MASTER OF SCIENCE IN ELECTRICAL AND ELECTRONIC ENGINEERING

Optimization of the US Probe Design and the RF Signal for Focused US Tissue Heating

Department of Electrical and Electronic Engineering
Islamic University of Technology (IUT)
Board Bazar, Gazipur-1704, Bangladesh
28th October 2021.

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By

Nchouwat Ndumgouo Ibrahim Moubarak

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IN

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CERTIFICATE OF APPROVAL

The thesis titled "Optimization of the US probe design and the RF signal for focused US tissue heating" submitted by Nchouwat Ndumgouo Ibrahim Moubarak, student identity number 181021013 of Academic Year 2018-2020 has been found satisfactory and accepted as partial fulfillment of the requirement for the Degree of MASTER OF SCIENCE in Electrical and Electronic Engineering on the 28th October 2021.

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This work is dedicated to my parents

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LIST OF ABBREVIATIONS OF TECHNICAL TERMS

DCIS	**Ductal Carcinoma In Situ**
LCIS	**Lobular Carcinoma In Situ**
IDC	**Invasive Ductal Carcinoma**
ILC	**Invasive Lobular Carcinoma**
LHRH	**luteinizing Hormone-Releasing Hormone**
US	**Ultrasound**
FUS	**Focused Ultrasound**
HIFUS	**High Intensity Focused Ultrasound**
MRI	**Magnetic Resonance Image**
CT	**Computed Tomography**
FDTD	**Finite Difference Time Domain**
FEM	**Finite Element Method**

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ACKOWLEDGEMENT

I would like to express my unparalleled gratitude to Almighty Allah for divine blessing without which it would not have been possible to complete this thesis successfully, and to my parents for their blessings.

My special and heartiest gratitude is entrusted to my supervisor Dr. Md. Taslim Reza, Associate Professor, Electrical and Electronic Engineering Department, Islamic University of Technology (IUT), Gazipur, for the encouragement and valuable advice provided to me during completion of my thesis. I couldn't have completed my research without his continuous guidance and support.

I am thankful to Professor Dr. Md. Ruhul Amin, Professor and Head, EEE Department, IUT, for his valuable support throughout the two years of my M.Sc. course.

I would like to thank all the faculty members and staff of the Department of EEE, IUT for their inspiration and help.

Finally, I would like to thank my friends for having faith in me throughout the times of this thesis.

Nchouwat Ndumgouo Ibrahim Moubarak October 2021.

ABSTRACT

Focused ultrasound (FUS) hyperthermia is a non-invasive therapeutic technique applied to the selectively and targeted ablation of cancerous lesions in the breast. This is done by the thermal effect (bio-mechanical heating) and non-thermal effect (e.g. cavitation), with minimal deleterious effects to the surrounding healthy tissues. The prime objective of this work is to optimize an ultrasound transducer design and the radiofrequency signal for focused ultrasound that will result in the creation of a very high acoustic pressure at a focal point inside the normal breast tissues by FUS energy to favor a potential in improving both oncologic and cosmetic results in breast cancer therapy. To attain this objective, an Ultrasound (US) probe which increases the targeted volume of cancer and that preserves neighboring healthy tissues from being ablated in a modeled realistic breast is designed using a finite element analysis (FEA) tool in this work. The acoustic pressure field and focal point of the FUS were characterized by optimizing the transducer frequency and initial water temperature values at 1.3 MHz and 20°C respectively. This optimal condition yielded qualitative properties of the Focused Ultrasound (FUS) at the focal point which are extendable to wider areas. This enable the achievement of quantitative results by displacing the probe at reduced time intervals of less than 60s. An elliptical focal volume of 10.2 mm (along beam axis) × 4 mm (in the transverse direction) at 50s of dosing for a tumor diameter of 10mm, corresponding to a fractional healthy tissue damage of 2.1%, a temperature rise of 99°C above the ablation threshold temperature of 42°C, at 100s of sonication and an increased pressure oscillation at the focus that favors tumor ablation by cavitation are obtained. The optimal condition of the setup is therefore found to be mostly sensitive to variation of the transducer frequency on which depend the attenuation coefficient and thermal conductivity of the tissue as well as the surface intensity of the transducer

Chapter 1

INTRODUCTION

1.1 Chapter overview

In our present era, non-negligible percentages of dead are accounted for by the late or false diagnosis of diseases, by human errors committed by medical experts during medical results analysis or by the improper treatment of the diagnosed diseases, amongst which are cancers. These result from the poor quality of images produced by the conventional imaging techniques and the long time needed to confirm an infection by biopsy as well as the inappropriate therapeutic approach adopted in treating the various kinds of diseases including cancers. Although the conventional medical imaging techniques are noninvasive in nature, X-ray uses radiations that may cause cancer if a patient is exposed to it for a long time, MRI is expensive and is not readily available and CT-SCAN can only be operated by experts. Ultrasound is the only pure noninvasive technology that provides comparative oncological, cosmetic and therapeutic advantages in medical applications, with minimal deleterious effects to healthy tissues. The conception, design, optimization and proper handling of the ultrasonic devices are therefore primordial in medical applications, notable in cancer imaging and therapy.

1.2 Project's background

Amongst the deadliest diseases common in the world's population in our present era, is cancer on the top of the list after the cardiovascular and cerebrovascular diseases. Cancer is considered as the second leading cause of death in the world, with nearly 8.8 million deaths (15.7% of total) each year [1]. Excluding lung cancer, Breast cancer is the most prevalent type of cancer. Malignant tumors capable of spreading via underarm lymph nodes to other parts of the body and that result from untreated cancerous breast cells increase the risk of death. The lifetime breast cancer risk for a woman is 1/8 against 1/833 for a man. It is estimated that 281550 new cases of invasive and 49290 non-invasive (in situ) breast cancer are expected to be diagnosed women against 2650 new invasive cases in men in the United States in 2021.An approximate of 43.600 of those affected would die as a result of these breast cancers. These death rates would exceed those of other cancer types, with the exception of lung cancer, for women in the USA [2]. As a result of these high death rates, an effective and safe diagnosis and treatment of breast cancers amongst others, is therefore necessitated, so as to drive the mortality rate caused by cancers to a minimum zero level. FUS is chosen in preference in breast cancer therapy because of its non-invasive mode of application and its level of safety to the surrounding healthy tissues.

1.3. Project's statement

Focused ultrasound hyperthermia presents substantial side effects in its procedure of application. These include: Firstly, the appearance of local pain. The application of the FUS for a period between 10 to 60 minutes on the breast surface in order to converge the beam in a targeted zone within the breast sometimes causes discomfort and pain to the patient [2-3]. Secondly, skin burns. The high intensity focused ultrasound (HIFUS) technique usually applied for a period ranging from 0.1 to 30 seconds sometimes causes the burning of sensitive skin [2-3]. Also, the injury and damage to surrounding tissue is a drawback of using FUS. The cancerous masses and lesions targeted are sometimes not bounded with precision hence the focal zone of the ultrasound is not always obtained accurately. This causes the destruction of healthy tissues around the targeted zone and together with some healthy tissues traversed by the beam within the breast before reaching the targeted lesion.

1.4. Project's objective

An effective design of a US probe with optimized RF signal selection would reduce the pain and the healthy tissue burnt. A computation model closer to a realistic human breast is modeled and the acoustic field together with the focal region of the US wave are characterized for an effective ablation of breast lesion at sonication periods far less than 15 minutes via an effective design of a US probe with optimized RF signal selection that reduce the pain and tissue burning. This work focuses on an optimized US probe design, effective RF signal selection and overall analysis of the tissue heating due to the US signal for the whole spectrum of the tissue. These are articulated around:

- Designing US probe and a model of the lesion surrounded by healthy tissues via simulation tool. The parameters of the transducer considered during the design are chosen based on the detailed properties of the breast. These parameters include; the radius of curvature of the transducer, that will determine its focal length and the diameter of the transducer, that will determine the sonication area and hence the intensity of the sonication at the focal region.
- Optimizing the RF signal pattern and heating time to avoid local pain, skin burns and injury to surrounding tissues. The RF frequency is the frequency above 20 KHz used by

the transducer. The higher the frequency used the less penetrating the ultrasound signal into the breast tissues and the lower the frequency, the more penetrating the signal becomes. So a proper value of the frequency at the range the RF range is then required to be selected so as to ensure the focusing of the beam at the premeditated region.

- Analyzing and presenting the cancer tissue destruction through US signal and the impact to the surrounding tissue. This analysis will involve the reduction of the volume of the targeted healthy tissue by the ultrasound beam by simultaneously maximizing the volume of lesion targeted. This proceeding will be done by selecting the appropriate frequency of sonication on which depend other properties like the attenuation coefficients of the tissues and the design parameters so as to render the focal region more spherical in shape contrarily to the cylindrical existing shape.

1.5. The methodology

The extent of this thesis is to understand the mechanical properties of the various lesion types and the breast environment, followed by the design and simulation of the equivalent breast region and US probe model using Multiphysics simulation software (COMSOL). This would foster the Understanding of the impact of US signal with tissue burning during US scanning via an equivalent simulation model and the analysis of the impact of the tissue burning all through the equivalent breast region including normal tissues and lesions. We would be able to analyze the effects of different tissue heating properties for the constitutive layers making the anatomy of the breast. These constitutive layer structures are subcutaneous fat, gland tissue, and tumor tissue. Finally we optimize the parameters for both US probe and the signal for effective use of tissue burning for cancer tissues and safer impact for normal tissues.

