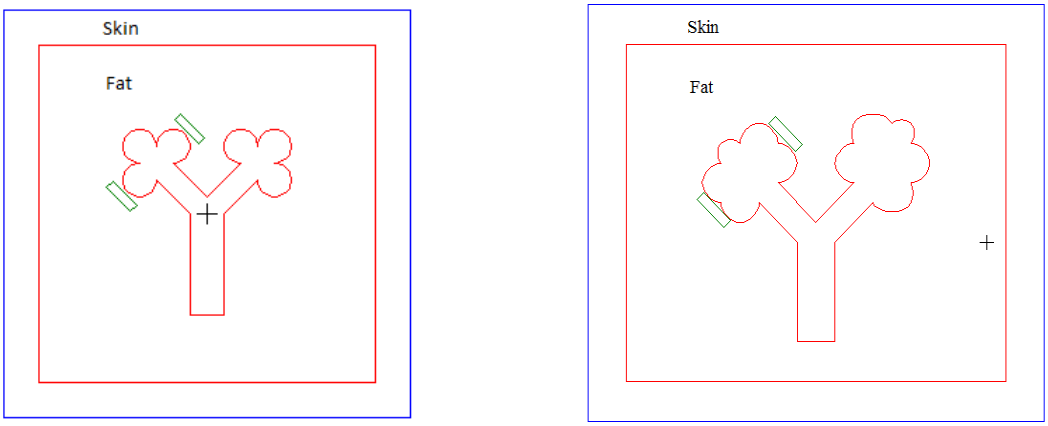
An improved version of the above 3-segment model is the 5-segment lobular model developed to realistically represent the actual physiology of the human breast lobule. Figure 3.3b shows this configuration, which is more representative of the anatomy in Figure 3.2. The rest of the model details remain the same as the three-segment lobule model. The number of elements in the model is increased due to the increased curved area in segments and the mesh is more intricate. The results obtained in this case are more accurate. Dimensions of electrodes and tissue are given are the same at the 3-

segment lobule listed in Table 3.1.The model with fat and skin layers included for the 5-segment breast lobule is shown in Figure 3.4b.



(a) (b)

*Figure 3.3.*Electric-field model of 3-(a) and 5-(b) segment breast lobule.



(a) (b)

Figure 3.4. Electric-field model of 3-(a) 5-(b) segment breast lobule with fat and skin layers.

Table 3.1. *Dimensions of tissue and electrodes for lobule and duct model*

Component	Dimension (mm)		
	Length	Breadth	Radius
Duct	12	4	-
Ductile	5.6	2	-
Lobule	-	-	4.24
Electrode	4	1	-

3.3.3. Modeling of Human Breast

Modeling of the entire human breast will help study electric fields in tumors that are present in the breast and have spread significantly. These can be any type of cancer – in situ or invasive, lobular or ductal. When cancerous cells have spread significantly and grown beyond their region of origin, tumor sizes increase and are more difficult to treat. Depending on the tumor size, appropriate electrode configurations are selected. Various tumor sizes and suitable electrode arrays are shown in this section. Dimensions of all model components are listed in Table 3.2.

Table 3.2. *Dimensions of model components in model of human breast*

Model Component	Length x Breadth (cm x cm)	Diameter (cm)
Parallel plate electrode	2.5 x 0.5	-
Needle electrode	-	0.2
4x2 Needle Electrode array	1.4 x 0.6	-
4x4 Needle Electrode array	1.4 x 1.4	-
Breast Tissue	-	7
Tumor	1 x 0.4 (ellipse)	-
Large Tumor - 1	2 x 1 (ellipse)	-
Large tumor - 2	-	2

3.3.3.1. Normal Breast Using Parallel Plate Electrodes

Figure 3.5 represents a normal human breast tissue. The shape of the tissue is semi-circular so that it is similar to actual physical conditions. Electrodes are parallel plate electrodes, placed on either side of the breast. Voltage is applied at electrode 1 where as electrode 2 is grounded. This model is used to study electric field distribution of a normal breast so that values obtained with tumor tissues can be compared.

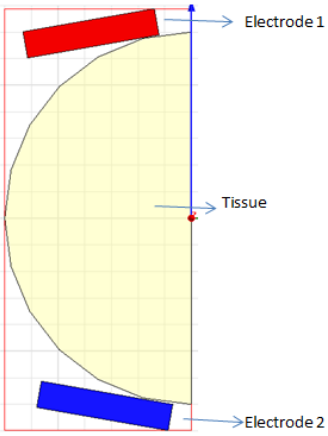


Figure 3.5. Electric field model of normal human breast tissue.

3.3.3.2. Breast with Tumor Using Parallel Plate Electrodes

The Figure 3.6 represents a human breast with tumor present. Parallel plate electrodes placed externally are used to apply voltages. The electrical characteristics of normal tissues and tumor tissues are different and will cause changes in electric field distribution.

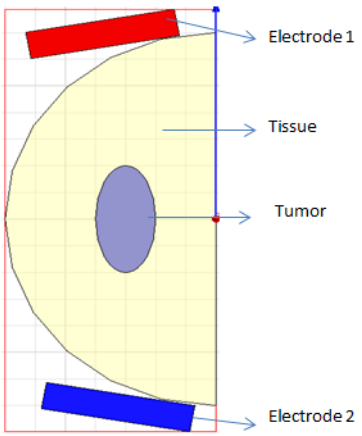
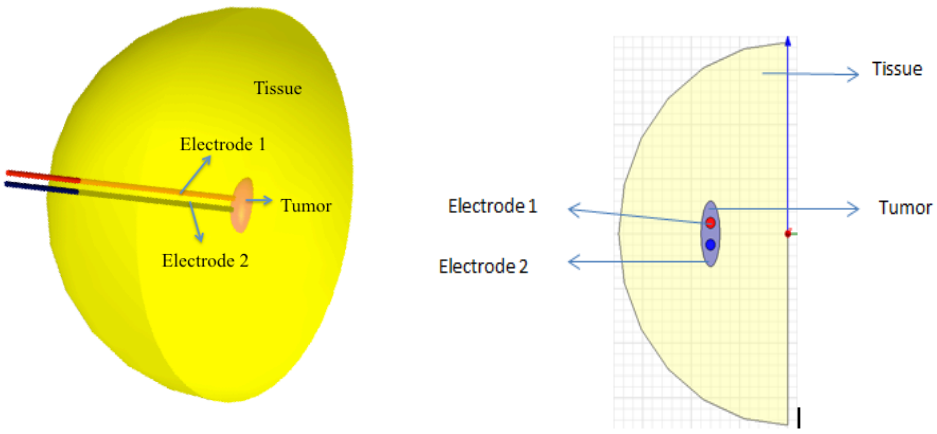


Figure 3.6. Electric field model of human breast tissue with tumor.

3.3.3.3. Breast with Tumor Using Needle Electrodes

The model of breast with tumor shown in Figure 3.7 is used to study the electric field distribution using needle electrodes. The needle electrodes are placed internally at the tumor site. The dimensions of needle electrodes are much smaller (2mm) than the parallel plate electrodes (2cm) and the gap between electrodes is also reduced since it covers only the tumor region and not the entire tissue. Figure 3.7a shows the 3D image of how the needles are placed exactly in the tumor of the breast tissue. Figure 3.7b is a planar slice of the 3D figure. All simulations are run on the 2D model as the model is axis symmetric and the electric field would be the same across all planes.

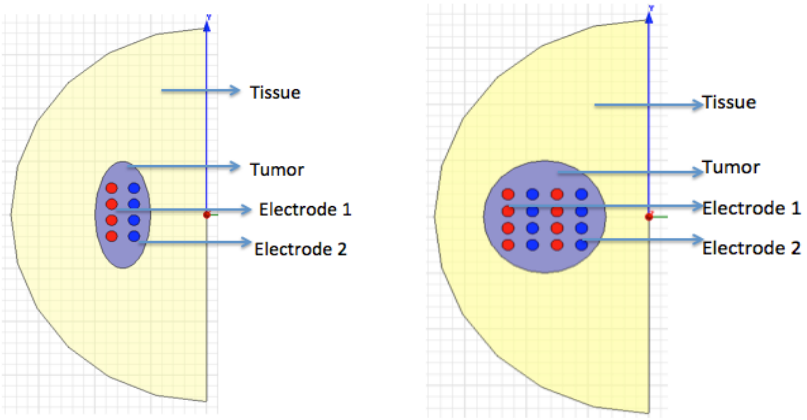


(a) (b)

*Figure 3.7.*3D (a) and 2D (b) Electric field model of human breast with tumor and needle electrodes.

3.3.3.4. Multi-needle Electrode Arrays for Larger Tumors in Breast

Tumor sizes can vary from a few millimeters to a few centimeters. Tumors that were only in the breast lobule model were in the range of a few millimeters and the tumor in breast was about 1 cm. Lager tumors (>= 2cm) can also occur in the breast. After removal of infected breast, cancer can also occur in the chest wall and is called chest wall carcinoma. Tumors in the breast and chest wall can be as large as 5 cm of sometimes even larger and at multiple locations. Electrode arrays are used instead of a single pair of electrodes, for larger tumors. Depending on the tumor size, the size of the electrode array is determined. Figure 3.8a and b show larger tumors. The tumor size and electrode dimensions are listed in Table 3.2.



(a) (b)

Figure 3.8. Electric field model of human breast with tumor with 8-needle (a) and 16-needle (b) electrode array.

3.3.4. Electrode Configurations in 3D

The efficacy of electroporation depends on electrode geometry and type. In order to study the electric field distribution in the entire area, three-dimensional models were developed. The analysis of electric field distribution has been done in two and three-dimensional modes. The tissue is assumed to be a rectangular block and electric field distributions due to various electrode sizes and shapes are studied. Table 3.3 lists the names of components in the model and their labels and Table 3.4 shows the dimensions of these components.

Table 3.3. *Names of Model Components for electrode design*

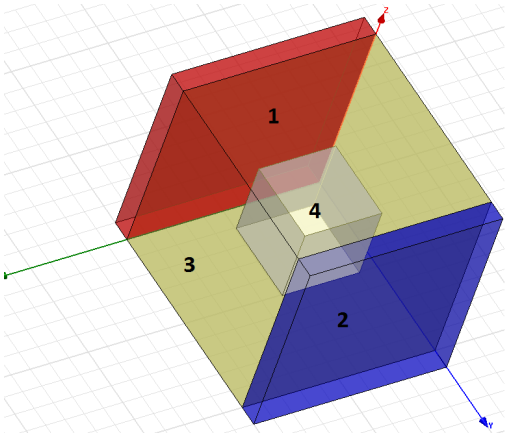
Name of Component	Number
Positive electrode	1
Negative electrode (grounded)	2
Tissue	3
Tumor	4

Table 3.4. *Dimensions of model components for electrode design*

Model Component	Length x Breadth (mm x mm)	Height (mm)	Diameter (mm)
Parallel plate electrode	10 x 1	10	-
Needle electrode	-	7	1
Tissue	10x10	10	-
Tumor	5x5	5	-
Large Tumor	14x10	10	-

3.3.4.1. Parallel Plate Electrodes

Figure 3.9shows the model of a tumor within a normal tissue. Parallel plate electrodes are placed on either side of the tissue for application of voltage. Since parallel plate electrodes can only be places externally, they are placed on either side of the normal tissue.

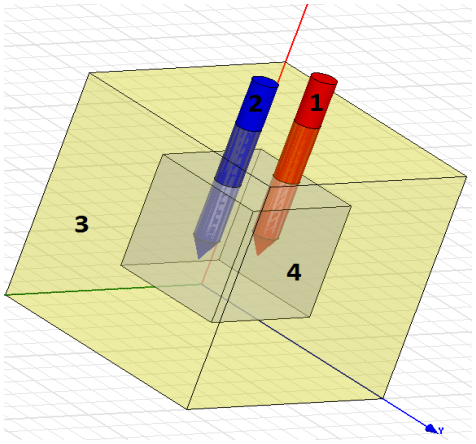


1	Electrode 1
2	Electrode 2
3	Tissue
4	Tumor

Figure 3.9. Electric field model of tumor and tissue with parallel plate electrodes

3.3.4.2. Needle Electrodes

Figure 3.10 shows the model of tissue and tumor with needle electrodes inserted in the tumor. The needles are inserted right into the center of the tumor so that the drug is targeted mostly to the tumor.

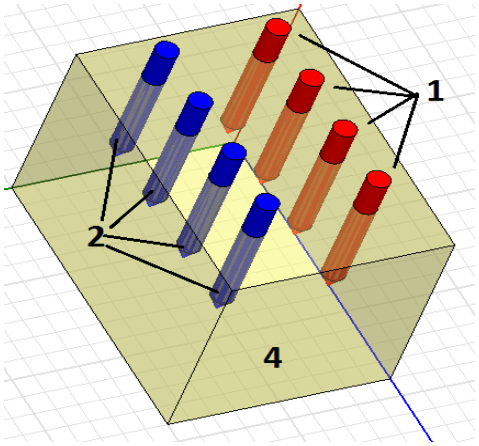


1	Electrode 1
2	Electrode 2
3	Tissue
4	Tumor

Figure 3.10. Electric field model of tumor and tissue with needle electrodes

3.3.4.3. Multi-needle Electrode Array for Large Tumors

For cancers such as chest wall carcinoma and melanoma, tumor areas are very large and using a single pair of electrodes may not be very efficient. Therefore, for large areas, multi-needle electrode arrays are used, in order to save treatment time and patient sedation time. Figure 3.11 shows a large tumor with a 4x2 needle electrode array. One column of electrodes is positive and the other column is grounded. The needle diameter is 2mm with a 4mm inter-electrode gap, similar to single pair of needle electrodes. The gap between adjacent rows of needles is 2mm. 8-needle electrode arrays similar to the model shown in Figure 3.11 have been used recently (Gothelf et. al., 2003).



1	Electrode 1
2	Electrode 2
4	Tumor

Figure 3.11. Electric field model of tumor with multi-needle electrodes.

3.3.5. Tissue and Electrode Parameters

The electrical characteristics of cancer cells are different from normal cells (Haltiwanger, 2003). The main properties that are required for modeling and analysis are relative permittivity and conductivity of materials. The properties that are used in all of the models in this research thesis are summarized in Table 3.5. (Wilke et. al., 2005; Chaudary et. al., 1984).