1.6 The scope of the thesis

COMSOL Multiphysics is used in this work to design and simulate a proposed model of FUS used in breast tumor ablation. The US wave propagation through the healthy breast tissues and the tumor were simulated. The parameters of the US probe and their effects on pressure and thermal fields within the normal and tumor tissues were selected. These were necessary for the qualitative characterization of the focal point for the effective ablation of the lesions within the breast. The results obtained were validated by comparing them to a computational study of FUS undertaken on a realistic patient model in the model proposed in [1].

1.7. Organization of the thesis

This book is comprehensively organized in seven chapters with discussions;

In chapter two involving the literature review on the subject matter. A comprehensive review of the basic scientific knowledge on the related breast lesions types, their origin, modes of spreading and level of danger represented by each are evoked. Various types of ultrasound therapies are elaborated as well as the different types of ultrasound transducers. Finally the different types of computational techniques are also studied.

In chapter three concerning the work done in the thesis in proper. The detailed methodology is outlined and comprehensive explanation of each step brought forward and the materials with the methods adopted in this thesis elaborately discussed.

In chapter four pivoting on the results analyses. The validation of the results obtained is done with comparison to a previous work done on a realistic patient. Different plots of temperatures and pressure intensities in the breast domain are analyzed.

In chapter five concerning a detailed discussion on the results obtained.

Finally, chapter six and seven address the sensitivity and conclusion themes respectively.

Chapter 2

LITERATURE REVIEW

There exist several cancer types, most of which are very deadly and others relatively deadly that end up becoming life threatening if not properly diagnosed in time and properly handled. Some of these lesions are mentioned in this chapter and their mechanisms of spreading are discussed. Several methods of cancer therapy are being used in our modern era, including invasive techniques like surgery, chemotherapy and non-invasive techniques by using ultrasound transducers. These different techniques used in therapy are briefly discussed in this chapter.

2.1. Overview on the types of breast Cancer

Breast cancers are of different types, corresponding to various levels of severity and can originate anywhere in the breast. Different types of breast cancer could be characterized by different cell structures, how and where they develop and spread out. The cancer types frequently diagnosed in the breast are; invasive lobular carcinoma, ductal carcinoma in situ and invasive ductal carcinoma. Malignant and benign types are also recurrent as the mostly diagnosed forms of breast cancers [3].

2.1.1. Non-invasive breast cancers

These cancer types are by definition cancers found within the lobules or milk ducts in the breast. They are termed carcinoma in situ and are sometimes or simply pre-cancers [4]. These are cancer types that are localized and have not yet spread to other parts of the healthy tissues at the time of their diagnosis. These include;

Ductal carcinoma in situ (DCIS)

DCIS is the most recurrent and diagnosed type of non-invasive breast cancer. The milk ducts are its site of origin. Its non-invasive nature is due to the fact that it is localized at a specific spot and has not yet swarmed to other healthy sites. DCIS is not deleterious to life so long as it remains localized and is early managed, but improperly managing DCIS increases the probability of developing lethal cancer types later in life [4].

Lobular carcinoma in situ (LCIS)

LCIS is by the definition non-invasive in nature. It is breast cancer that grows in the lobules. It is also localized and has not found its path to other parts of the body hence known as non-invasive. LCIS is also not too dangerous but would become dangerous if improperly managed [4].

2.1. 2. Invasive breast cancers

These are breast cancers that have already spread and passed beyond their site of origin outside the ducts or lobules of the breast into the neighboring healthy calls. They are termed 'Early breast cancer' because they are found in the breast and have probably spread to the neighboring tissues or elsewhere in the body [4]. They include;

Invasive Ductal Carcinoma (IDC)

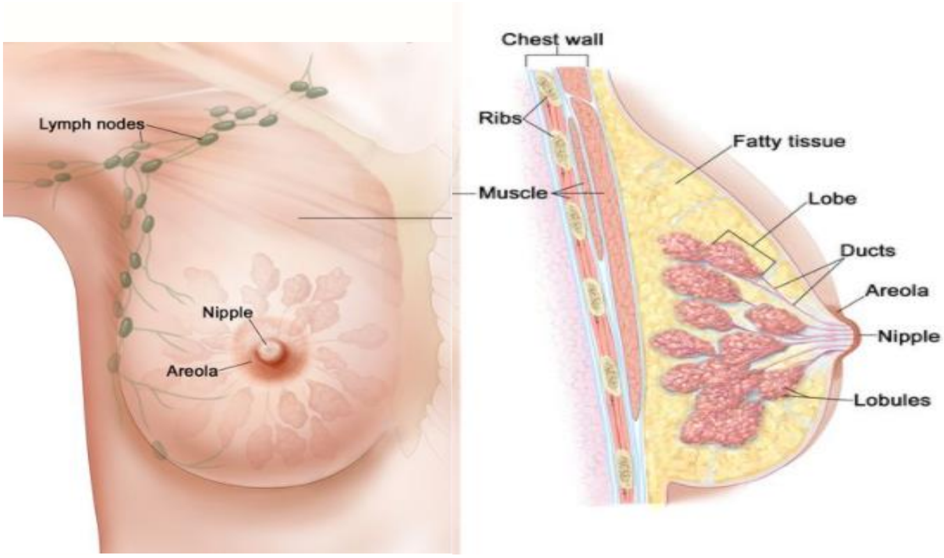
IDC is the most recurrent form of breast cancer. Close to 80% of all diagnosed breast cancers are of this type. IDC signifies that the cancer that originated in the breast's milk duct broke through the lining of the latter and spread into the close neighboring breast tissue. In the course of time IDC can reach other parts of the body [4].

Invasive Lobular Carcinoma (ILC)

ILC comes after IDC in its invasive nature. ILC refers to cancers originating from the milk-producing lobules of the breast that break through the lining of the lobule and spread into neighboring breast healthy tissue. With time, ILC reaches other parts of the body via lymph nodes [4].

2.2. The need to kill breast cancer cells

The need for an effective and safe non operative technique used in the destruction of breast cancers with a minimal destruction of the surrounding healthy tissues, together with the preservation of patients comfort has been a point of concern for researchers in the past decades [5]. Amongst the new strategies that are used to ablate the cancer of the breast include; hyperthermia, biological therapies, gene and inhibitors of angiogenesis, photodynamic therapy and laser treatment, Most of the cited techniques above still need to be optimized [5]. Hyperthermia is a technique proven to be the most effective and safe technique among the alternative methods used in cancer therapy [1-10]. This is because it is a purely non-invasive technique, using heat at moderate temperatures to destroy cancerous cells [7].



(a) (b)

Figure 2.1: Structure of a healthy breast (a) front view (b) side view [4].

2.3. The Standard treatment of breast cancer

Many approaches are being adopted to cure breast cancers amongst which include invasive and non-invasive approaches. Some of these technique are discussed in this subsection as follows;

2.3.1. Surgery

This involves the invasive removal of cancer from most patients. A pathologist injects a radioactive substance or blue dye into the breast near the suspected tumor mass. He monitors the movement of this substance under a microscope. The first lymph node to receive the dye (called sentinel lymph node) is removed, a process called sentinel biopsy. In case of no presence of cancer, no further removal of sentinel lymph nodes is required. But if cancer is found, dissection is then done (the removal of sentinel lymph nodes by separate incision) followed by the conservation of cancer mass removal, the process called mastectomy [4].

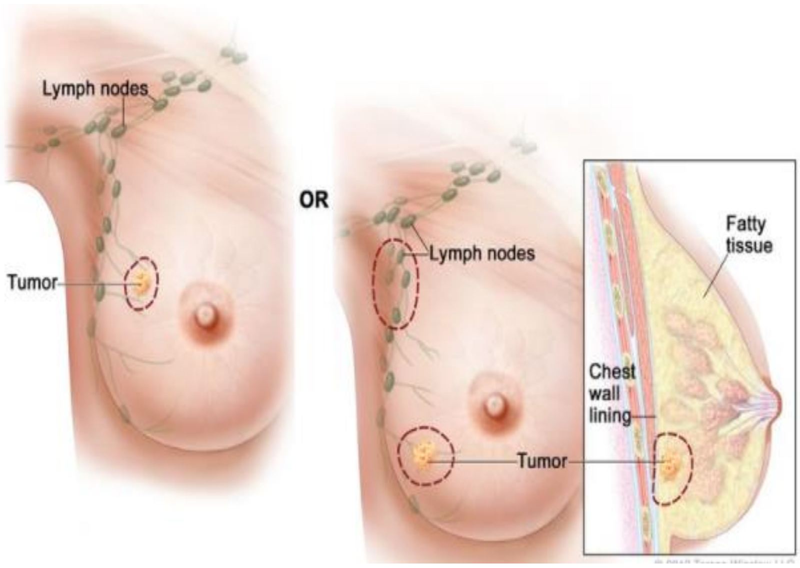
Mastectomy is removal of the cancer and some normal tissue around it during a chirurgical operation, avoiding the entire breast removal. When the cancer is located near the chest, a portion of its lining is also removed along with the cancer. Mastectomy is also termed as breast-sparing surgery, lumpectomy, segmental mastectomy, partial mastectomy, or quadrantectomy [4]. Mastectomy is sub classified as follows;

Total mastectomy

This is removal of the whole breast mass by surgery and it is also known as a simple mastectomy procedure. The removal and checking for cancer of some of the lymph nodes under the arm may be done here simultaneously or after breast surgery and in a separate incision procedure [4].