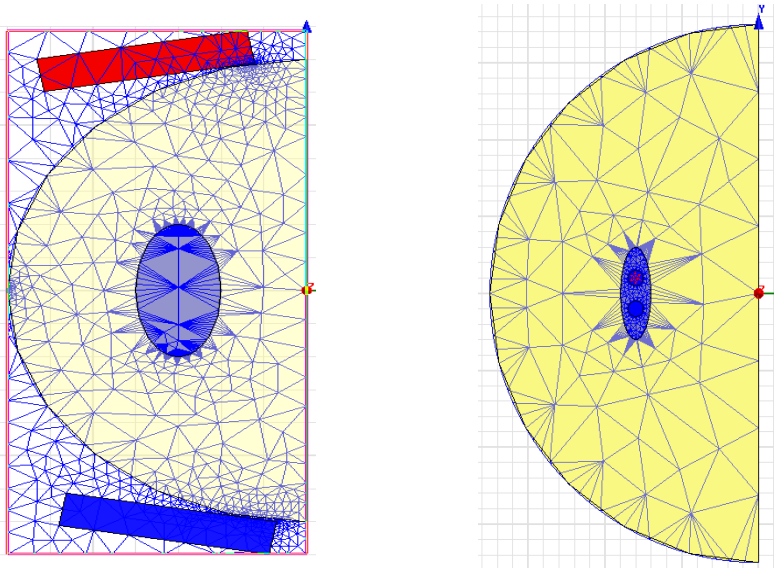
Previous studies indicate that 800-1300 V/cm is the required electric field for electroporation. For the purpose of this thesis, 1200-1300 V/cm is used for simulation of breast tissue models (Mir et. al., 1991; Gehl et. al., 2000; Campana et. al., 2009; Larkin et. al., 2007; Belehradek et. al., 1993; Domenge et. al., 1996; Heller et. al., 1996; Rudolf et. al., 1995). Parallel electrode gaps are dependent on the thickness of the tissue between the electrodes. Needle electrodes are placed with a gap of 4mm between them, which is in line with previous literature (Gothelf et. al., 2003).

Table 3.5. *Model Parameters*

Tissue Type	Parameters	
	Rel. Permittivity	Conductivity (/ohm.m)
Normal Tissue	200	0.4
Cancer Tissue	1000	2
Fat	15	0.2
Skin	33.5	0.7

3.4. Mesh Generation

After modeling and setting up of parameters, the software generates a mesh. The software that was used generated mesh automatically. The mesh consisted of several finite elements that are created to plot the required characteristics. In the finite element method, the field at every node is obtained from the solution of the previous node and the solution to the entire domain is obtained at the end of the simulation. Figure 3.12a and b show the mesh generated for the breast tissue model with parallel plate and needle electrodes respectively. Both the figures consist of 5000 triangular elements but the distribution of elements depends on the stress points in the model. Majority of the elements are concentrated in the curved regions of the model and the tumor has more triangular elements than the normal tissue.



(a) (b)

Figure 3.12. Mesh generated for breast tissue model with parallel plate electrodes (a) and needle electrodes (b).

3.5. Summary

This chapter explained the framework and methodology used in this research. The various tasks that the project is split into and the process of finite element modeling is explained in the first section. The models created and electrical parameters associated with them are discussed under methodology. The simulation results for each of the models are discussed in the next chapter.

CHAPTER 4. RESULTS AND ANALYSIS

This chapter presents electric field and voltage distributions obtained for all models developed and studied. The voltage distribution, electric field distribution, energy distribution are plotted and analyzed for optimum values suitable for electroporation. Breast Lobules and whole breast models are studied first and then various electrode configurations are compared for optimum design. Thermal calculations are also shown to prove that electroporation is a non-thermal phenomenon.

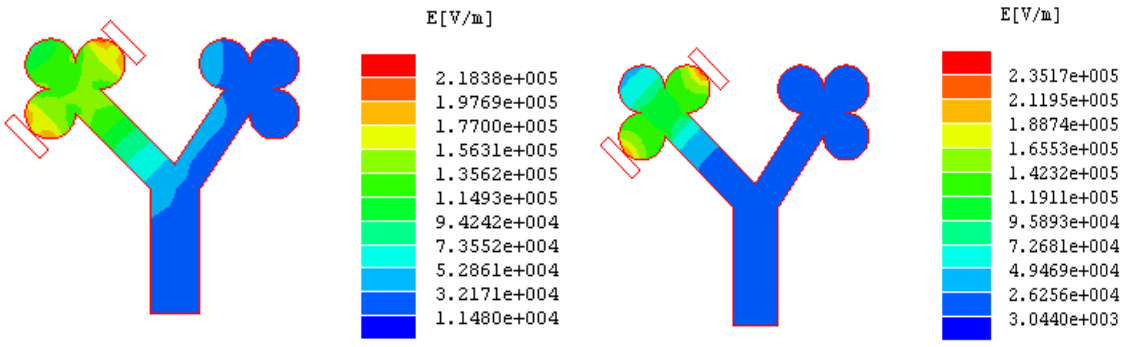
4.1. Electric Field Distribution in Breast Lobules

Models of Breast lobule and duct and developed first as described under 'Methodology'. Results obtained from 3-segment lobules and 5-segment lobules are discussed in this section. Normal and tumor tissues are compared first. The effect of fat and skin layers over the tissue is analyzed and then effect of source type is observed.

4.1.1. Normal versus Tumor Tissues

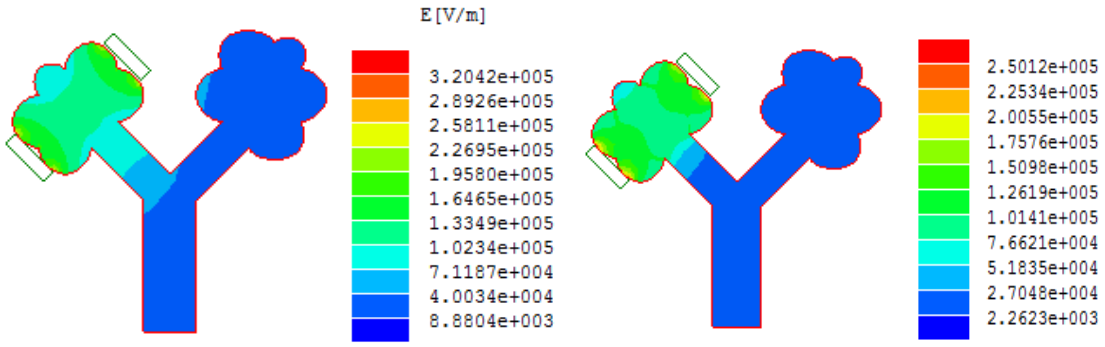
Figure 4.1a and b show the electric field distribution of the 3-segment breast lobule. Figure 4.1ashows the electric field in a normal tissue and Figure 4.1b shows the electric field in a tumor tissue of a 3-segment breast lobule. The electric field distribution in the improved 5-segment model can be seen in Figure 4.2a and b. In the normal tissues

(Figure 4.1a, 4.2a), the electric field is higher near the electrodes and reduces towards the center of the lobule at which electrodes are placed (lobule 1 – which is on the left). Electric field is much lower in lobule 2, which is the lobule on the right. Comparison with malignant tissue electric field distribution (Figure 4.1b,4.2b) indicates that the cancer tissue has an electric field distribution mush lower than that of normal tissue illustrating the difference between the tissue characteristics. Figure 4.3 and Figure 4.4 show the comparison of electric field magnitudes of normal and tumor breast lobules at various points in the tissue between the electrodes. As can be seen, the tumor tissue has an electric field much lower than the normal tissue in both cases – 3-segment and 5-segment. This makes the tumor more susceptible to externally applied voltages than normal tissues and hence proves useful for electroporation applications.



(a) (b)

Figure 4.1. Electric field distribution of normal (a) and malignant (b) 3-segment lobule.



(a) (b)

*Figure 4.2.*Electrical field distribution of normal (a)and malignant (b) 5-segment lobule.

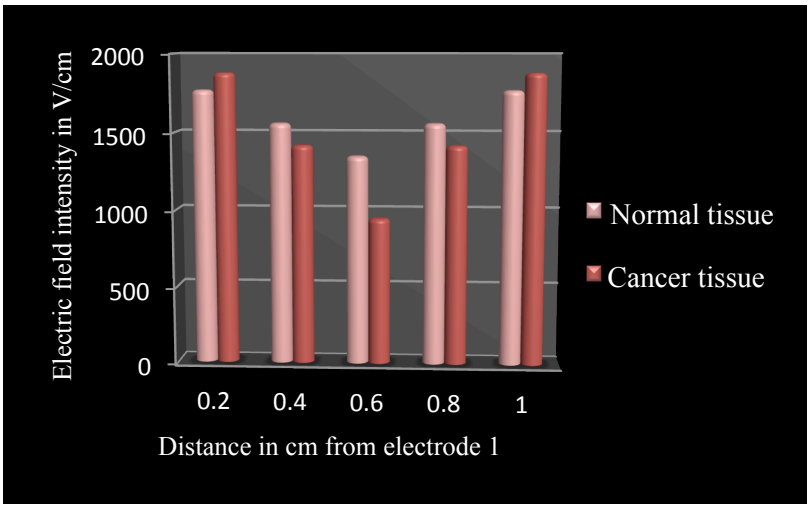


*Figure 4.3.*Electric field intensity in normal and cancer 3-segment breast lobule.

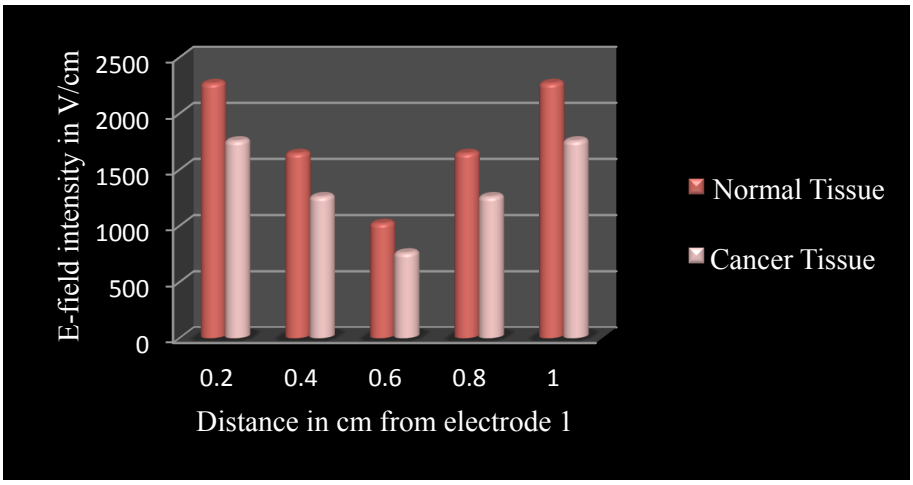


*Figure 4.4.*Electric field intensity in normal and cancer 5-segment breast lobule.

4.1.2. Effect of Fat and Skin Layers

In order to simulate conditions close to reality, fat (20 mm) and skin (2mm) layers are introduced in the model. Figure 4.5 - 4.8show the electric field intensities at various points of normal and cancer tissue with the layers included for both 3-segment and 5-segment lobules. It is observed that electric field is lower in case of cancer tissue than normal tissue with layers included in all the cases (with or without skin and fat layers included). The electric field intensity is highest near electrodes and reduces with distance from the electrode in any tissue. It is also seen that the values of electric field intensity do not vary too much with the introduction of layers. Figure 4.5 and 4.6 show that the trend remains the same for normal and tumor tissues and values of field intensity vary only within a small range. The same is seen for Figure 4.7 and 4.8. The electric field is not constrained within the tissue itself, but the fat and skin layers around absorb some of the applied field depending on the electrode position and voltage applied. There is not much of a difference between the case when fat is added to the model and fat and skin are

added to the tissue model. This is because the electrodes are closer to the tissue and fat and skin layers that are away from the tissue have little or no influence on the electric field distribution inside the tissue itself.

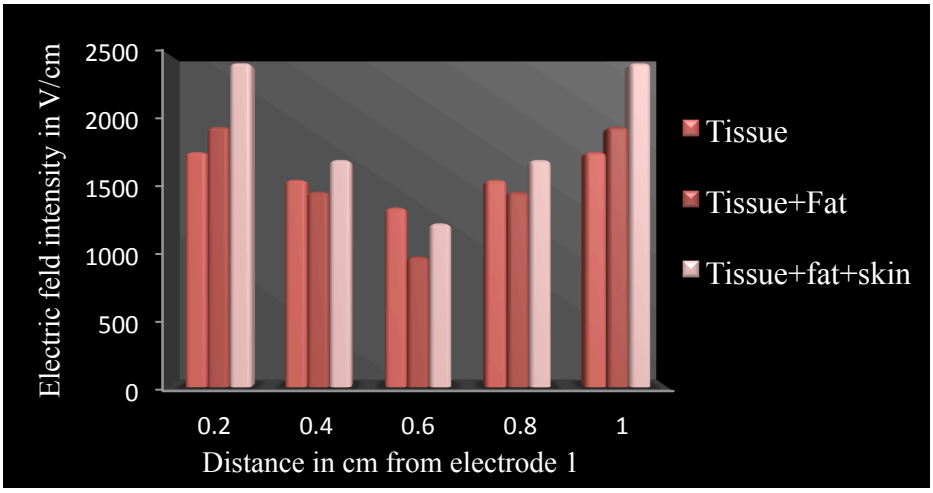


Figure 4.5. Electric field intensity of normal 3-segment lobule with fat and skin layers.

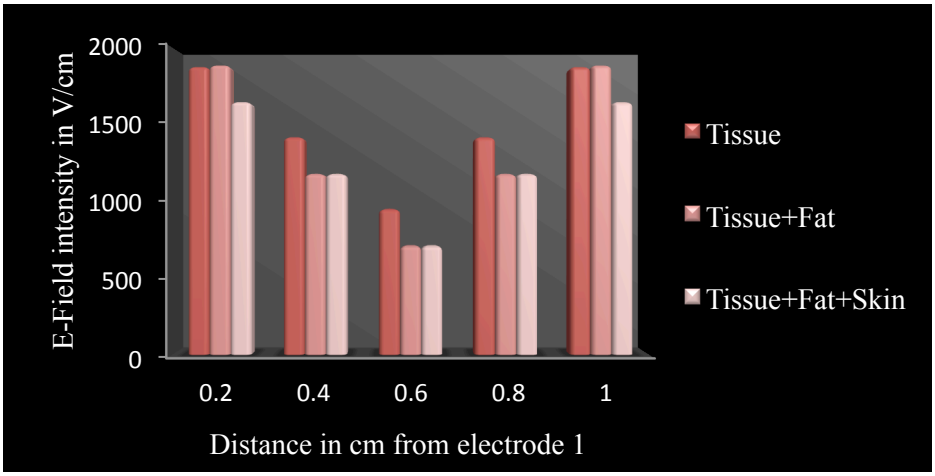


Figure 4.6. Electric field intensity of malignant 3-segment lobule with fat and skin layers.

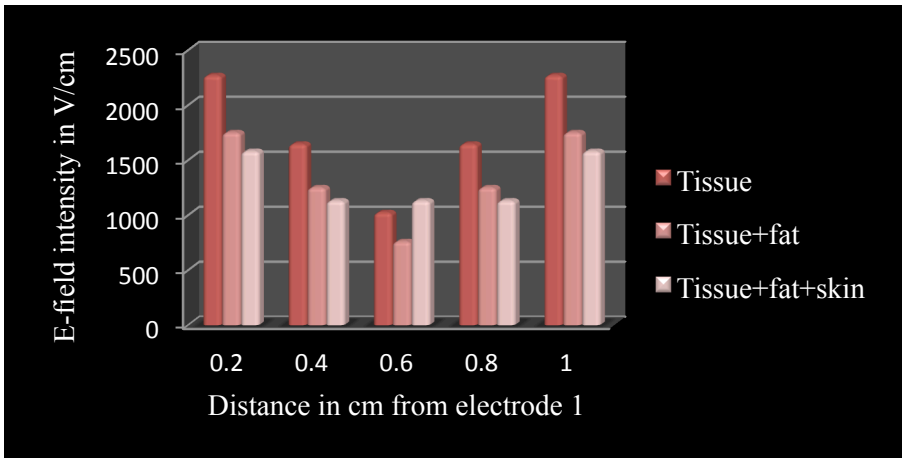


Figure 4.7. Electric field intensity of normal 5-segment lobule with fat and skin layers.

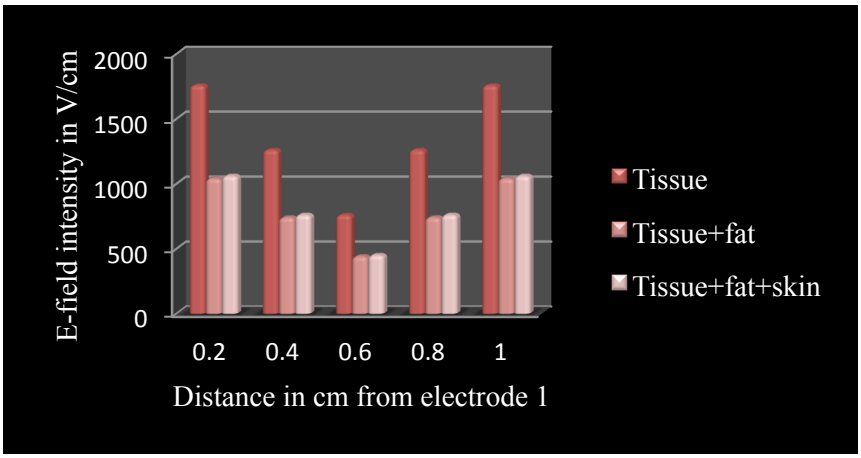


Figure 4.8. Electric field intensity of malignant 5-segment lobule with fat and skin layers.

4.1.3. Effect of Source Type (DC Versus AC)

Simulations were run for all normal and tumor tissues with a DC voltage input of 1200 V/cm. The tissues were then subject to an AC voltage of the same amplitude (RMS voltage of 1200 V/cm and 0 phase) and frequency of mm1Hz and their electric field distributions were compared. Figure 4.9shows the comparison for AC and DC source

types of various 3-segment breast tissue models and Figure 4.10 shows the same for 5-segment breast lobules. As can be seen in Figure 4.9, AC conduction yielded much lower electric field than DC. The plot is drawn to compare the field intensity at the center of the breast lobule.

There is a minimum decrease of 22 % (tissue type 3) and a maximum reduction of 117 % (tissue type 1) in the electric field intensities of AC over DC for 3-segment breast lobules. The trend is similar for the 5-segment model. The decrease in electric field ranges from 28 % to 98 % for the 5-segment lobule. The charges accumulate more in case of DC due to uni-polarity of source and charge accumulation is much smaller in case of AC source due to its bipolarity. Since charges are much lower, the electric field is also much lower in case of AC sources.

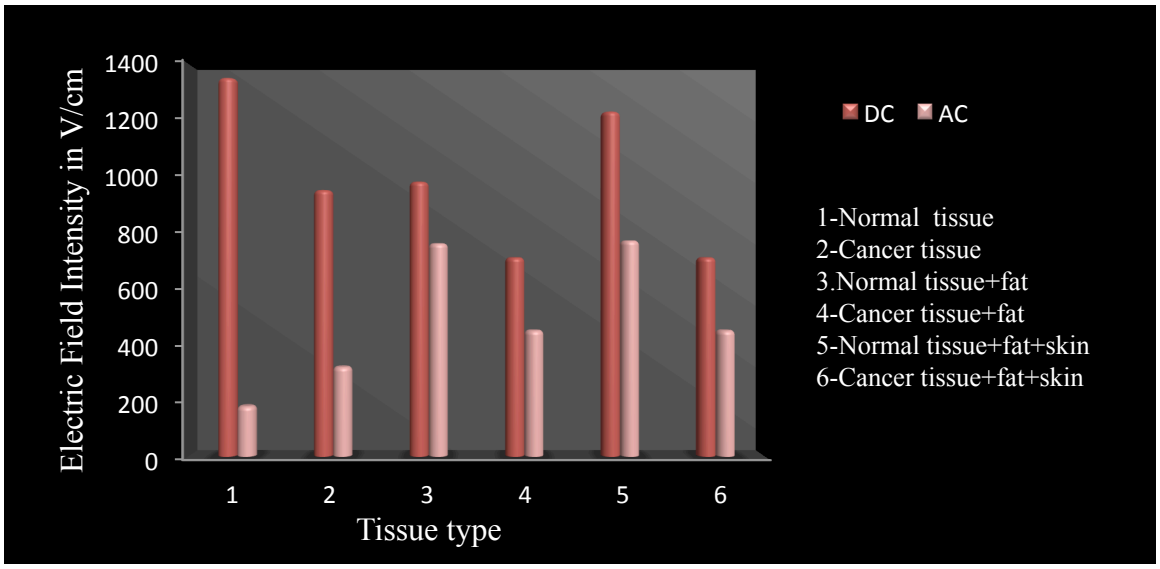


Figure 4.9. Comparison of DC versus AC source for various models with 3-segment lobule.

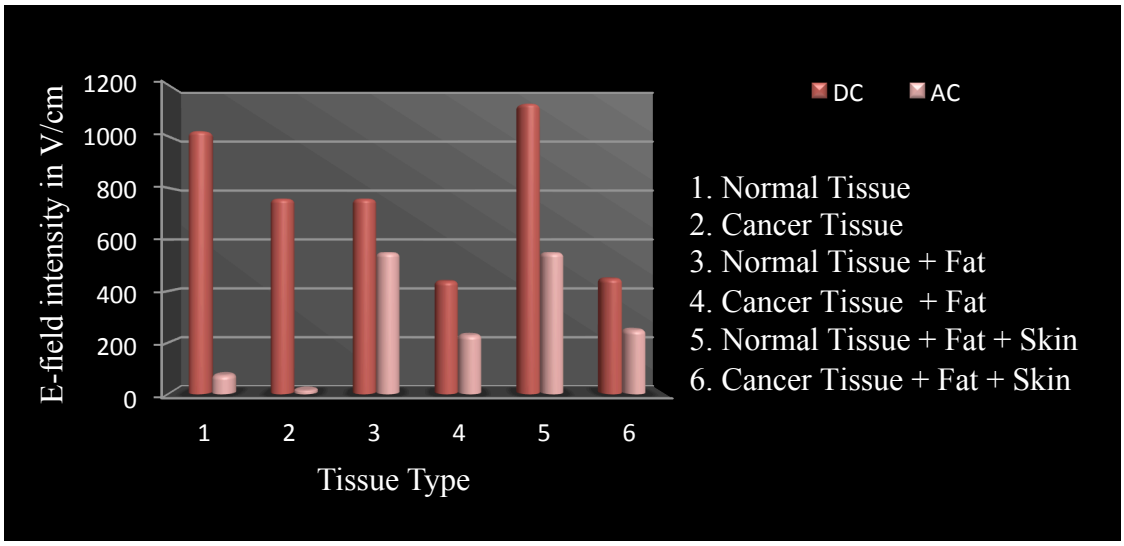


Figure 4.10. Comparison of DC versus AC source for various models with 5-segment lobule.

4.2. Electric Field Distribution in Human Breast Model

The human breast, which consists of 12-15 lobules, is studied as a whole in this section. Invasive cancers spread quickly and more than often, women end up removing the entire breast to get rid of the cancer. Electric field distribution studies of the breast will help in designing electrodes and planning treatment of whole breast for all the various types of cancers that occur in the breast.

Figure 4.11 shows a tumor in a breast tissue. The tumor can be located in any part of the breast. For the purpose of our research, the tumor is modeled in the center of the breast for studies using parallel plate and needle electrodes. Section 4.2.3, which discusses the effect of the location of the tumor shows the tumor at different regions in the breast.

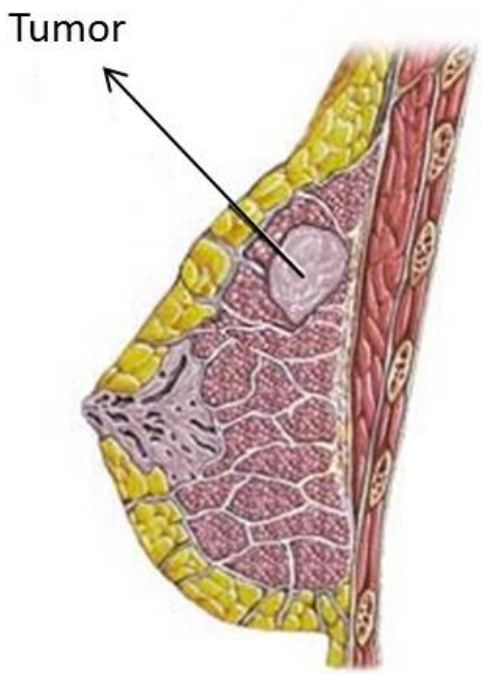


Figure 4.11. Human breast with tumor.
(Fibroadenoma of the breast (n. d.). *A.D.A.M.* Medical encyclopedia. Retrieved on August, 2011)

4.2.1. Electric Field Distribution of Human Breast Using Parallel Plate Electrodes

The voltage distribution of breast tissue with 8400V applied across the 7cm diameter using parallel plate electrodes is shown in Figure 4.12. The entire voltage of 8400V is distributed between the two electrodes and the distribution is the same in case of normal and malignant breast tissues. The voltage is maximum near the positive electrode and reduces gradually towards the negative electrode.

The electric field distribution of normal breast tissue is shown in Figure 4.13a and that of a breast tissue with tumor is shown in Figure 4.13b. A voltage of 8400V causes an electric field of magnitude between 350 – 500 V/cm in the normal breast tissue (Figure 4.13a). A similar model with a rectangular block of tissue showed that the field was 1150

V/cm, close to the calculated value (Figure 14.3c). This reduction in electric field in case of breast tissue is due to the shape of the tissue and the difficulty in placing plate electrodes exactly parallel to the tissue.

The electric field in case of malignant breast tissue with parallel plate electrodes is shown in Figure 4.13b. The electric field in the tumor with parallel plate electrodes was found to be 146 V/cm. Tumor in the tissue results in 60 % reduction of electric field as compared to normal breast tissue. The field in the normal tissue surrounding the tumor is higher than the tumor itself because of the change in its electrical parameters (Haltiwanger, 2010).

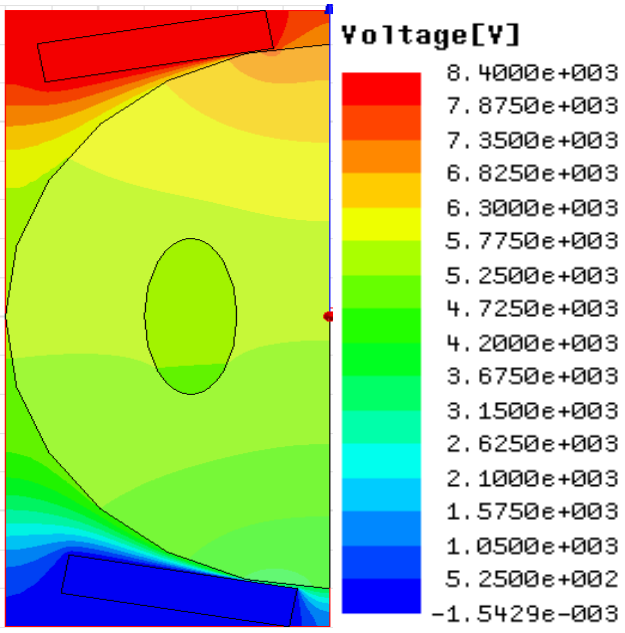
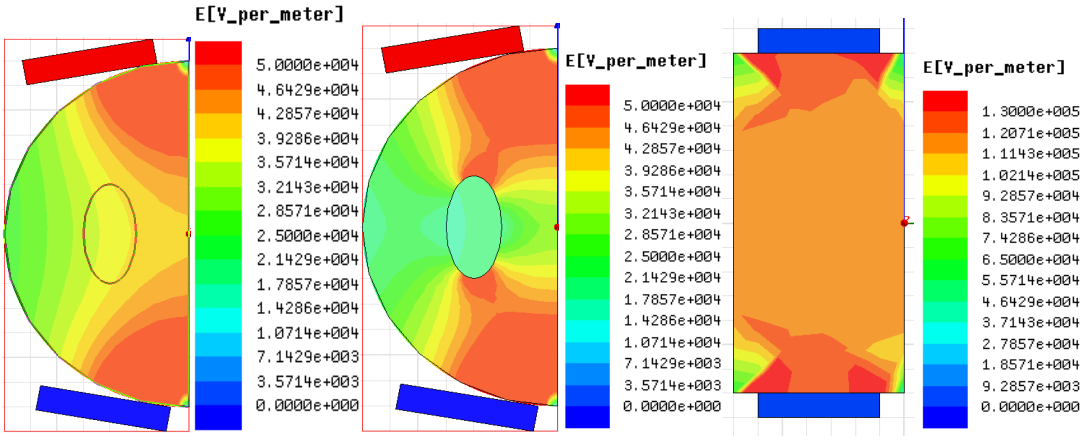


Figure 4.12. Voltage distribution of normal breast tissue with parallel plate electrodes.