Modified radical mastectomy

This involves surgery to remove cancerous breast and the surrounding affected tissues including the chest lining.



(a) (b)

Figure 2.2: Structure of the cancerous breast showing the (a) Front view (b) Side view [4].

2.3.2. Chemotherapy

This is cancer treatment by the use of chemical compounds to strongly hinder the cancerous cells from growing, by preventing them from further multiplying themselves or simply killing them. The chemical substances are into the body by oral means or by inoculation into the veins, where they end up entering the blood streams and finally the cancer sites, the process known as systemic chemotherapy [4].

Chemotherapy sometimes precedes and or follows surgery for the complete treatment of the tumor. When it is done before surgery, it helps to shrink the tumor and minimize the amount of removable tissues during surgery. Chemotherapy done prior to surgery is called preoperative therapy or neoadjuvant therapy. Apart from chemotherapy, other treatments like targeted therapy, or hormone therapy , may be done on some patients after surgery, for the complete removal of any cancerous cell left behind. This type of treatment following surgery to prevent cancer from reappearing is called postoperative therapy or adjuvant therapy[4].

Breast reconstruction may be done during or after mastectomy. This may be done using some other tissues from the patient's body or using artificial implants filled with saline or silicone gel [4].

2.3.3. Radiation therapy

This is cancer treatment making use of radiations with high energies like X-rays, to ablate cancer tissues or prevent their further growth. Two factors determine the application of radiation therapy in cancer treatment. These are: the type of the cancer and the stage at which the cancer being treated is at that moment. Radiation therapies include;

The external radiation therapy. This uses a machine outside the body to send radiation toward the area of the body with cancer [4]. It is mostly used to treat breast cancer.

The Internal radiation therapy . Radioactive substances are sealed here in needles, seeds, wires, or catheters, placed directly into or near the cancer. It is mostly used to relieve bone pain caused by breast cancer that has spread to the bones by using strontium-89 (a radionuclide).

2.3.4. Hormone therapy

This is a cancer treatment process involving the removal or prevention of hormonal actions so as to hinder cancer cells development. Hormones are bloodstream-circulatory biochemical substances manufactured by special glands in the body. Some of these biochemical substances can favor the growth of some cancers. Cancer cells, having sites where hormones can attach them are called receptors. These cancers are detected by special medical tests and the hormones to be attached to them to favor their growth are hindered either by surgery, drugs or radiation therapy to get attached to the cancer. Estrogen a hormone mainly made by the ovary is an example of a hormone favoring the growth of some breast cancers. Ovarian ablation is then the treatment undertaken to hinder the ovaries from producing estrogen. [4].

Tamoxifen hormone therapy is usually done on patients with early diagnosed and removable localized breast cancer by surgery and those with metastic breast cancer Tamoxifen or estrogens hormone therapy increases the risk of developing endometrial cancer because it acts all over the body . Pelvic exam should be done on women taking tamoxifen to check for any sign of cancer. Menstrual bleeding is the only regular virginal bleeding that should not be reported to a medical specialist, else any bleeding should be reported to a doctor as soon as possible [4].

The other types of hormone therapies include: Hormone therapy with a luteinizing hormone-releasing hormone (LHRH) agonist and Hormone therapy with an aromatase inhibitor [4].

2.3.5 Targeted therapy

This type of treatment identifies and attacks specific cancer cells by using drugs or other substances. These procedures are usually less harmful to normal cells contrarily to chemotherapy or radiation therapy. The types of targeted therapies used in the treatment of breast cancer are; tyrosine kinase inhibitors, Monoclonal antibodies, mammalian target of rapamycin (mTOR), inhibitorscyclin-dependent kinase inhibitors, and PARP inhibitors [4].

Monoclonal antibodies

T-antibodies are immune system proteins antibodies, artificially produced in the laboratory for some diseases treatment like cancer. These antibodies are able to attach themselves to specific targets on cancer cells or other cells that may help cancer cells grow, hence killing the cancer cells. Monoclonal antibodies may be used alone or to carry drugs, toxins, or radioactive material directly to cancer cells and are given by infusion [4]. The Types of monoclonal antibody therapy include the following: Trastuzumab (HER2),Trastuzumab deruxtecan, Pertuzumab,Ado-trastuzumab emtansine and Sacituzumab govitecan.

Tyrosine kinase inhibitors: (TKI)

This is a treatment involving the blocking of signals necessary for tumor growth. TKI may be used with other anticancer drugs as adjuvant therapy [4]. TKI include; Tucatinib , Neratinib and Lapatinib.

Cyclin-dependent kinase inhibitors

This is a treatment protocol based on the blocking of proteins called cyclin-dependent kinases (CDKs), which cause the growth of cancer cells. Advanced hormone receptor–positive HER2 negative breast cancer may be effectively treated by the combination of Hormone therapy with

CDK4/6 inhibitors [4]. Cyclin-dependent kinase inhibitors include the following; Palbociclib , Ribociclib ,Abemaciclib and Alpelisib.

Mammalian target of rapamycin (mTOR) inhibitors

This involves the blocking mTOR proteins, hence hindering cancer growth and prevent the development of new blood vessels necessary for tumor growth [4]. An example of mTOR inhibitors is Everolimus.

2.3.6 Immunotherapy

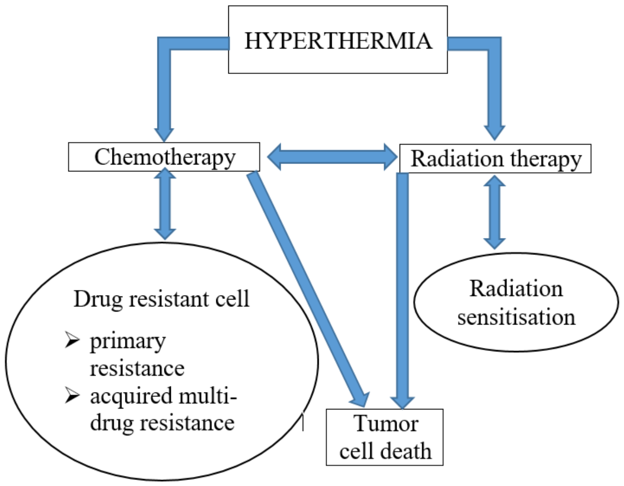
The use of the patients' immune system to fight cancer is called immunotherapy. Immunotherapy is a type of biologic therapy. Here Laboratory made substances or substances naturally made by the body are used to boost, direct, or restore the body's natural defenses against cancer.

The different types of immunotherapy include:PD-1 and PD-L1 inhibitor therapy. PD-1 is a protein on the surface of T cells that helps keep the body's immune responses in check. PD-L1 is a protein found on some types of cancer cells. When PD-1 attaches to PD-L1, it stops the T cell from killing the cancer cell. PD-1 and PD-L1 inhibitors keep PD-1 and PD-L1 proteins from attaching to each other. This allows the T cells to kill cancer cells. Atezolizumab is a PD-L1 inhibitor used to treat breast cancer that has spread to other parts of the body [4].

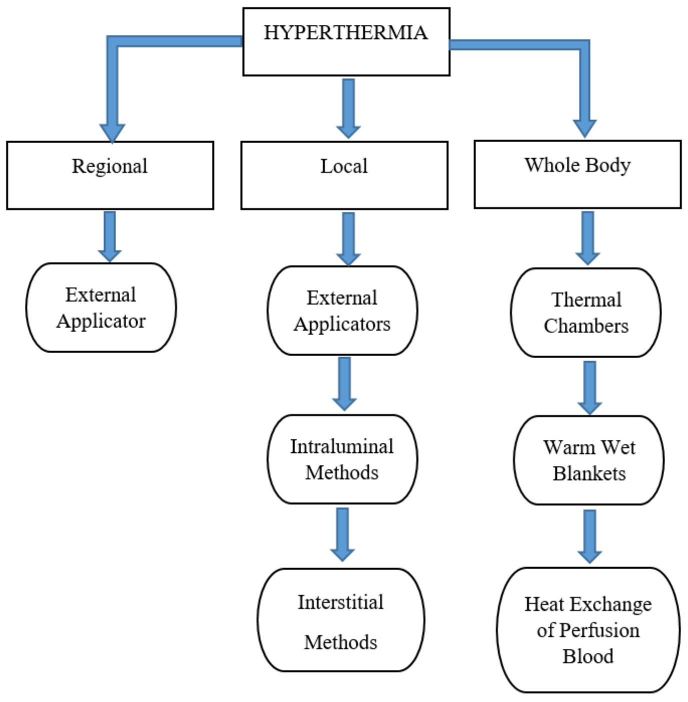
2.4. Possible methods used to kill breast cancer

Many energy-based approaches (hyperthermia) have been used in cancer treatment during the past years. Hyperthermia is mostly used as a complement to other therapies like radiotherapy and chemotherapy to eliminate radio and drug resistant tumor cells respectively as shown in figure 2.3(a) [6, 8].