(a) (b) (c)

Figure 4.13. Electric field distribution of normal (a), malignant (b) breast tissue with parallel plate electrodes and a rectangular block of tissue (c).

4.2.2. Electric Field Distribution of Human Breast Using Needle Electrodes

In this study, needle electrodes are directly inserted into the tumor and these results in different electric field magnitudes compared to parallel plate electrodes. The voltage distribution of the tumor in the breast model in case of needle electrodes with 4 mm gap is shown in Figure 4.14. Maximum voltage is concentrated in the tumor region and did not affect the surrounding normal tissue. The voltage distribution in case of normal tissue, without the tumor present is the same for the same electrode position. The electric field in the case of needle electrodes with 4mm gap is shown in Figure 4.15a and b for normal and tumor breast tissues respectively. Here, the electric field varies from 2200 to 2800 V/cm in case of normal breast tissue. This is much higher than the case of parallel plate electrodes using an applied voltage is 480V to give the required electric field intensity of 1200 V/cm. This is because of

the electrode shape and proximity. The electric field in the case of tumor within breast is in the range 2100 to 2500 V/cm. There is a 5-11 % reduction in electric field in the tumor region.

Another observation from the field distribution is that all the electric field is concentrated in between the electrodes, which is the tumor. There is very little field affecting the surrounding normal tissue, which is again a desirable outcome.

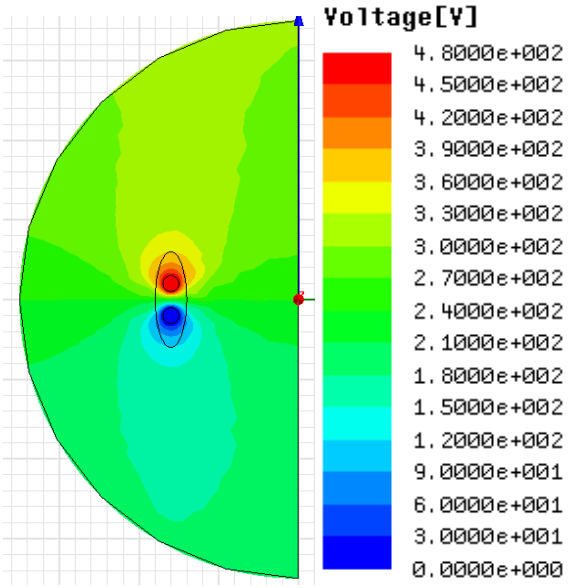
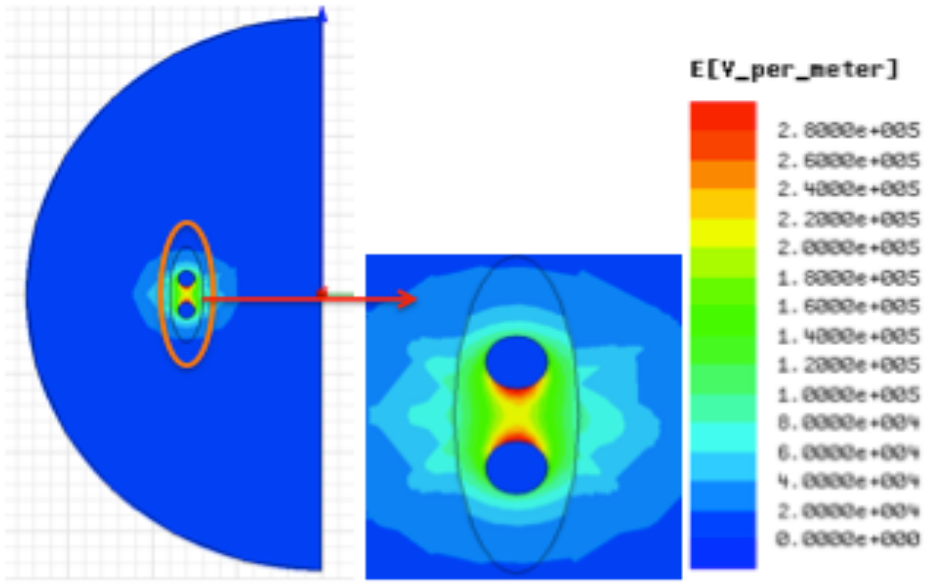
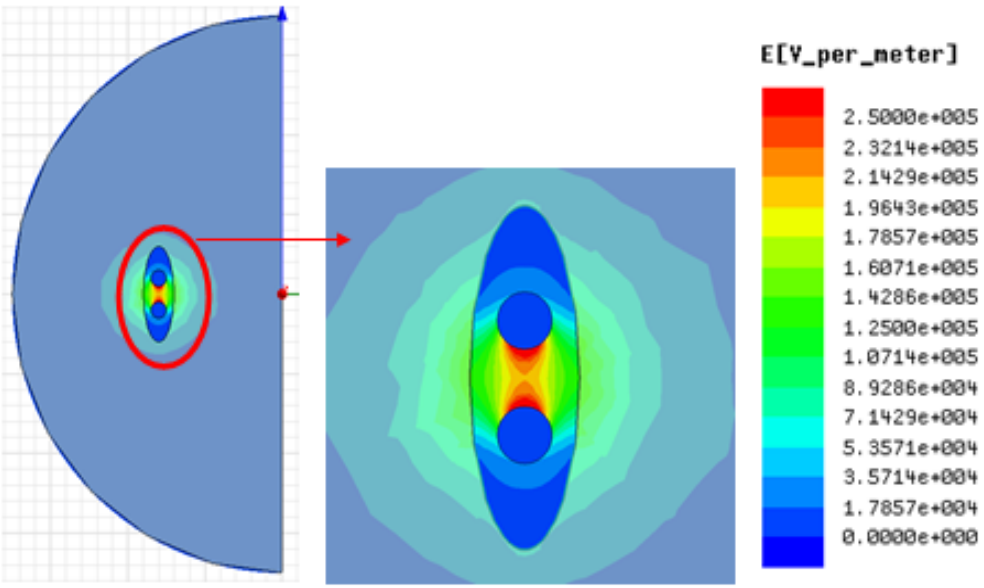


Figure 4.14. Voltage distribution of normal and malignant breast tissue with needle electrodes.



(a)



(b)

Figure 4.15. Electric field distribution of normal (a) and malignant (b) breast tissue with needle electrodes.

4.2.3. Electric Field Distribution of Tumor at Various Locations in Breast

Tumor can occur in any region in the breast. It can originate in any of the lobules and ducts and spread in the surrounding region. Needle electrodes can be placed exactly in the tumor region so that maximum region of the tumor is treated and normal tissues are untouched. Figure 4.16 shows four different locations of tumors and how needle electrodes can be placed exactly in the tumor region. Figure 4.16d has the tumor located as in tumor image Figure 4.11.

Figure 4.17 shows the voltage distribution of the tumor in the breast tissue when a voltage of 480V is applied in between the electrodes. Since the needles are inserted in the tumor, most of the voltage is distributed in the tumor region, which is in between the electrodes and minimal voltage goes to the surrounding normal tissue. No matter where the tumor is present, the voltage is distributed evenly in the tumor region as can be seen all three cases, a, b, c and d.

Figure 4.18 shows the electric field distribution for all three locations of tumor. As can be seen, all four tumor locations have the same electric field distribution within the tumor as the needle electrodes are placed exactly where the tumor is located. The field distribution is also the same as that in the case of a tumor right in the center of the breast as assumed in the section 4.2.2 previously (Figure 4.15). The electric field at all points in the surrounding normal tissue is 200 V/cm.

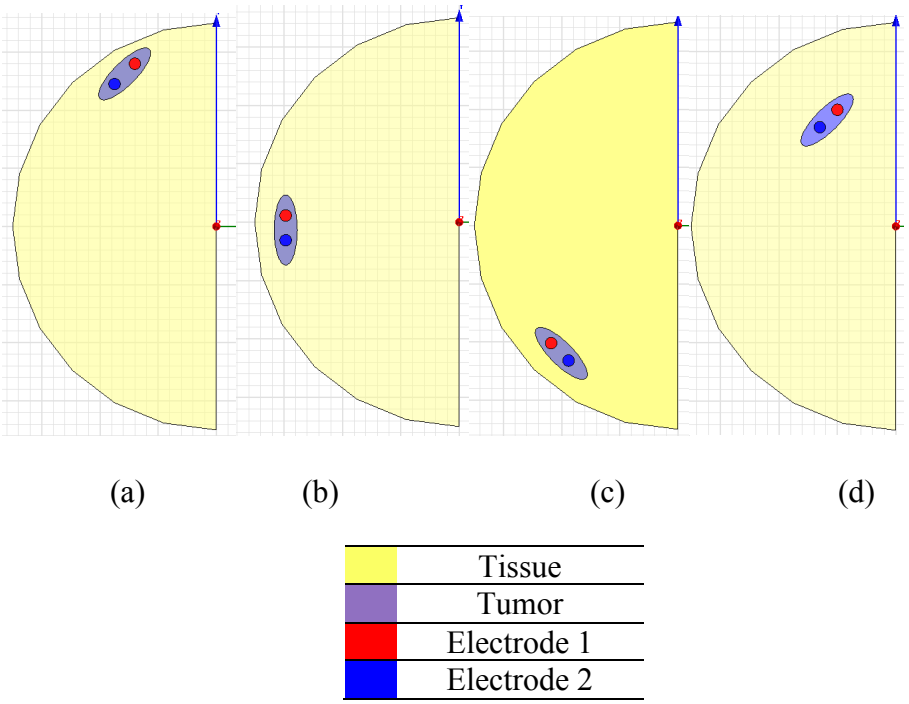


Figure 4.16. Models of tumor at various locations in the breast tissue - top (a), center (b), bottom (c) and top-center (d).

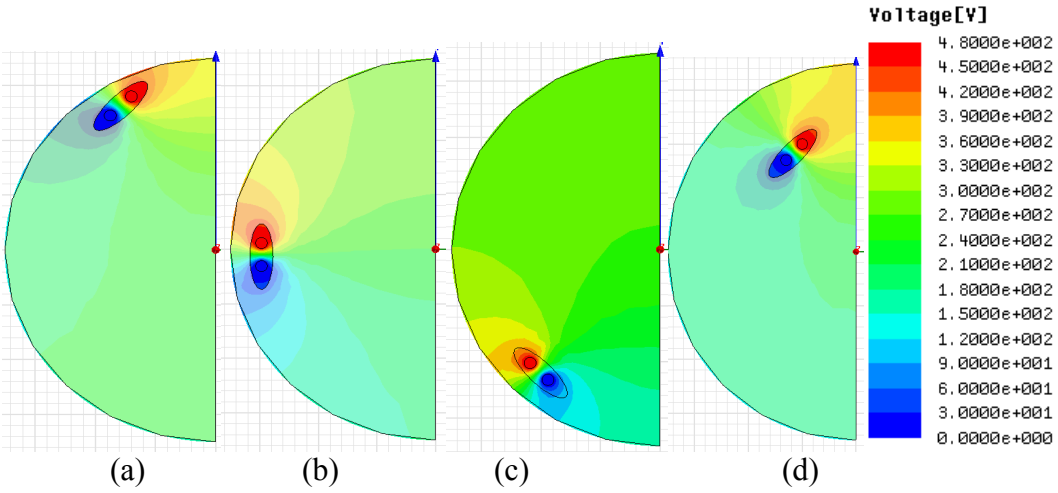
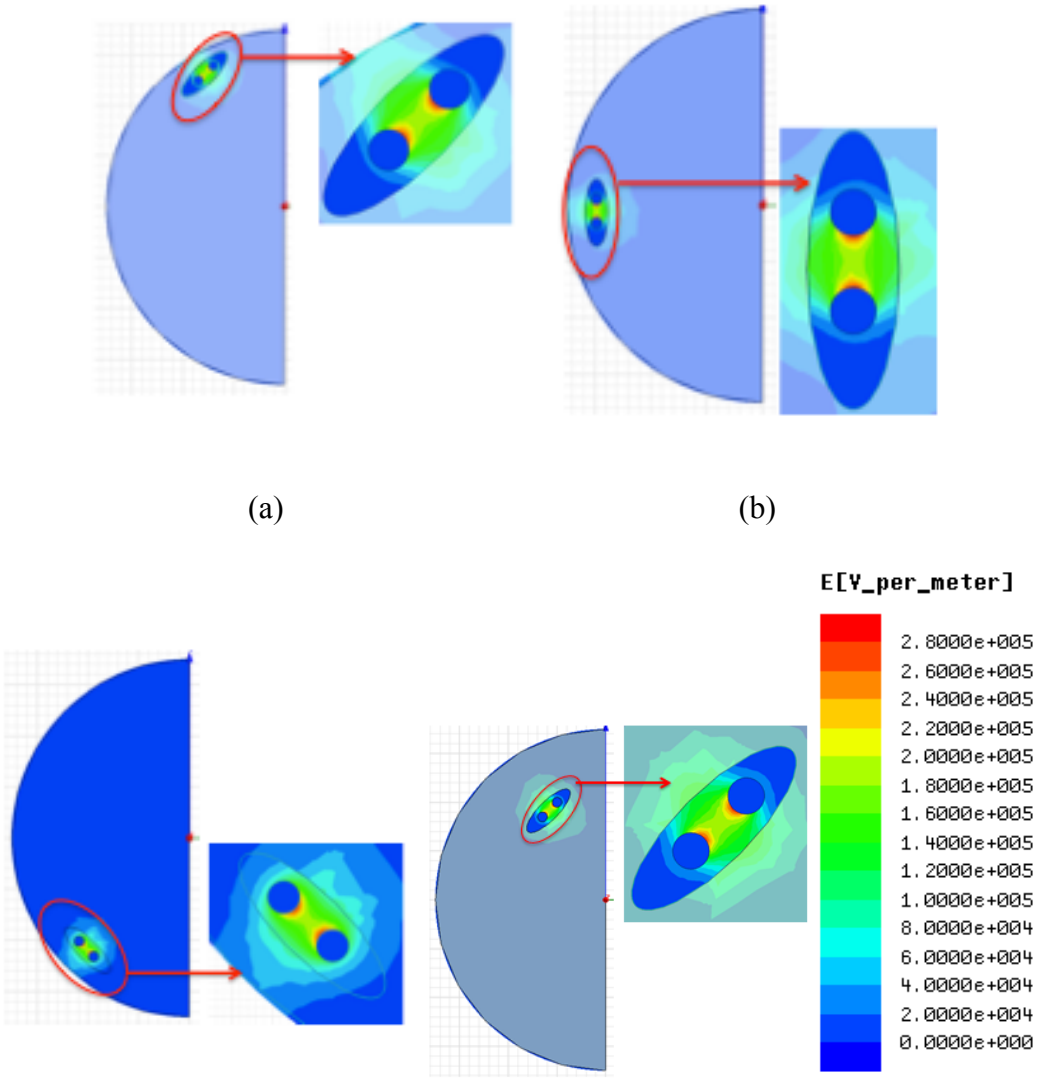


Figure 4.17. Voltage distribution of tumor at various locations in the breast tissue - top (a), center (b), bottom (c) and top-center (d).



(a) (b)

(c) (d)

Figure 4.18. Electric field distribution of tumor at various locations in the breast tissue - top (a), center (b), bottom (c) and top-center (d).

4.2.4. Electric Field Distribution of Tumors of Various Shapes in Breast

Tumors can be of various shapes in the human breast. This section presents the analysis of the electric field distribution in three different tumor shapes: elliptical,

spherical and an irregular shape. Needle electrodes of 2mm diameter and 4mm gap are used in all three cases and are placed exactly in the center of the tumor. Figure 4.19 shows the models created to represent the various shapes of tumors that are studied.

Figure 4.20 shows the voltage distribution obtained in the three tumor shapes. As can be seen, irrespective of the tumor shape, the voltage is distributed evenly between the two electrodes. The voltage distribution depends more on the electrode placement than the shape of the tumor. Electrodes that cover more of the tumor region would be more effective.

The electric field distribution in the tumor is shown in Figure 4.21 for all the three shapes – ellipse (a), circle (b) and irregular shape (c). In case of the ellipse, the electric field covers most of the tumor region. In case of the circular and irregular shaped tumor, the electric field is strong between the needles but certain regions of the tumor do not have sufficient electric field. These regions have to be treated again by re-positioning the electrodes and applying voltage again. Though the electric field magnitude is the same between the electrodes in all three cases, the region of tumor covered is different. Since the electrode dimensions and gap would remain constant in design and cannot vary for different tumors, multiple treatments at various locations is the only way to treat the entire region with two-needle electrodes. Another alternate method is to use multiple electrode arrays, which is discussed later in this chapter.

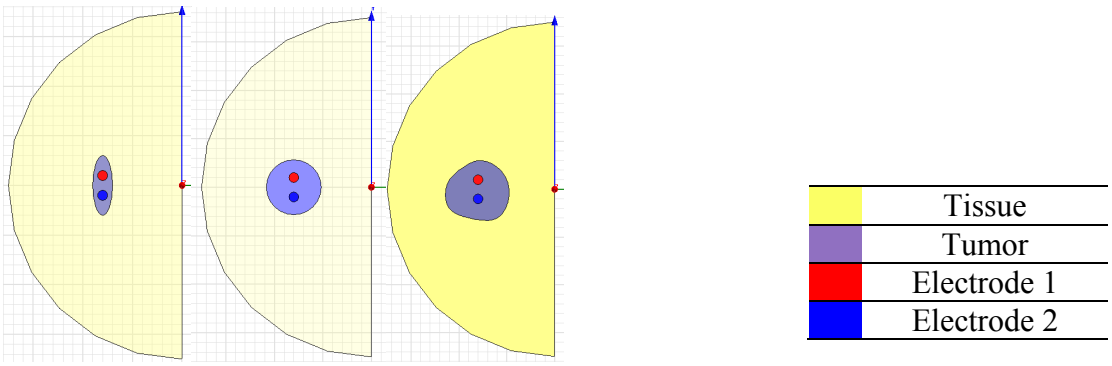


Figure 4.19. Models of tumors of various shapes in the breast tissue - ellipse (a), circle (b) and irregular (c).

Table 4.1. *Dimensions of tumors of various shapes*

Shape	Dimension
Ellipse	1.2cm×0.4cm
Circle	1cm diameter
Irregular	1cm diameter

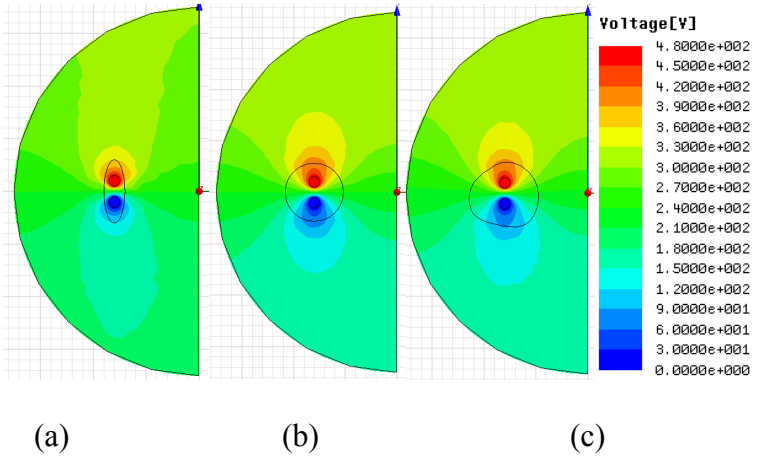
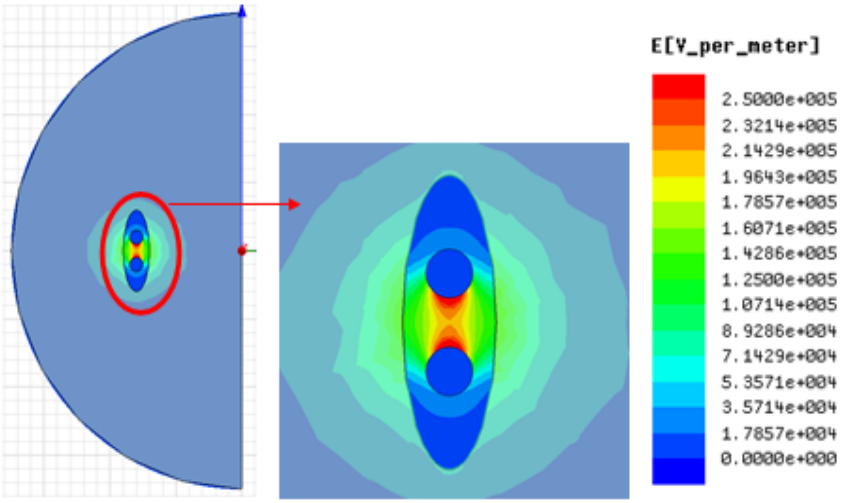
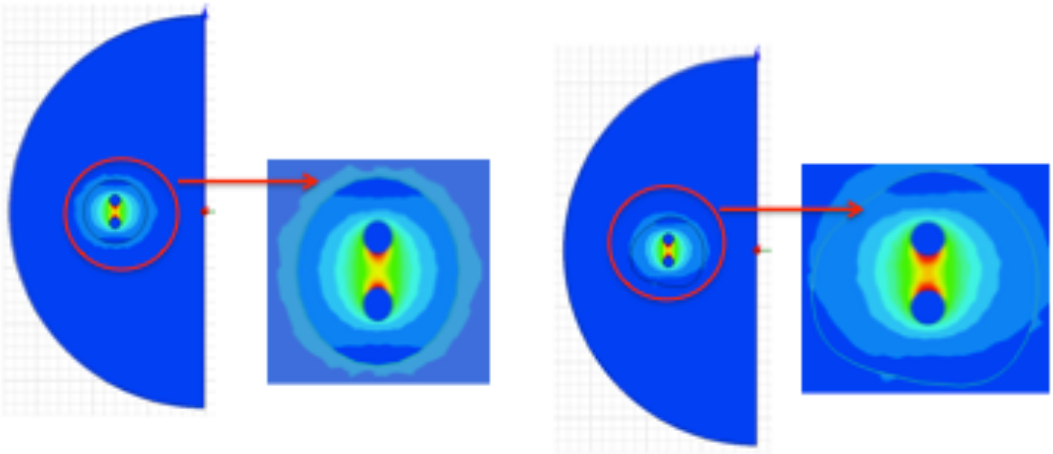


Figure 4.20. Voltage distribution of tumors of various shapes in the breast tissue - ellipse (a), circle (b) and irregular (c).



(a)



(b) (c)

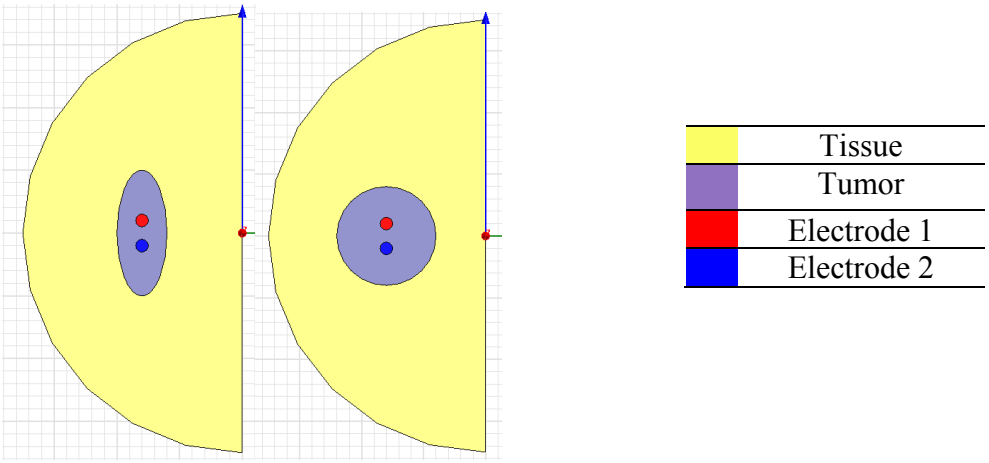
Figure 4.21. Electric field distribution of tumors of various shapes in the breast tissue - ellipse (a), circle (b) and irregular (c).

4.2.5. Electric Field Distribution of Tumors of Various Sizes in Breast

The tumor sizes considered in the previous section are approximately 1cm. Tumor sizes can be larger or smaller. This section shows the electric field distribution for bigger sized tumors. Elliptical and Spherical tumors are taken into consideration. The models created are shown in Figure 4.22 and the dimensions of the tumor are given in Table 4.2

The voltage distributions in the tumors are given in Figure 4.23. The voltage is distributed between the two needle electrodes and as can be seen, it is concentrated in the tumor region with very little voltage in the surrounding normal tissue. The needle diameter and electrode gap are kept at a constant of 2mm and 4mm respectively.

The electric field distribution is as displayed in Figure 4.24. As seen in previous cases, the electric field is concentrated in the region between the electrodes and is not dependent on the tissue size or shape. Since the inter-electrode gap and electrode dimensions are constant, bigger tumors need to be treated multiple times in order to be covered completely. In Figure 4.24, most of the tumor region is not treated and using the same two needles multiple times would be more time consuming and strenuous. A more efficient way of treatment would be to use multiple electrodes at the same time so that a larger tumor area is treated at once.

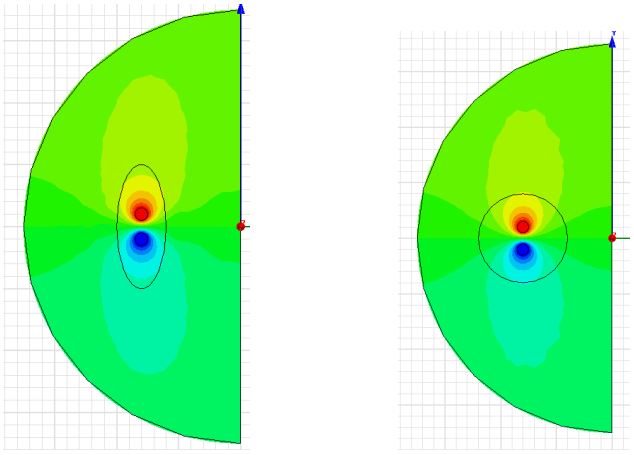


(a) (b)

Figure 4.22. Models of tumors of bigger sizes in the breast tissue - ellipse (a), circle (b).

Table 4.2. *Dimensions of bigger sized tumors*

Shape	Dimension
Ellipse	2cm×0.8cm
Circle	1.5cm diameter



(a) (b)

Figure 4.23. Voltage distribution of tumors of bigger sizes in the breast tissue - ellipse (a) and circle (b).

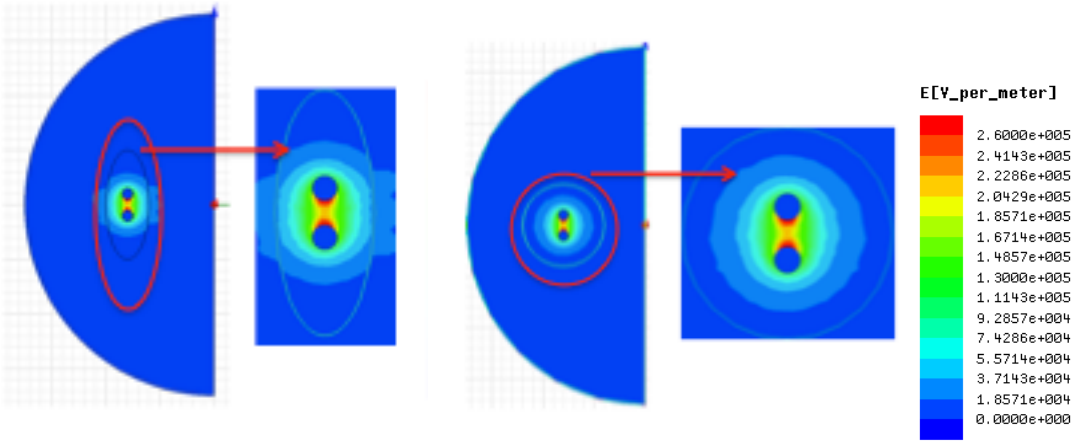


Figure 4.24. Electric field distribution of tumors of bigger sizes in the breast tissue - ellipse (a) and circle (b).