The most widely used hyperthermia techniques are radiofrequency ablation, laser thermotherapy, the frequency enhancers, Microwaves, with ultrasound surgery being truly a non-invasive technique, since acoustic waves are emitted by an external transducer [9]. These processes are termed Thermal ablation techniques. They use a locally generated heat (within the cancer tissues themselves) to kill the cancer tissues. When the energy of the waves are absorbed in a dissipative medium (tissues), they are converted to heat. Thermal ablation therapy can be achieved by increasing the tissue temperature above a standard level to change the properties of targeted tissue [10]. This increase in temperature changes the properties of targeted tissues by causing coagulative necrosis and protein denaturation of the lesion cells within only a few seconds.



(a)



(b)

Figure 2.3: (a) Hyperthermia for tumor cell death (b) Different Methods of Hyperthermia techniques [6].

The three [7] hyperthermal processes include; heating the whole body to 38° – 40°C to stimulate body immunity, heating cancer cells to 42 – 43°C to ablate them and the localized killing of cancer cells by using high temperatures of between 60°C – 90°C. The second procedure is followed in this work. Figure 2.3 (b) summarizes the different methods of hyperthermia techniques [6, 8].

2.5 The different types of hyperthermia techniques

Hyperthermia by definition is the application of heat concentrated at a particular area in medical applications especially in therapeutic applications. There exists several of these techniques based on how the heat is being generated and how it is being utilized. The most important and widely used hyperthermia techniques are explained in this section.

2.5.1 Ultrasonic Hyperthermia

This is the type of hyperthermia that makes use of the energy of ultrasound waves propagated at frequencies between 2-20 KHz. Ultrasound has the ability to focus energy at a precise point and has a small wavelength. Part of the acoustic energy is absorbed by the tissue at that point and heat is generated. Simulation using interstitial ultrasound transducer gives the adequate penetration that could be achieved by driving small cylindrical transducers of outer diameter of approximately 1mm at 6-10 MHz [11]. The ultrasound wave is generated by transducers of different shapes and are either focused into the body from the outside or introduced through the rectum into the body. Threshold temperatures for cancer ablation could be seen on the 3D simulations to be temperature distribution of 41.5-44ºC [12]. Ultrasound has the ability of minimal damage to neighboring healthy tissues and is applied in ablating cancers of the breast, lungs, cervix etc. Flexibility is provided in the heating patterns when treating lung cancer via hyperthermia by the use of both liquid filled lung ultrasound and convective lung ultrasound [13]. Building a realistic brain phantom is proposed by a methodology for low interstitial ultrasound dose therapy of the brain. This yields results that plan magnetic resonance based temperature distribution and also the use of phantom for treatment scheduling [14].

2.5.2 Hyperthermia with external radio frequency devices

This form of hyperthermia is the generation of heat needed for cancer ablation by using electromagnetic waves with frequencies lying in the RF-range (above 100-2000 MHz). Here magnetic materials sensitive to EM waves that can be heated by the application of high frequency EM waves applied externally are placed in the body. A 3D modeling of the EM field is required to effectively compute the specific absorption rate (SAR) in hyperthermia treatment and planning of tumors [15]. The electric field integral equation (EFIE), magnetic field integral equation (MFIE) are calculated experimentally using three dimensional numerical models to compute the SAR in a tumor. The aperture and incident fields may be determined by presenting accurately the source of the RF by the Gaussian beam model (GBM). It has been shown from results that GDM is the best characterization mode used in hyperthermia for cancer treatments. RF applied for up to an hour helps to raise the temperature in targeted areas to threshold temperatures by approximately 43^{o}C keeping surrounding tissues intact. Thermal dose in hyperthermia cancer treatment using a model predictive controller (MPC) is developed, the latter that can be raised by the use of simulations associated together with one point and one dimension model of a tumor [16]. The control of thermal dose is then possible in this case for the optimal and effective cancer ablation. Sensitive magnetic materials placed in the body are driven by the rotational field and due to this fact, the capability of the material to cause the heat to take less than 40 minutes to heat the entire tumor, and to achieve heating temperatures above 45^{o}C with effective heated area 18.8mmxx10.6mm [17]. Breast carcinoma is treated by using an applicator called conformal microwave array (CMA). This applicator water bolus that are temperature controlled in its procedure [18].An early stage breast cancer is The effectively curing of breast cancers at their early stages is achieved by designing an array of antenna using a method of optimal constrained power focusing (OCPF) to effectively focus waves at microwave frequency [19]. The focusing is done in 1to 3 GHz frequency [20].

2.5.3 Hyperthermia Perfusion

This is a very common thermal treatment usually associated with chemotherapy or radiotherapy used in the pathological treatment of a region of the body such as the limbs. When regional perfusion is to be done with the help of surgery, the isolation of blood flowing to the part of the body concerned is done. The isolated blood is now pumped to flow into a heating device where it acquires heat then flows back to the target region where the acquired heat is given out. This new circuitry of blood flow is closely monitored by a computerized system. The fluid path between the patient and the external fluid treatment subsystem is controlled by the feedback signal coming from the coupled sensor to the patient [21]. Diffusion of the drug to the neighboring healthy tissues with dimensions in order of 0.48mm is predicted and ensured by this process [22]. The application of hyper thermic intraperitoneal chemotherapy (HIPEC) for the treatment of ovarian cancer increases the survival rates by being applied at different time points [23]. The treatments of malignant mesothelioma of the peritoneal are not standardized because their diagnosis is quite difficult and they are also very uncommon tumors. CHPPC procedures of treatment yield results that present high survival rates and better patient condition after the therapy [24].

2.5.4 Hyperthermia by frequency enhancer

At the KHz range of frequency, living tissue is less absorptive to waves. The injection of polystyrene Nanoparticles with the use of ultrasound at 20 KHz would improve the delivery of chemotherapeutic agent 5- fluorouracil so as to reduce the volume of the tumor. Focal and metastatic tumors are both effectively being treated by the application of this hyperthermia technique [25]. The addition of biocompatible fluids enhances the RF energy and microwave radiation absorption in living tissues. RF absorption by the tumor tissues can significantly be enhanced by the combination of separate treatment mechanisms like ion cyclotron resonance and resistive heating [26], RF absorption is also enhanced by its coupled energy by a transceiver and the injection of aqueous solutions rich with suspended particles that are electrically conductive in nature [27].

2.5.5 Microwave hyperthermia

Microwave hyperthermia is one of the most effective means of cancer treatment because human tissues have high water content. Single wave guides and frequencies of 434,915 and 2450 MHz are used [28]. The solution of the analysis is done by a finite element method in 2D. An antenna with frequency 2.45 GHz [29] and with one to three coaxial air slots based on TM mode is used. The Penne's equation is solved in a condition of transient state.

2.6. The chosen method of hyperthermia and its mechanism

Microwave and ultrasound (US) are the two major local hyperthermia techniques used in breast lesions therapies [30, 31]. Ultrasound is preferred over microwave because it has high penetrating power in biological tissues and generates a desirable focal spot at the normal/cancerous tissues interface due to its short wavelength. However, due to the short wavelength of the ultrasound, just a small focal spot is generated after focusing. This will require several focusing to cover the entire tumor size, hence increasing the therapeutic duration. Based on the thermal dose of US energy we can distinguish two major classes: Focused Ultrasound (FU) hyperthermia and High Intensity Focused Ultrasound (HIFU) surgery. During the hyperthermia treatment, the targeted tissue is exposed to the acoustic energy at a low intensity level for a long period of time (10-60 minutes), so as to evaluate and maintained the heated tumor at 41°-45°C. In contrast, HIFU uses the ultrasonic energy at a high intensity field to increase the temperature of focused area up to 56°C with a short ablation time (from 0.1 to 30s) [32].

Focused ultrasound therapy (FUS) is a novel noninvasive and safe method of surgery applied in the curing of numerous pathologies, notably tumors [33]. Acoustic energy from the outside is precisely converged onto the targeted focal point by FUS that makes use of the geometry of a therapeutic transducer and piezoelectric effect to generate a high acoustic pressure. Tumor tissues are then ablated either thermally (i.e. tissue necrosis) or mechanically (i.e., inertial cavitation) by this high generated pressure, with little damaging effect on the neighboring healthy tissues [34]. When the acoustic wave from the transducer traverses the tissues of the breast, a portion of the acoustic energy is absorbed and converted into heat. The generated heat is greatest at the focal region of the ultrasonic propagation field. Due to the small spot generated by the FUS at the focal region, the adjustment of the transducer is required after each thermal exposure to target a new region of the tumor thereby ensuring the entire coverage of the malignant mass by the FUS [35]. The size of each lesion depends on many factors such as the characteristics of transducer and the acoustic properties of targeted tissue, but typically a single insonation covers a cigar shape region with dimensions approximated to be 8-15 mm (along beam axis) × 1–3 mm (transverse direction). The postoperative imaging data show that two weeks following FUS, the periphery of the ablated regions would be replaced by proliferative repair tissue [36]. Ideally, excess temperatures of 54°C, are attained within the tumor in order to induce tissue ablation. Hence thermal exposures, usually under 10s are maintained in HIFUS. Additionally, the desired reduction of the treatment complications is achieved by avoiding excess heating of the surrounding healthy tissue [37].