4.2.6. Effect of Source Type (DC Versus AC)

Figure 4.25 shows the comparison of electric field values in the tumor region of the tissue for DC and AC sources in various cases. In 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 case of AC, an RMS voltage of 1200V/cm was applied with zero degree phase angle at 1 Hz. 1Hz is selected as the AC frequency since current electroporation treatments induce pulses at 1-second intervals. As shown in Figure 4.18, the electric field in case of AC source is always lower than DC. The reduction is greater in case of normal tissue (31%) and much lower in case of tumor tissues (22% and 7% for parallel and needle electrodes respectively).

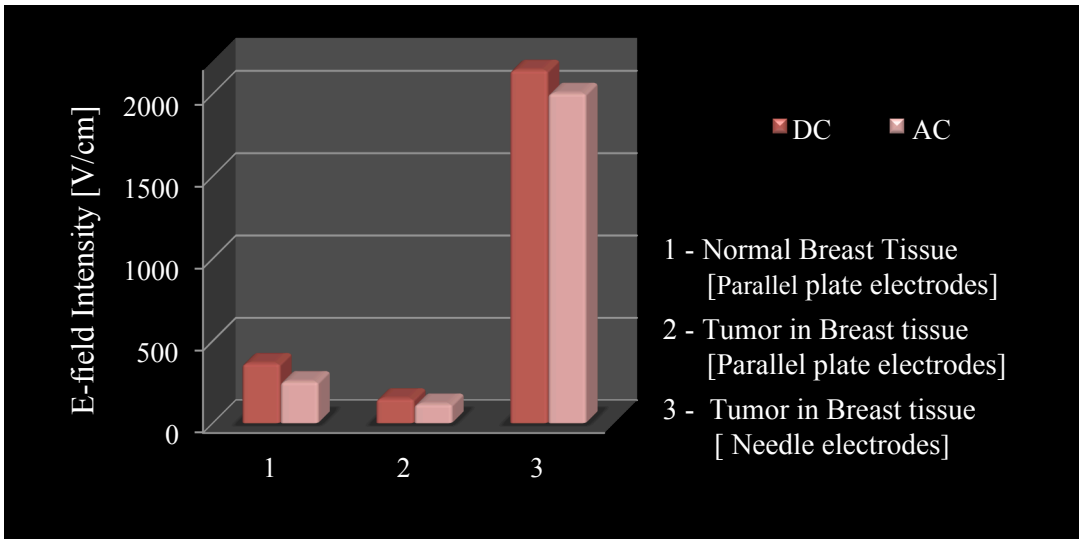


Figure 4.25. Comparison of electric field distribution in human breast tissue with DC and AC sources

4.2.7. Electric Field Distribution in Inter-electrode Gap of Tumor

In order to study the electric field distribution in various gaps 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 4 mm to 8 mm, with increments of 2mm. The electric field distribution for the three gaps is plotted in Figure 4.26. The electric field distribution is highly non-linear due to the size and shape of electrodes used. The field in the case of 4mm gap is maximum (>2 kV) and is almost uniform. The field magnitudes reduced with increase in gap and the variation of the field in the gap increases. Hence a small gap is most suited for such treatments.

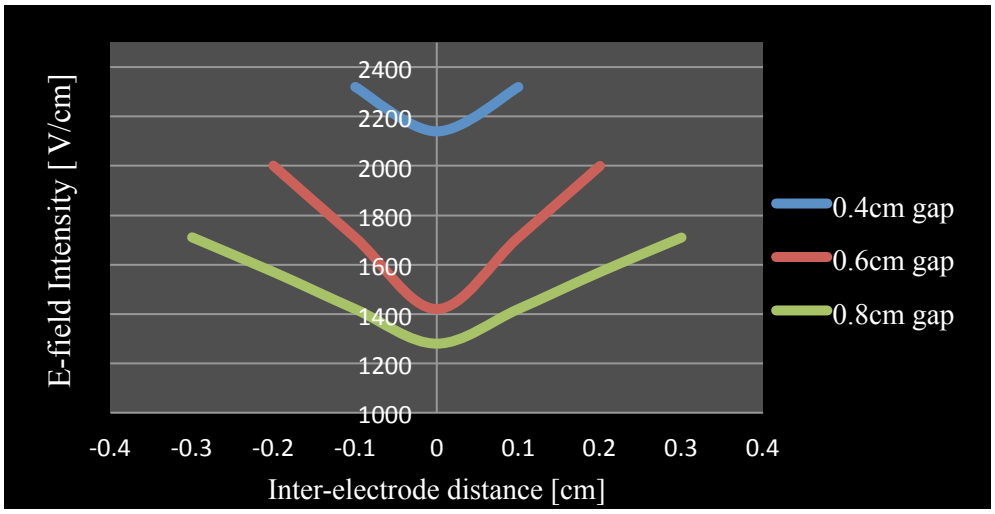


*Figure 4.26.*Comparison of electric field distribution in tumor with various inter-electrode gaps.

4.2.8. Multi-needle Electrode Arrays for Large Tumors

Most breast cancers are invasive, which means that they spread fast into the surrounding normal tissues. In some cases even after the infected breast is removed, cancer occurs in the chest wall and is known as chest wall carcinoma. 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 requiring the patient to be sedated for longer durations. The treatment time also increases for the oncological surgeon. Hence, a novel, multi-needle electrode array, which would cover larger areas, would be more efficient and convenient. Figure 4.27 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 – 2500 V/cm) and is duplicated across each of the 4-pairs of electrodes. Figure 4.28 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 efficient treatment of invasive cancers.

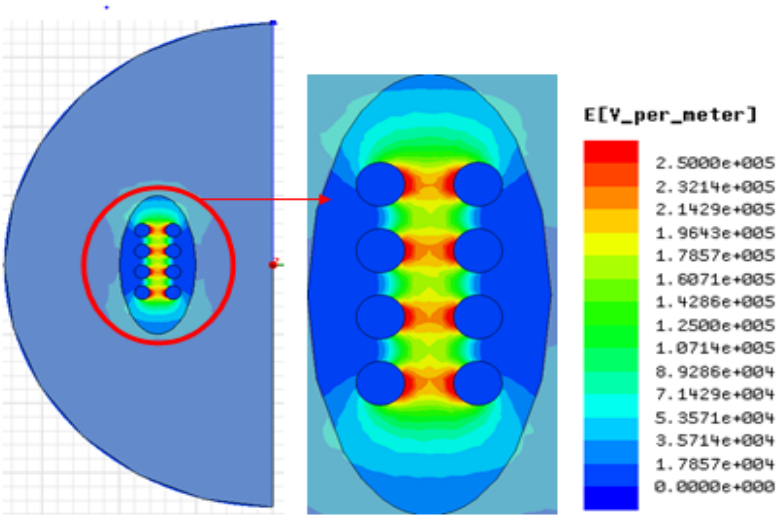


*Figure 4.27.*Electric field distribution of large tumor in breast tissue with 8-needle electrodes.

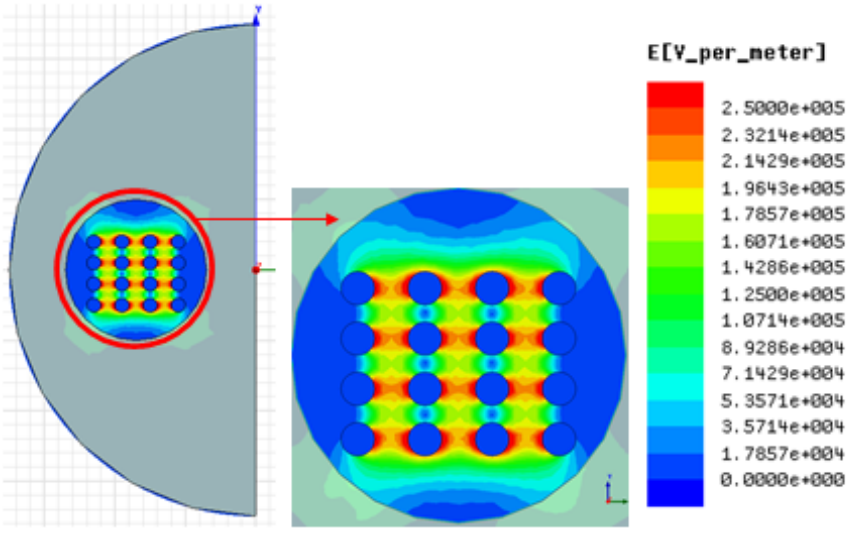


*Figure 4.28.*Electric field distribution of large tumor in breast tissue with 16-needle electrodes.

4.2.9. Effect of Electrode Polarity on Electric Field Distribution

To test the effect of electrode polarity on the electric field distribution on breast tissues and tumors, the models were simulated for positive and negative voltages of the same magnitude. The voltage distribution reversed but the electric field distribution remained the same in all tissue models. This study proves that electrode polarity has no effect of electric field distributions in tissues.

4.2.10. Parametric Studies on Breast Tissues

The two main parameters or elements that are considered in finite element modeling are permittivity and conductivity. Tumor tissues have a much higher (5 times higher) permittivity and conductivity than normal tissues. In order to observe the influence of each of the parameters individually, simulation tests were done by varying only the conductivity and only the permittivity. There was no change observed in the electric field distribution of tissues when the parameters were changed individually. However when both parameters are changed (as in the case of tumor tissue as compared to normal tissue) there are significant changes in electric field observed which are different as discussed between tumor and normal tissues in other sections.

4.3. Electrode Configurations in 3D

This section focuses on electrode shape and dimensions. Models of electrodes are created in two and three dimension and inserted into tissues, which are simple blocks in this case. Parallel plate electrodes and needle electrodes are compared and analyzed. Multi-needle electrode arrays are explored for application in larger tumor areas.

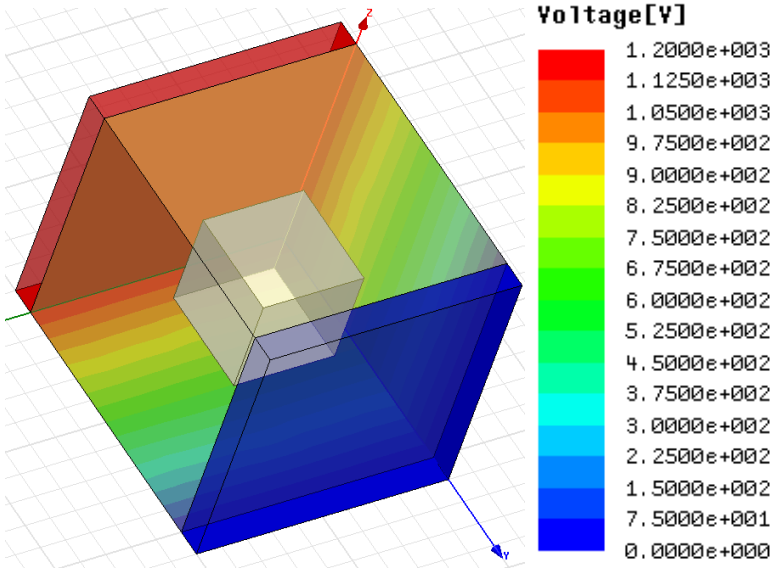
4.3.1. Parallel Plate Electrodes Versus Needle Electrodes for Tumor Treatment

In this section the voltage, electric field and energy distribution of parallel plate and needle electrodes are compared. Figure 4.29 shows the voltage distribution of the tumor using parallel plate (a) and 2 needle electrodes geometry (b). Parallel plates are placed externally, on two sides of the normal tissue and needle electrodes are inserted internally, within the tumor in the tissue. The voltage is evenly distributed between the positive and negative electrodes in case of parallel plate electrodes where as 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 as the distance from electrodes increase. Hence the position where needles are placed is important when inserted inside the tumor and tissue area.

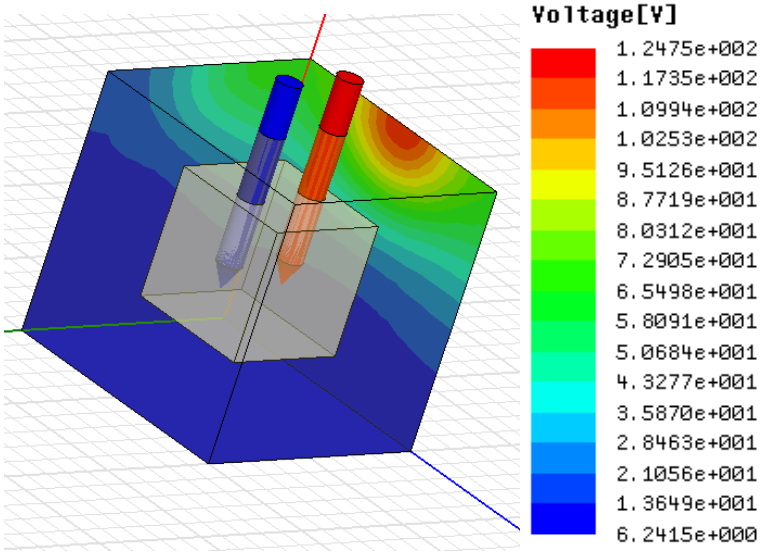
Figure 4.30 shows a comparison of the electric field for both the types of electrodes using both tumor within tissue model and tissue alone model to illustrate the difference between the nomral and malignant tissues. The electric field inside the tumor and normal tissues is homogenous in the case of parallel plate electrode configuration and is highly non-uniform for needle electrode configuration. The magnitude of electric field is one order (10 times) less for needle electrodes than parallel plate electrodes. This

could be due to the fact that the electrodes are placed directly on the tumor tissues which has different electric properties than the normal tissue (Haltiwanger, 2003). Previous studies at an Ireland hospital (Larkin et. al., 2007) on 2-dimensional models also show similar electric field trends as discussed in the 'Literature Review' chapter. The electric field in the region around needles was found to be 25 % less than that of parallel plate electrodes inside a tumor. This correlates very well with our research and shows that directly electroporating tumor tissues results in a different phenomenon than applying parallel plates over the surrounding tissue and skin. Also, on comparing electric field distributions of tumor tissue (Figure 4.30) with a normal tissue (Figure 4.31), it can be seen that the electric field is lower when there is a tumor in the tissue than a normal real life situation, which is a normal tissue. With parallel plate electrodes there is a 5 % reduction in electric field where as in case of needle electrodes there is 15 % reduction. This shows that needle electrodes inserted into the tumor region would be more effective. This difference exists because of the change in electrical properties (resistivity, conductivity, permitivity) of the tissue when affected with cancer.

The energy distribution shown in Figure 4.32 reveals that energy is 2 orders (100 times) of magnitude lower in the tumor than in the surrounding tissue in the case of needle electrodes compared to parallel plate configuration, since the electric field is lower in the tumor than on the normal tissue. The energy is non-homogenous in the case of needle electrodes where as it is uniform in case of parallel plate electrodes.

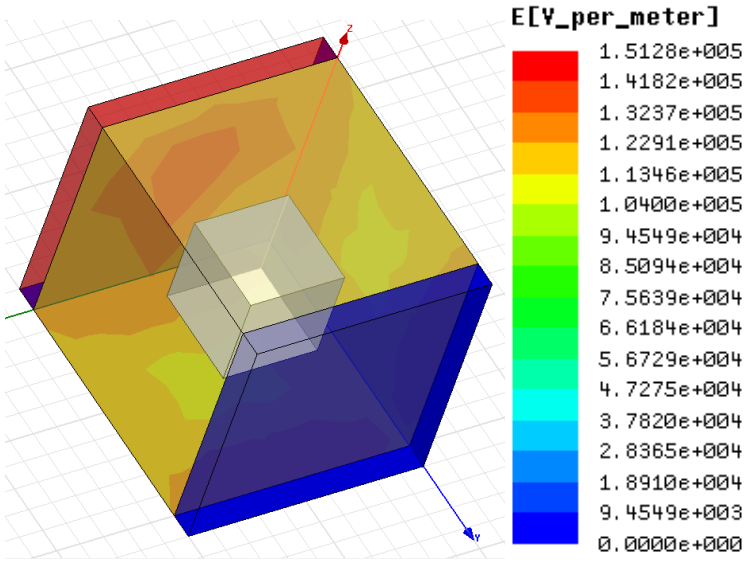


(a)

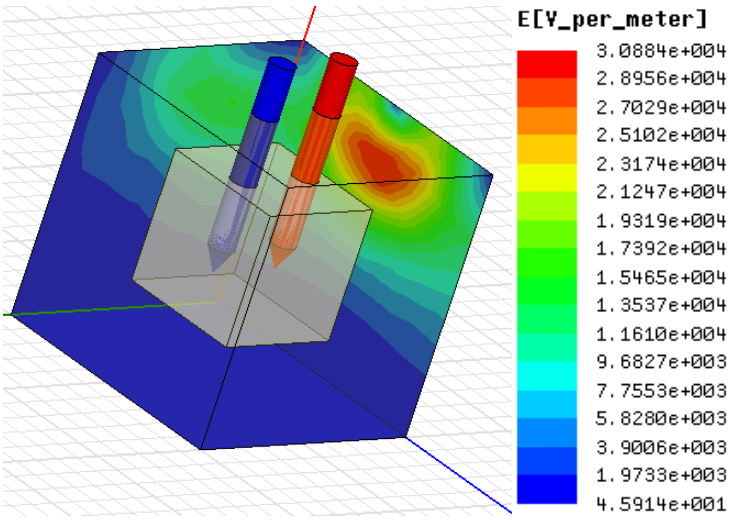


(b)

Figure 4.29. 3DVoltage distribution of tumor within tissue with parallel plate electrodes (a) and needle electrodes (b).

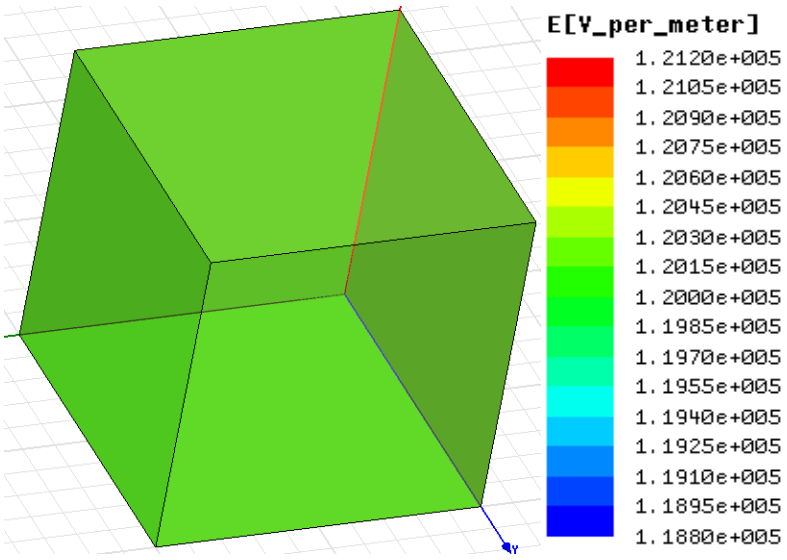


(a)

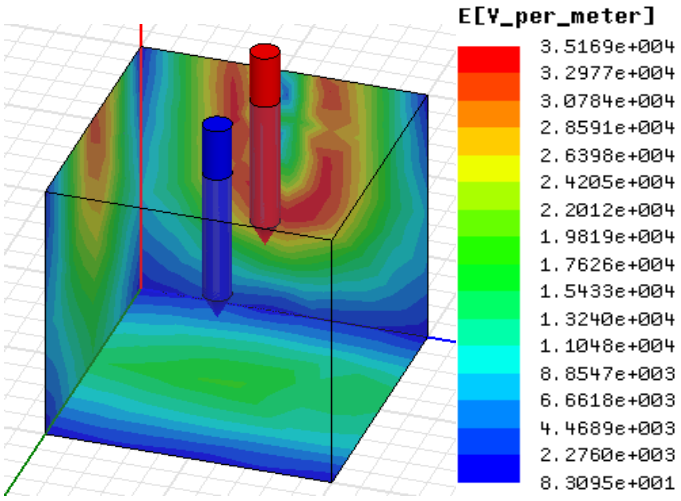


(b)

Figure 4.30. 3DElectric field distribution of tumor within tissue with parallel plate electrodes (a) and needle electrodes (b).

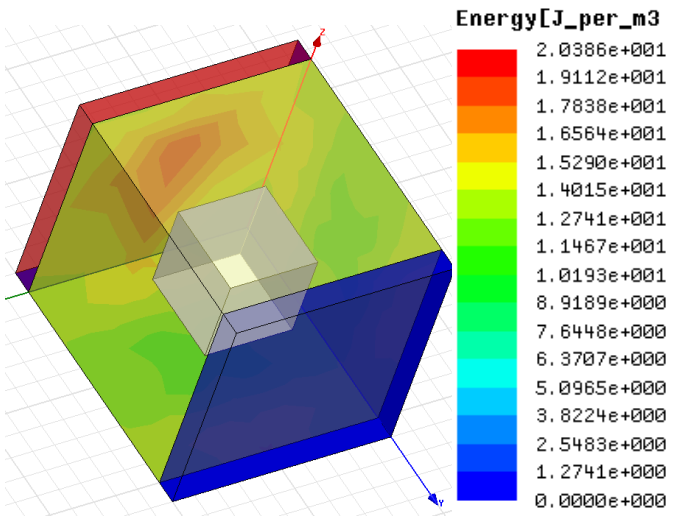


(a)

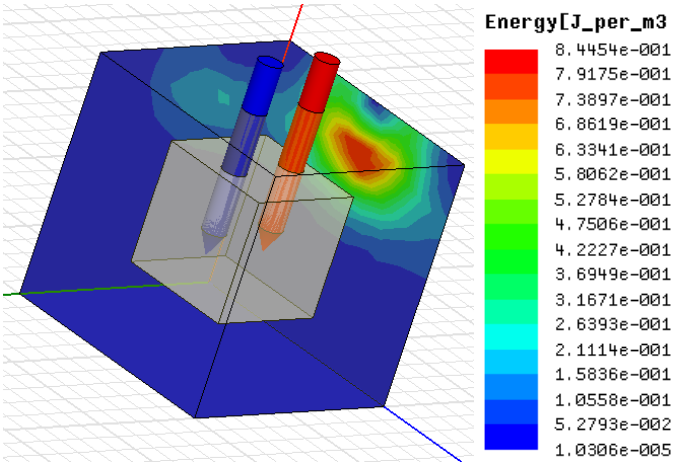


(b)

Figure 4.31. 3DElectric field distribution of normal tissue with parallel plate electrodes (a) and needle electrodes (b).



(a)



(b)

Figure 4.32. 3DEnergy distribution of tumor within tissue with parallel plate electrodes (a) and needle electrodes (b).

4.3.2. Multi-Needle Electrode Arrays for Large Tumors

Tumors can vary in size depending on the type of the tumor and the stage of the cancer. Clinical trials on patients have revealed that tumors can be less than 3mm or even greater than 30mm in size (Campana et. al., 2009). For large tumors, if a single pair of

needle electrodes with 4mm gap is used, the tumors would have to be treated multiple times at different locations in order to cover the entire area. This would not only be more time-consuming, but the drug effect may also reduce (the pulses have to be applied within a few minutes of the drug injection) and also the patients have to be sedated for longer durations. Thus, it is desirable to have a large multi-needle electrode array which would produce the same effect in a larger area with a fewer attempts than it is being practiced currently. Another serendipitious outcome of using large needle array is the advantange that the electric field in this case is stronger and more uniform with multiple needle electrodes than a single pair of electrodes.

Figure 4.33 shows the 2D electric field distribution in the tumor using multi-needle electrodes, with arrays of 4 (a), 8 (b), and 16 electrodes (c). The electric field is evenly distributed between the positive and negative column of electrodes in case of the 4 electrode array and it is the same in the case of 8 and 16 electrodes also. The magnitude of electric field is 1100 V/cm, close to the desired value of 1200 V/cm in the tumor region between electrodes in case of 4 needle electrodes. Similar values are obtained for the 8 and16 electrode arrays too.

Figure 4.34 shows the 3D distribution of the electric field using 8 multi-needle electrode array. The electric field distribution in the 3D model with 8 needle electrode array is similar to the values obtained in 2D. The energy distribution (Figure 4.35) shows a maximum magnitude of 55J/m^3 of energy in the region between the electrodes. Hence depending on the size of the tumor, multiple electrodes can be arranged side-by-side to form a larger electrode array and produce a uniform field in a large tumor area.

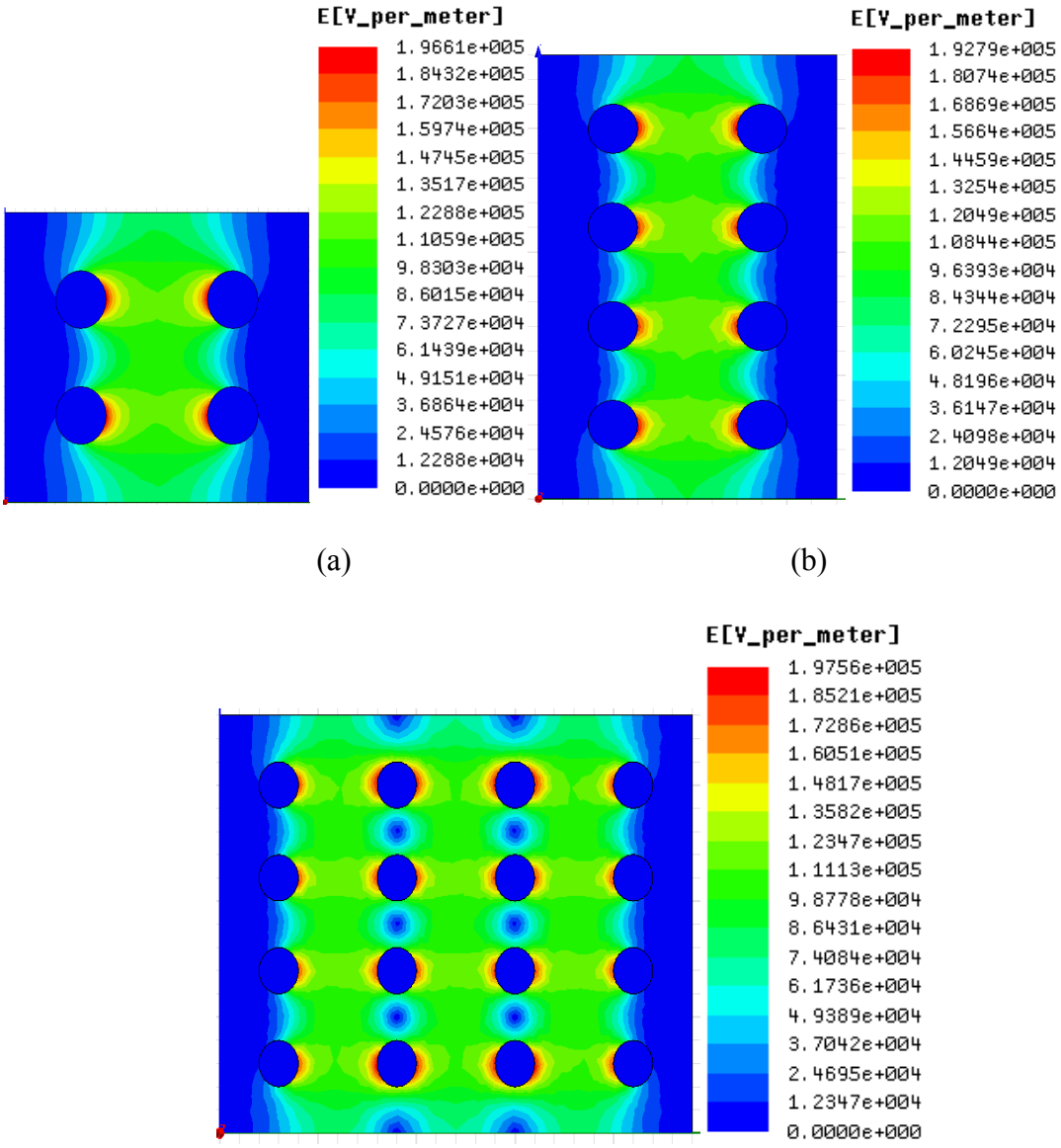


Figure 4.33. 2D Electric field distribution of 4-(a), 8-(b) and 16-(c) needle electrode array.