2.7. Characterization of simulation environment

The Patient’s safety during FUS has been a great concern for researchers [38]. The necessity for a proper therapeutic environment is required to ensure a very limited time of exposure to the FUS waves hence preserving the patient’s comfort. Therefore, the characterization of FUS pressure fields is extremely important [39]. This involves the proper setting of the basic characteristic parameters of FUS fields. These include: measurements of pressure and intensity, pressure variations on acoustic axis (the peak positive and negative), measurement of the time waveforms around and at the focus, and the measurements of the tissue and water temperatures. The determination of the ultrasound-induced biological effects in both the healthy and cancerous tissues is also conditioned by the proper characterization of ultrasonic fields and focal points [33, 35, 37]. The accuracy, stability and frequency parameters of FUS systems should constantly be checked, to ensure that they lie within acceptable ranges for the patient's safety during FUS.

2.8 Various methods used in simulation and the chosen method

Several computational approaches have been adopted for the establishment of different models of FUS applied in breast cancer therapy. These include the Finite difference Time domain (FDTD), Finite difference Technique (FDT) and Finite Element Analyses (FEA). The FEA shows a comparative advantage compared to the others because it solves the boundary condition problems and computation time. COMSOL Multiphysics is the software used for the FEA in the modeling of our proposed model [1].

2.8.1. Finite-difference time-domain (FDTD)

FDTD is a popular computational electromagnetics (CEM) technique. It is easy to understand, implement and possess a full wave solver. The magnitude of work in FDTD is at least one less than the solver in either a Finite Element Method (FEM) or method of moment (MOM). FDTD presents the sole method in which one is able in a reasonable time frame to implement himself, and for precise problems. A single simulation run covers a wide frequency range because it is time domain, keeping the time step small enough to meet the Nyquist–Shannon sampling theorem criterion for the desired highest frequency [40]. The partial differential for of Maxwell's equations is implemented in software after being modified to the central difference equation and discretized. A cyclic approach is used to solve the equation where electric and magnetic fields are solved each after particular instances one after the other and repeated over and over.

2.8.2. Discontinuous time-domain method

Thus is also called discontinuous Galerkin time domain (DGTD) method. It is one of the time domain methods of analysis and has become popular recently. This popularity is solely due to the fact that it combines both the advantages of the finite element time domain (FETD) and the finite volume time domain (FVTD) methods. The operations of discontinuous Galerkin time domains are local and easily parallelizable because of the use of numerical flux to exchange information's elements that are neighbors, just like in the FVTD method. In DGTD just like FETD, an unstructured mesh is used and is capable of yielding accuracies of very high-order, provided the high-order hierarchical basis function is employed. The advantages of DGTD discussed above, permits DGTD method to be widely implemented especially in applications where transient analysis of multiscale problems involving large numbers of unknowns are required.

2.8.3. Finite element method (FEM)

Approximate solutions of integral equations and partial differential equations (PDE) are found by using FEM. Obtaining a solution necessitates an approach based either on steady state analysis(eliminating the time derivatives completely), or converting the PDE into an equivalent ODE, the latter is then solved using a method like finite differences, which is one of the standard solvers.

In solving PDE, the foremost challenge is to put into place a numerically stable equation which can accurately approximate the equation to be studied with minimal errors. PDE over complex domains with desired precisions are preferably solved with FEM.

2.8.4. Pseudo-spectral time domain (PSTD)

This is a marching-in-time technique used in computing Maxwell's equations. Either discrete Fourier or discrete Chebyshev transform is used to calculate the spatial derivatives components of the electric and magnetic field vector. These components are arranged in a unit cell in either a 2-D grid or 3-D lattice manner. Negligible numerical phase velocity anisotropy errors are caused by the application of PSTD in computing Maxwell's equations relative to FDTD. Problems of much greater electrical sizes can then be modeled as a result of the occurrence of these less errors.

2.8.5. Transmission line matrix

Several means can be used to shape an EM-equation into a Transmission line matrix (TLM). The resulting TLM IS a direct set of lumped elements. These Lumped elements can be solved directly by a circuit solver like SPICE, HSPICE, or as a custom network of elements. They can also be solved via a scattering matrix approach. Contrary to FDTD method, TLM is a very flexible analysis and more robust in capabilities, with lesser codes available as compared to FDTD engines.

2.8.6. Locally one-dimensional

This method is implicit and solves Maxwell equations in a two-dimensional case, in two steps. In a three-dimensional case, Maxwell equations are computed by being divided into three spatial coordinate directions. The Stability and dispersion of the system while solving Maxwell equations in the three-dimension in LOD-FDTD method has to be monitored.

In this work, COMSOL Multiphysics, a finite element analysis (FEA) tool is used to design and simulate a proposed model of FUS used in breast tumor ablation.

2.9. The mechanism of ultrasound technique

This is the application of a FUS from sources placed either outside the body or inside the body through the rectum. Acoustic energy is delivered to a target by the precise focusing of the ultrasound beam in a non- invasive or minimally invasive manner [41]. When the acoustic waves propagate through the tissue, the medium particles start to vibrate, resulting in alternating cycles of compression and rarefaction pressure inside the tissue. The ultrasound beams then converge into the focal area where the resulting acoustic pressure reaches the highest amplitude [1].

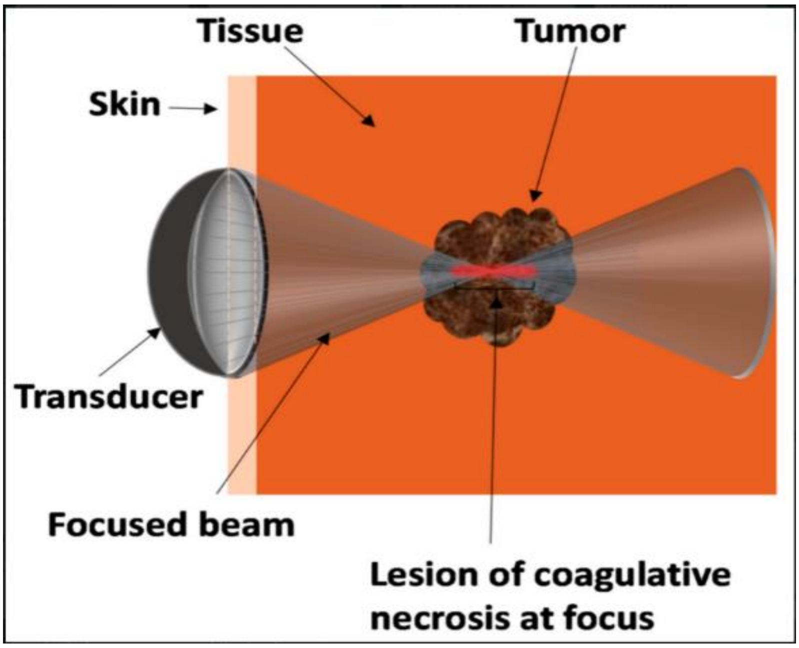


Figure 2.4: Focused ultrasound with all the domains of the process [47].

The biological and physical effects of the high acoustic pressure of ultrasound lay the basis of various therapeutic applications thermally and non-thermally in tissues. The Helmholtz equation characterizes the time independent form of the wave equation which is the pressure field [42]. Coagulative necrosis is the thermal effect resulting from the increase of temperatures above 55°C at a selected area, inducing immediate cell death [1]. Cavitation is the non- thermal phenomenon induced by pressures higher than vapor pressure of water bubbles. Pressure variations in a fluid induce the creation and oscillation of gas bubbles, hence cavitation. These pressure variations induce alternate expansion and collapse of water bubbles at the focus hence generating at each collapse, an ablation force on the nearby cells. In this work, just the thermal effect was implemented using the Pennes' bioheat equation.

2.9.1 Helmholtz and Pennes' Bioheat Equation

The pressure field in a given medium (tissue) can be characterized by the generalized Helmholtz equation below;

$$\nabla^2 P + \left(\frac{\omega}{C_c}\right)^2 P = 0 \tag{1}$$

Assuming that the acoustic wave propagates linearly in the medium with pressure wave amplitudes being much higher than those of the shear waves, the effects of nonlinearities together with those of shear waves are neglected hence writing equation (1) in 2D axisymmetric cylindrical coordinates yields a homogeneous Helmholtz equation as;

$$\frac{\partial}{\partial r}\left[-\frac{r}{\rho_c}\left(\frac{\partial p}{\partial r}\right)\right] + \mathrm{r}\frac{\partial}{\partial z}\left[-\frac{1}{\rho_c}\left(\frac{\partial p}{\partial z}\right)\right] - \left[\left(\frac{\omega}{c_c}\right)^2\right]\frac{rp}{\rho_c} = 0 \tag{2}$$

Where p is the acoustic pressure, r and z are the radial and axial coordinates respectively and ω is the angular frequency. The density,ρ_c and the speed of sound, c_c, are complex-valued to account for the material's damping properties.