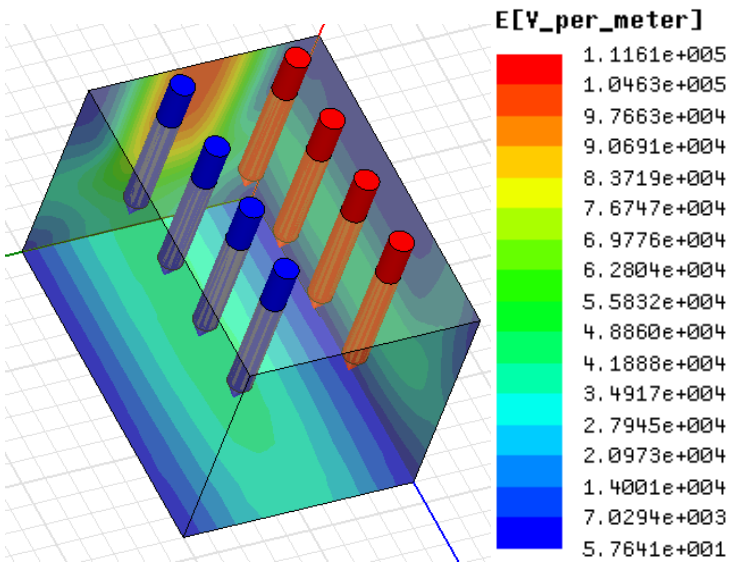


Figure 4.34. 3D Electric field distribution of 8-needle electrode array.

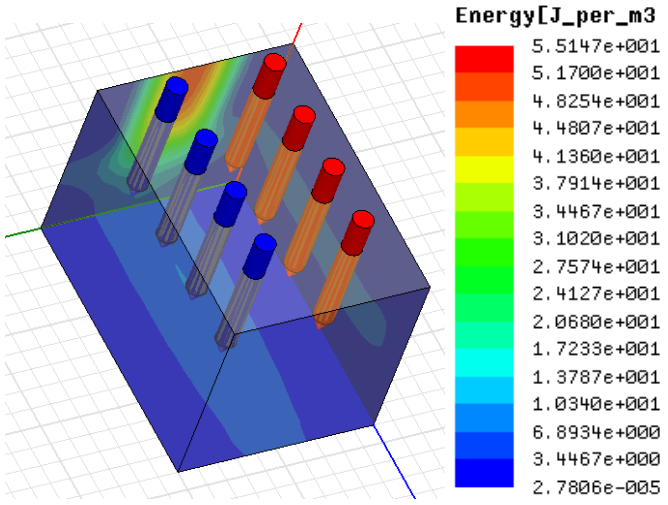


Figure 4.35. 3D Energy distribution of 8-needle electrode array.

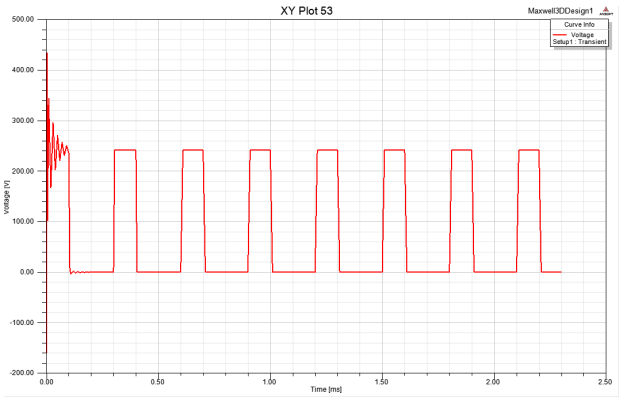
4.3.3. Electrode Polarity

Simulation tests were done on the 3D models with parallel plate and needle electrodes to check if electrode polarity makes a difference to the electric field in the

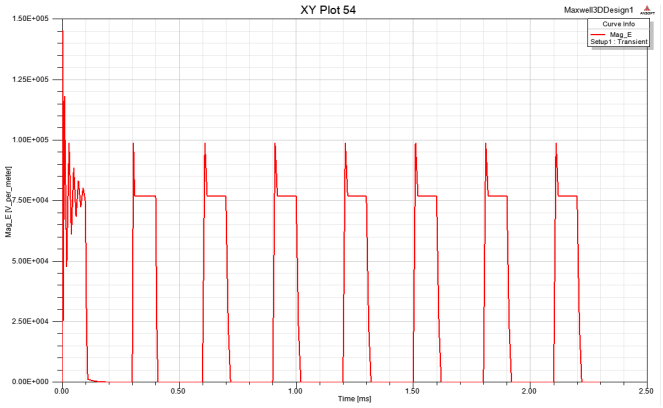
tissue. There was no change in electric-field distribution when the polarity of voltages in the electrode was interchanged, that is when a negative voltage is applied. The electric field distribution was similar to the obtained in Figure 4.30. This confirms that the electric field is independent of voltage polarity.

4.3.4. Pulsed Electric Fields

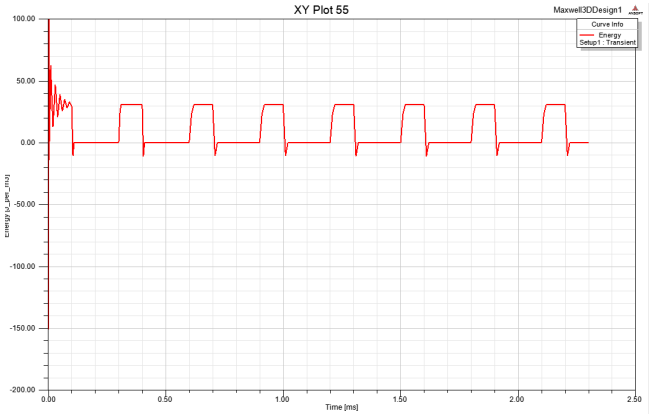
The breast lobule, breast model and electrode design were considered to be electrostatic and simulations were run for constant DC or AC type voltages. In this section, pulsed voltages are applied to simulate conditions close to actual practical treatment conditions. 100μs pulses are most commonly used in current treatments. 1200V/cm is applied to a rectangular block of tissue as in the previous sections, but in this case 8 pulses of 100μs duration and an interval of 200μs are applied. The voltage distribution (a), electric field distribution (b) and energy distribution (c) are as shown in Figure 4.36. The voltage of 250V yields an electric field of about 750 V/cm during the pulse. The energy during the pulse was 32 J. This model and simulation is the first step towards transient analysis. Further work in this area is recommended and will prove beneficial for electroporation studies since time for which pulses are applied are very small in real-time applications.



(a)



(b)



(c)

Figure 4.36. Voltage (a), electric field (b) and energy (c) distribution for pulsed voltages in tissues.

4.4. Thermal Effects of Electroporation

The temperature rise due to Joule heating during electroporation is determined from the equation (1) (Miller et. al., 2005).

$$\Delta T = \frac{tE^2}{r\rho c_p} \qquad (4.1)$$

where ΔT is the temperature rise in degree centigrade, *t* is the pulse length that causes the temperature rise, *E* is the electroporation voltage gradient, *r* is the resistivity of the medium,ρ is the density and c_p is the specific heat of the medium.

Using equation (4.1), temperature rise is calculated for pulse parameters that are used in standard electroporation protocols. Table 4.3 lists the various pulse duration and voltages used and the corresponding temperature rise. Figure 4.36 shows the temperature rise for various parameters graphically. As can be seen, there is not much heat dissipated for the pulse parameters used at present. The maximum rise is around 3°C. Similar studies by Weaver indicated that temperature rise is around 1°C per pulse, which correlates with our results obtained (Weaver, 1993). Care should be taken during design and planning so that there is no significant damage to tissues because of joule heating. Previous studies have indicated that a temperature rise above 50°C can cause thermal damage and electroporation parameters have always be chosen so that they produce minimal heat dissipation (Miller et. al., 2005; Davalos et. al., 2003;Edd et. al., 2006).

Table 4.3. *Temperature rise due to electroporation*

Pulse duration	Voltage	Temp rise (°C)
300ns	10kV	0.10204
10ns	300kV	3.0612
100µs	1200V	0.4897
25ms	125V	1.3286
10ms	200V	1.3605

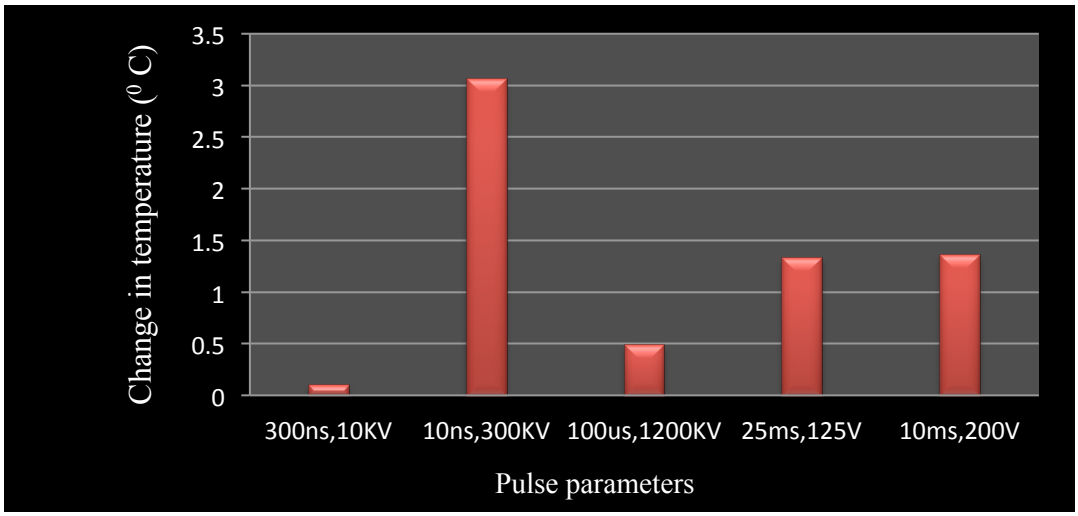


Figure 4.37. Temperature rise at various pulse parameters during electroporation.

4.5. Summary

Simulation results for the various models under different conditions are illustrated in this chapter. The main results obtained from the research can be summarized as:

1. Electric field distribution of tumor tissue is much lower than that of normal tissues (5% in case of breast tissues to 50% in case of breast lobules depending on tissue and electrode type and position).
2. Fat and skin layers have very little impact on the electric field of breast tissue.
3. AC sources yield much lower electric fields than DC (22–117% reduction).
4. Needle electrodes are more effective than parallel electrodes for treatment of deep tumors (5-10% increased reduction of electric field).
5. Electrode polarity has no effect on electric field distribution.
6. Multi- electrode arrays are more suitable for large tumors. 2×2, 4×2, 4×4 needle electrode arrays are developed for varied tumor sizes.
7. Temperature rise during electroporation is a maximum of 3°C. Hence, thermal effects are negligible.

Simulation of human breast tissue will help in improving electroporation techniques for all types of breast cancers. Results obtained under from comparison of parallel plate and needle electrodes and thermal calculations will help in electrode design. Multi-needle electrode arrays will help improve current methods significantly.

CHAPTER 5. CONCLUSION AND RECOMMENDATIONS FOR FUTURE WORK

5.1. Conclusions

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.

Electrochemotherapy is a viable technique, whose efficacy depends on the electric field distribution and the magnitude. In this research, the efficacy of needle and parallel plate electrode geometries for both normal and tumor breast models was explored. Electric field distribution trends were studied in various models: breast lobules and whole breast models. The effect of electrode position, source type and surrounding tissues was analyzed. For large tumors, multi-electrode arrays were developed to study even field distribution in large areas.

Key results from this research can be summarized as:

- The electric field intensity in tumors is less than that of normal tissues illustrating the different electrical characteristics of the malignant and normal tissues and hence their susceptibility to electrochemotherapy. Tumor tissues had electric field strengths that were 5-50% lower than normal tissues depending on the electrode configuration.

- 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 reduction in electric field was higher in needle electrodes (5-10% higher) than parallel plate electrodes making them more effective for electroporation.
- The ac electric field intensities are lower (7-31% in case of whole breast and upto 117 % in case of lobules) than dc for the same voltage. This is due to slower charge accumulation because of the bipolar nature of the ac voltage applied.
- With increase in tumor size and more the tumor spreads from its originating area, the more difficult it is to cover the tumor area with a single pair of electrodes. A pair of electrodes covers only a portion of the tumor, making it necessary to have multiple treatments. However, the location of tumor does not cause a problem as needle electrodes can be inserted accordingly and varied needle lengths also make it convenient for treatment of deep tumors.
- 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.
- Electrode polarity has no effect on electric field in normal and tumor tissues. Reversing the polarity of source voltage did not change the field distribution in tissues.

- Thermal calculations indicate that the maximum temperature rise due to electroporation is 3°C for the current pulse parameters. This ensures that electroporation is a non-thermal phenomenon and does not cause tissue heating and burning.

To conclude, electroporation is an effective way to target tumor tissues and get rid of them while normal tissues are still unaffected. Modeling and simulation studies show favorable electric field distributions that can be used in the development of electrodes and setting pulse parameters for practical treatment. These results emphasize the fact that cancer tissues are more susceptible to external electrical influences and will help improve electrochemotherapy techniques to treat tumors that are not receptive to conventional therapies.

5.2. Recommendations for Future Work

Our two and three-dimensional models can be used as the fundamental block and can be built upon further. Simulation studies of breast tissues and carcinoma will help improve techniques for tumor treatment. Since there has not been much work done in this area previously, this project provides a good understanding of basic tumor behavior and electrical characteristics. However, a more detailed model is necessary to study in-depth characteristics and behavior of breast cancer cells and tissues. A three dimensional model with pulse voltages for short durations can be studied to understand the effects of electroporation in order to implement it as a treatment for breast cancer. Transient behavior and characteristics is crucial for electroporation as very short duration pulses are

applied to tissues. A study of magnetic characteristics along with electrical would help to obtain a broader perspective and understanding on this subject.

Electrochemotherapy is a promising technique with several advantages over conventional therapies. Theoretical simulations and improvements of existing techniques will help in improving the efficacy and efficiency of electroporation as an anti-tumor treatment.

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LIST OF PUBLICATIONS

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Agoramurthy, P., Campana, L. and Sundararajan, R. (2011). Finite element modeling and analysis of breast tissue for electrochemotherapy.Conference proceedings from CEIDP 2011.*Annual International Conference on Electrical Insulation and Dielectric Phenomenon.*Cancun, Mexico.

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Agoramurthy, P. and Sundararajan, R. Utilization of transient dielectric breakdown phenomena of live biological cells for electrical pulse-mediated cancer therapies. *Electrical Insulation Magazine (Invited).* In revision.

PAPER/POSTER COMPETITION AWARDS

First place for paper titled ‘Tumor electric field distribution studies using various electrode configurations’. *2011Annual Conference of Electrostatics Society of America*, Cleveland, Ohio, USA.

Third place for poster titled ‘Electric field distribution study of a novel breast tissue model’. *2011 Breast Cancer Discovery Group Retreat*, Purdue University, IN.