The acoustic intensity field is derived from the acoustic pressure field. The heat,Q from the transducer is related to the intensity and to the pressure as follows;

$$Q = 2\,\alpha_{ABS} I = 2\,\alpha_{ABS} I\,\left|Re\left(\frac{1}{2}pv\right)\right| \tag{3}$$

Where α_{ABS} is the acoustic absorption coefficient, I is the acoustic intensity magnitude, p is the acoustic pressure and v is the acoustic particle velocity vector.

In cylindrical coordinates (r, θ, z), the acoustic intensity amplitude of the transducer is given is given by;

$$I = \sqrt{I_r^2 + I_\theta^2 + I_z^2} \tag{4}$$

Where

$$I_r = 0.5|Re(pv_r)| \tag{5}$$

$$I_\theta = 0.5|Re(pv_\theta)| \tag{6}$$

$$I_z = 0.5|Re(pv_z)| \tag{7}$$

And

$$v_r = -\frac{\frac{\partial p}{\partial r}}{\rho ci\omega} \tag{8}$$

$$v_\theta = -\frac{\frac{\partial p}{\partial \theta}}{\rho ci\omega} \tag{9}$$

$$v_z = -\frac{\frac{\partial p}{\partial z}}{\rho ci\omega} \tag{10}$$

Pennes' Bioheat equation characterizing the heat transfer inside biological tissues. It is given by the relation;

$$pc\frac{dT}{dt} = \nabla \cdot (K \cdot \nabla T) - h_b c_b \omega (T - T_b) + Q_m \tag{11}$$

Substituting equation (3) in Pennes' Bioheat equation yields the total heat transferred in the biological tissue due to HIFU as;

$$pc\frac{dT}{dt} = \nabla \cdot (K \cdot \nabla T) - h_b c_b \omega (T - T_b) + Q_m + Q_{ext} \tag{12}$$

The right-hand side of the equation consists of: the first term describing the heat transfer by conduction and the second term describing the heat transfer by the blood perfusion and convection. k is the thermal conductivity of the tissue, p is the tissue density, T is the temperature inside the tissue at any point, C_b is the specific heat capacity of the blood, h_b is the heat convection coefficient of the blood, T_b is the blood temperature which is typically equal to 37°C, Q_{ext} is the heat generated by an external source and Q_m is the metabolic heat.

The Pennes' Bioheat Equation was solved by COMSOL for the computation simulation of the breast temperature profile. It applies the Finite Element technique to compute the solution of the bioheat equation and solves the problem of boundary condition. Q_m was considered and the values taken from [43]. The boundary heat transfer between the model and air was maintained at 0 by the perfectly matched layers.

2.10. Classification of ultrasonic probes

Ultrasonic transducers are the key components in ultrasound therapies where the sound waves at RF frequencies are being generated. There exist several types of these transducers current in use for many medical purposes ranging from disease diagnoses to their therapies. These transducers are of different structures and hence used for different purposes as explained in this section.

2.10.1. Classification of ultrasonic transducers according to their applications

Ultrasonic transducers for nondestructive testing use high-frequency sound waves to measure certain parameters. Inspectors use them in a range of industrial applications, including flaw detection, thickness gaging, and weld inspection. Ultrasonic transducers come in a variety of shapes and sizes, so it can be challenging to identify the right one. To help in determining the transducer that is most appropriate for their typical applications, here's an overview of five common types of industrial ultrasonic transducers.

Dual element transducers

This type of transducer has an acoustic barrier separating two crystal elements housed together in one case. A transceiver is formed with one of the elements acting as the wave source by generating the sound waves, and the other element playing the role of the receiver.

Here's how it works: the two elements are angled toward each other to create a V-shaped sound path in the test material. Essentially, the transmitted and received beams cross under the examination surface. This creates a pseudo-focus effect, which enhances resolution in the focal zone.

The increased sensitivity from the pseudo-focus effect is particularly helpful for examining parts with rough back wall surfaces—making these transducers the industry standard for measuring remaining wall thickness in corrosion applications.

Other common applications include;

- Crack detection in castings

- Porosity detection in forging
- Inclusions in castings
- High-temperature applications

Figure 2.5: Dual elements transducers [47].

Contact transducers

A contact transducer is used for direct contact inspections. This single element transducer has a wear-resistant surface optimized for contact with most metals—making it durable for use in rugged industrial environments. This transducer type is available in a variety of styles and configurations, such as fingertip for difficult-to-access areas.

Figure 2.6: Contact transducers. [47].

Inspectors use contact transducers for many applications, including;

- Detection of Straight beam flaw
- Gaging thickness
- Sizing delaminations
- Inspecting metallic and nonmetallic components

Angle beam transducers

This is a single element transducer used alongside with a wedge to introduce a refracted shear wave or longitudinal wave into a test piece. The removable or integral wedge introduces sound at an angle into the part. Inspectors commonly use angle beam transducers to test weld integrity, because weld inspection requires you to aim sound waves at an angle. Other common industrial applications include flaw detection and crack sizing techniques. Wedges come in a variety of sizes to meet specific needs. For instance, some wedges offer a shorter approach distance while others are suited for high-temperature applications. You can also customize select wedges to create nonstandard refracted angles and contours.

Figure 2.7: Angle beam transducers [47].

Delay line transducers

A delay line transducer is a transducer designed for use with a replaceable delay line and it is a single element transducer. As the name suggests, a time delay is introduced by this transducer between the generation instant of the sound wave and the arrival time of the reflected waves. This improves the near-surface resolution. The higher transducer frequency is ideal for inspecting or measuring thin materials, as well as locating small flaws while using the direct contact method. With the replaceable delay line, this transducer is well-suited for a variety of industrial applications. Some common applications include;

- Precision thickness gaging
- Flaw detection of thin materials
- Inspecting parts with limited contact areas
- High-temperature applications

Figure 2.8: Delay line transducers [47].

Immersion transducers

An immersion transducer is designed to operate in water and it is a single element transducer. Rather than making direct contact with a test piece, a column or bath of water is used by these transducers to couple sound energy into the material. The immersion technique enables uniform, fast coupling so inspectors can quickly scan parts. Inspectors can choose focused transducers to increase sensitivity and performance in a specific area of a part. Immersion transducers are often used for in-line or in-process tests on moving parts, automated scanning, and optimizing sound coupling into sharp radiuses, grooves, or channels in test pieces with complex geometry. Applications include: In-line thickness gaging, High-speed flaw detection, Through-transmission testing etc.

Figure 2.9: Immersion transducers [47].

2.10.2 .classification of ultrasonic transducers According to their structures

Ultrasonic transducers vary in shapes and sizes. These determine their intensities and hence their specific areas of application. The different types of probes based on structural classification are briefly mentioned and discussed in this section.

Linear Transducers

Figure 2.10: A Linear Transducer [47].

These types of transducers are constructed by aligning the piezoelectric crystal linearly, yielding rectangular shaped beams with high near-field resolutions. Depending on whether the products are for 2D or 3D imaging, the frequency, footprint, and applications of the linear transducer is decided with 2D imaging having a wider footprint and with a central frequency of 2.5 MHz – 12 MHz. These transducers are mostly used in applications on the breast, thyroid, tendon, ultrasonic and photoacoustic imaging.

Convex Transducers

These types of transducers are constructed by arranging the piezoelectric crystal in a curvilinear manner, hence the name curved transducers. An example is the GE-CI-6 transducer. The resulting beam generated is convex and the transducer is mostly used for in-depth examinations. The drawback using these transducers is that the resolution of the image decreases with increases in depth. Just like the linear transducers, the footprint, frequency, and applications also depend on whether the product is for 2D or 3D imaging. For example, the convex transducer for 2D imaging has a wide footprint and its central frequency is 2.5MHz – 7.5MH. In addition to the convex transducers, there is a subtype called micro convex. It has a much smaller footprint and typically, physicians would use it in neonatal and pediatrics applications. These transducers are applied in Transvaginal, abdominal, transrectal examinations etc.

Figure 2.11: A Convex Transducer. [47].

Phased Array Transducers

This is the most commonly used transducer. Here, the piezoelectric crystals are arranged in phased array form. It has a small footprint and low frequency with central value between 2 MHz – 7.5 MHz The beam shape is almost triangular with a poor near-field resolution it is used in abdominal, brain, cardiac examinations.

Figure 2.12: A Phased Array Transducers. [47].

Pencil Transducers

Figure 2.13: A Pencil Transducers. [47].

This is the CW Doppler probes. It is used in blood flow measurement and speed of sound in blood .It has a small footprint and uses low frequency with typical values between 2 MHz– 8 MHz.

Endocavitary Transducers

This is an ultrasound transducer of endocavitary type. They are designed to fit in specific body orifices hence internal examinations within the patient's body are possible with this probe. An example includes the Philips C10-4EC used in endorectal, endovaginal and endocavity examinations and the transesophageal (TEE) probe. Endocavitary transducers have small footprints and the frequency varies in the range of 3.5 MHz – 11.5 MHz and solely used for internal examinations. Sometimes, endocavitary transducers are used in cardiology with frequencies between 3 MHz – 10 MHz to obtain a better image of the heart through the oesophagus.

2.11 The concept of optimization

Optimization is described as the mathematical way used in finding an appropriate and best fitting solution to a problem amongst the various existing possibilities. Optimization facilitates the analysis of the problem related to a physical system and enhances final decision making. `

The Implementation of optimization to a physical system begins by the modeling of the said system. This is done by the meticulous identification and mathematical expression of the systems considering the objectives, variables and constraints associated with the systems. This step is followed by carefully sorting out the type of optimization to which your physical problem belongs. An optimization problem can therefore be either continuous or discrete, unconstrained or constrained, having one, many or no objectives, deterministic or stochastic. The final step in optimization involves the selection of the appropriate solving method adapted to your system.

Solving could be done numerically using software solvers or by trial and error methods. In this work, the trial and error method was adopted to figure out the best operating conditions for the ultrasound transducer design.

2.12. Similar recent works

Several computational works have been done to study the ablation mechanism of breast cancers by FUS therapy. These different studies presented different outcomes with specific results. Although acceptable results were obtained, many drawback were encountered in the course of performing these studies. Detailed discussions on the relevant works related to the one presented in this book are undertaken in this subsection.

A study was undertaken on a realistic patient by Moslem Sadeghi-Goughari, Soo Jeon and Hyock-Ju Kwon from the university of Waterloo and Toktam Beheshtian [1] from the cancer institute in Tehran. In their work, the geometry of the tumor and breast tissues were mimicked by the use of MRI data from a patient attained with breast cancer, for the simulation of both the heat transfer and the sound wave transfer by the finite element method. An existing concave transducer type with focal length of 62.64 mm was modeled. This transducer was then operated with variable frequencies for a duration of 15 seconds then turned off to leave paste to the breast to cool down. The temperature field in the breast was discretized by quadratic second order elements and the acoustic pressure field as well as the rest of the setup were discretized by quartic fourth order elements. The results obtained for a single insonation were volumes within the breast domain with dimensions of 8 -15 mm along the axial axis (z-direction) of the ultrasound beam and 1- 3 mm along the radial direction(x-direction) of the beam. The drawback of their proceeding was the achievement of a small targeted volume per dosing. This necessitated the application of many ablation regions placed next to one another to ensure the ablation treatment on the entire breast cancer volume for a complete necrosis to be achieved, hence increasing therapeutic time.

Osama. M. Hassan, Noha. S. D. Hassan, and Yasser. M .kadah [48] from the biomedical engineering department of the University of Cairo undertook a study on Modeling of Ultrasound Hyperthermia Treatment of Breast Tumors. They operated their model at several frequencies and found the frequency of 1.5 Mhz to be causing minimum damage to healthy tissues. Their study focused on the interaction of the ultrasound intensity with the tissues of the breast together with the lesion in other to find out rout of the temperature field acoustic wave field within the volume of targeted. These objectives were achieved except the fact that not all aspects of the wave attenuation and heat conduction were considered.

A M. Leylek, G. J. Whitman, V. S. Vilar, N. Kisilevzky and S. Faintuch [49] adopted a different technique with the aim of ablation breast cancer. This method involved the application of radiofrequencies in tumor ablation. The radiofrequency ablation (RFA) presented comparative advantages of low costs, less lethal to patients, with therapeutic success rates of 70 % to 100 %. Though this method seemed promising, it needed an image guided technique during its application to monitor what was happening, hence could not be used independently. The image guidance was done by utilizing either a real-time ultrasound or a real-time MRI device when a tumor in the breast vicinity was being targeted. More so, prior tests were necessary to be done before the application of RFA. These include the determination of the patient's eligibility prior to the application of RFA via the precise establishment of the procedural planning. This requires the utilization of ultrasound imaging technique or other imaging techniques hence inducing the need for other expertise and additional costs as well as increasing the duration of the therapy.

In this work a computation model closer to a realistic human breast is modeled and the acoustic field together with the focal region of the US wave are characterized for an effective ablation of breast lesion at sonication periods far less than 15 minutes via an effective design of a US probe with optimized RF signal selection that reduce the pain and tissue burning. This work focuses on an optimized US probe design, effective RF signal selection and overall analysis of the tissue heating due to the US signal for the whole spectrum of the tissue.

In this chapter, fundamentals on the different types of breast cancers have been discussed as well as the current methods used in curing these cancers which either may be invasive or noninvasive in nature. The different hyperthermia techniques have been studied and the different types of ultrasonic transducers that have been classified based on their applications and structures have been outlined. Finally, the chapter closes up by briefly mentioning the different types of optimization techniques and by pointing out and discussing relevant projects related to the work done in this book.

Chapter 3

METHODOLOGY

The computational analysis of tissue heating by ultrasound technique with application in breast cancer ablation as done in this work required and initial designing of the breast with all its constitutive layers with the cancer domain as well as the other simulation domains. This was followed by selection of the design parameters of a chosen transducer type (in this work a concave transducer is used) based on the properties of the designed breast so as to be able to achieve a desired focal point. This step was followed by the designing of the transducer then validating its performance by comparing its pressure field with an existing model. The designed model was optimized by finding the operating parameters that caused minimum damage to healthy tissues during therapy and finally, the model's sensitivity was tested by studying how it responds to variation of the thermophysical properties.

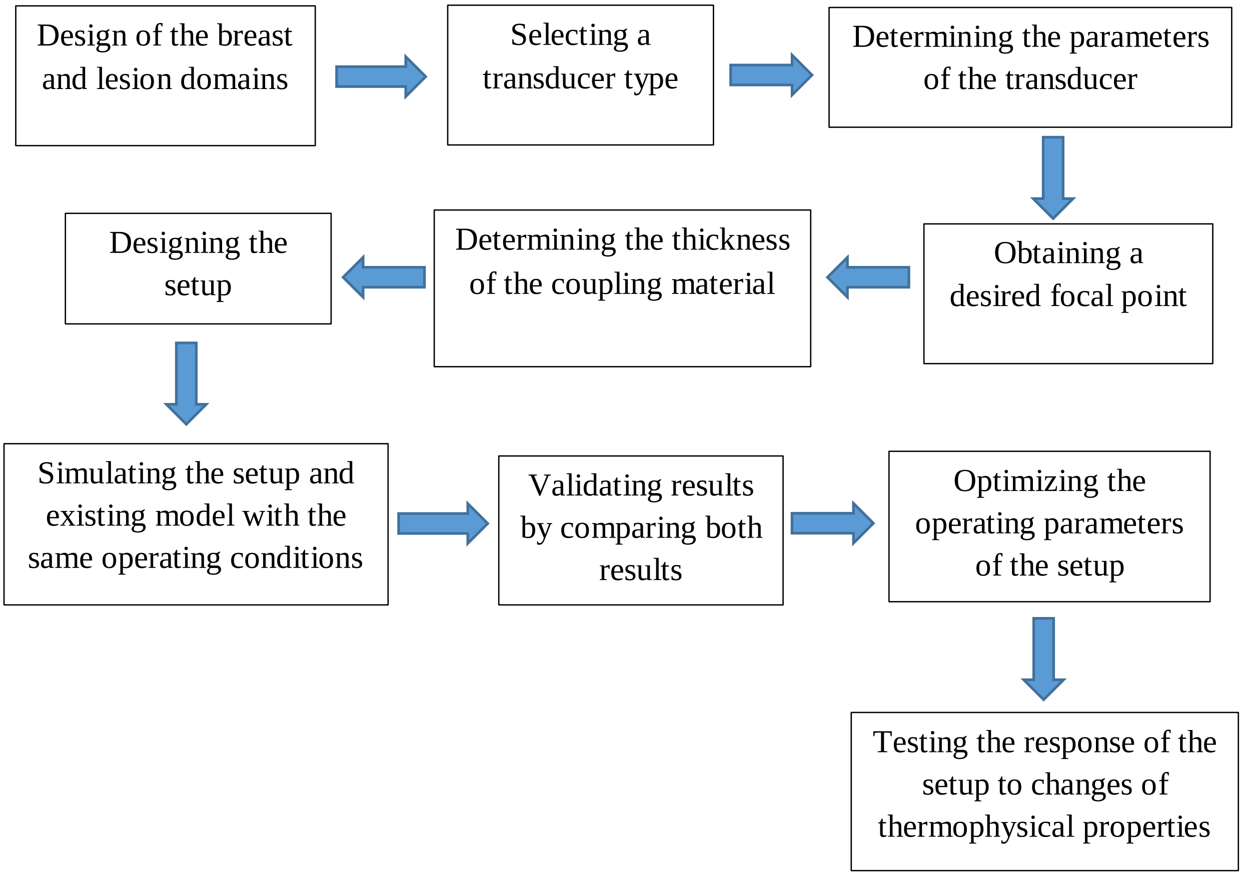


Figure 3.1: The flow chart of the thesis work.

3.1 Modeling of the breast and tumor domains

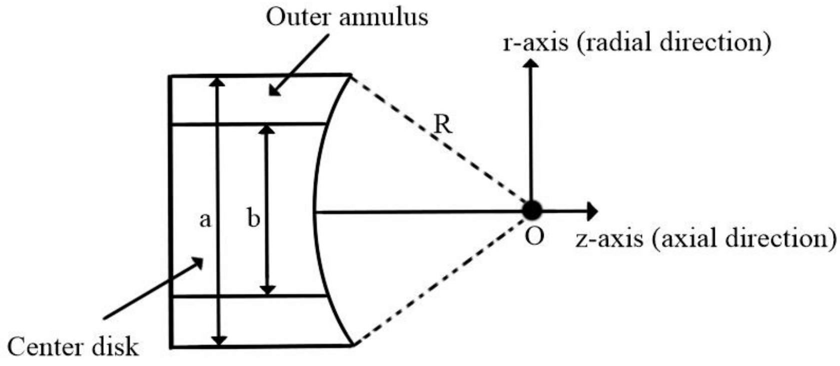
In this work, a model of the breast domain that was closer as possible to the real human breast was modeled .This entailed the modeling of a multilayered structure of the real human breast consisting of: the gland, fat, papillary dermis, reticular dermis and epidermis, Figure 3.2(a). The dimensions of the breast layers were taken from [43]. In order to reduce the computation time, the symmetry property of 2D design in COMSOL was used. The breast was modeled as a hemisphere representing half of the breast section with layers shown in figure 3.2. The entire modeled breast was immersed in water to serve as coupling material. The tumor was modeled as sphere with diameter of 10(mm) largely under 20mm, the latter being the maximum threshold to be able investigate early stage cancer [44].

A bowl-shaped transducer was designed, having an aperture of a = 96 mm in diameter, a hole of b =16mm in diameter at the center, corresponding to an effective insonation area of 7037.17 mm^2 and a focal length of R = 57.64 mm (figure 3.2 a). Three perfectly matched layers (P1-P3) were defined to absorb the outgoing and reflected waves. The simulation of pressure acoustics was done on all domains while the thermal analysis was applied only on the breast tissue domain (figure 3.2 b). For meshing procedure, quadratic (2nd order) elements were used to discretize the temperature (figure 3.2 c) in the breast domain and quartic (4th order) elements were applied to the acoustic pressure discretization in all domains encompassing the breast tissue, water, transducer and PMLs domains.

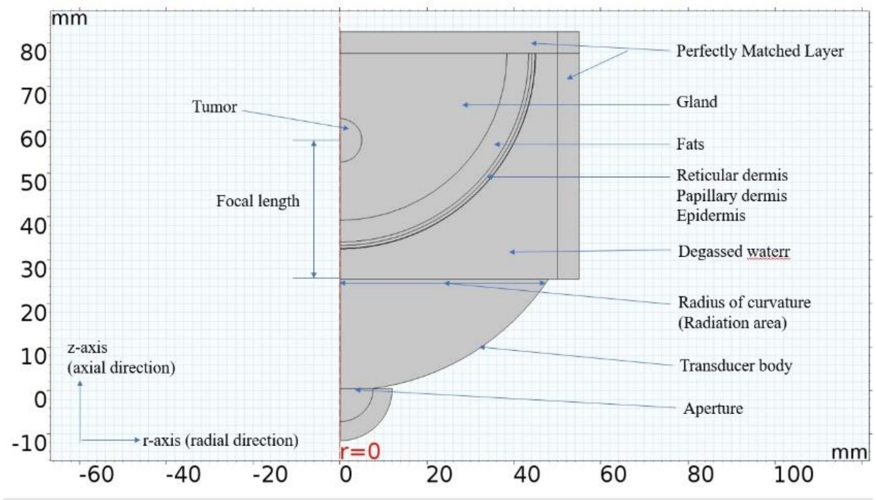
3.2 Design parameters of the Ultrasound transducer

Based on the modeled breast and cancer domains, the parameters of the concave transducer were selected by the trial and error method until a suitable and desire focal point was achieved. The thickness of the degassed water used as coupling agent was then determined and the whole setup built. Below are the parameters chosen for the proposed model with labels and vales of each part of the transducer being shown as compared to figure 3.2 (a).

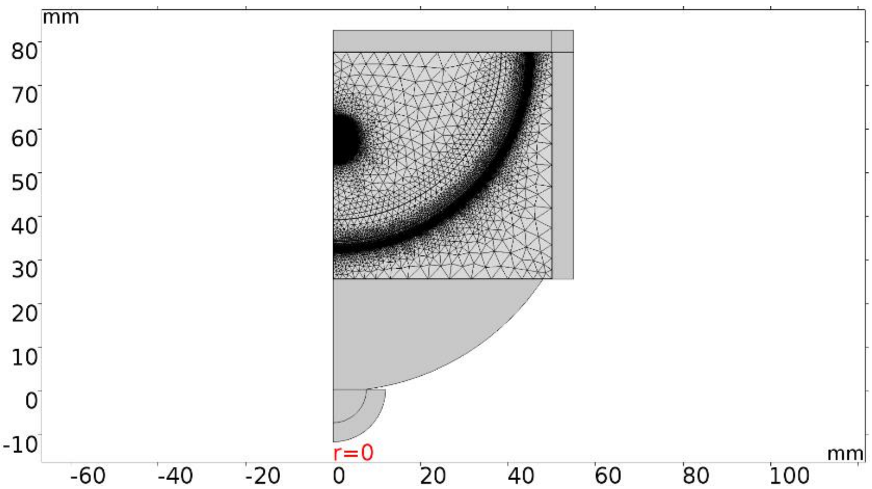
- Radius (a/2) = 48mm
- Focal length(R) = 57.64 mm
- Aperture radius (b/2) = 8 mm
- Aperture area, = 181.46mm^2
- Effective insonation area = 7037.17 mm^2
- Curvature, c = $5.22x10^{-6}$/ mm^{-3}



(a)



(b)



(c)

Figure 3.2: (a) The design parameters of the transducer, point O is the focal point (b)tissue layers of the breast used in the computational model (c) The generated computational quadratic (2nd order) mesh in the thermal field.

In this chapter, a breast model close as possible to that of a human breast is modeled by representing as much as possible the different layers constituting it. Parameters of a concave transducer are then chosen by the trial and error method to obtain a desired focal point. The transducer is then designed with an appropriate thickness of the coupling material.

Chapter 4

VALIDATION OF THE RESULTS

The performance of the proposed model is tested in this chapter by first reproducing the existing model in [1] then designing the proposed model and finally confronting the results obtained from the exiting model to those from the proposed model. This is done by analyzing the profiles of the pressure fields of both models at the same operating conditions of frequency and initial water temperature.

4.1. Validation

The frequency of 1.3 MHz and displacement amplitude of 4 nm and 0 elsewhere was selected and applied on the probe. The boundary temperature conditions were maintained at 0^oC. The initial water temperature was set a 20^oC.

Thermophysical properties of the breast layers and tumor were taken from [43] and the acoustic properties from [45]. The results obtained were compared to those from the reference model, the latter also ran with the similar parameters and conditions as our model. The thermophysical properties of water were set as a function of the temperatures. Figure 4 compares the pressure profiles of the proposed model (figure 4.1(a)) to that in [1, 24] (figure 4.1(b)). It can be seen that there is a clear agreement to an extent in the nature of both profiles.

Table 1: Thermophysical properties of the breast layers, Tumor and degassed water

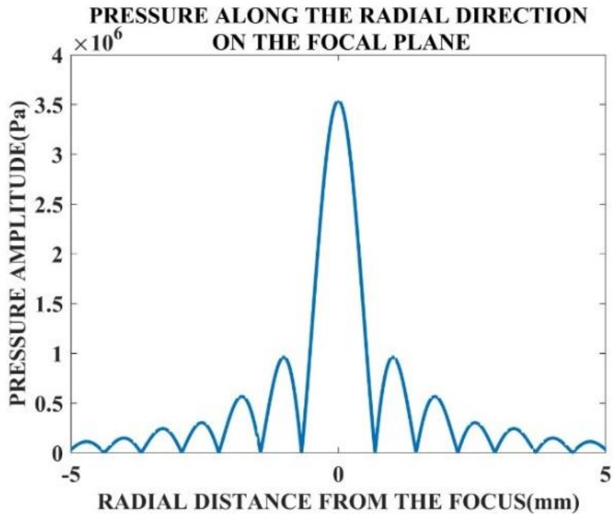
The domains	Thermophysical properties					
	Thickness *h* (mm)	Thermal conductivity K(W/m.K)	Density ρ (kg/m3)	Specific heat capacity C (J/kgK)	Metabolic heat Q (W/m3)	Blood perfusion rate ω_b (m3/s/m3)
Epidermis	0.1	0.235	1200	3589	0	0
Papillary	0.7	0.445	1200	3300	368.1	0.0002
Reticular	0.8	0.445	1200	3300	368.1	0.0013
Fats	5	0.21	930	2770	400	0
Glands	43.4	0.48	10500	3800	700	0
Muscles	15	0.48	1100	3800	700	0
Tumor	----	0.48	1050	3852	5000	0
Water	Optimized	Temperature dependent	Temperature dependent	Temperature dependent	0	0

Table 2: The acoustic properties of the breast layers, tumor and degassed water

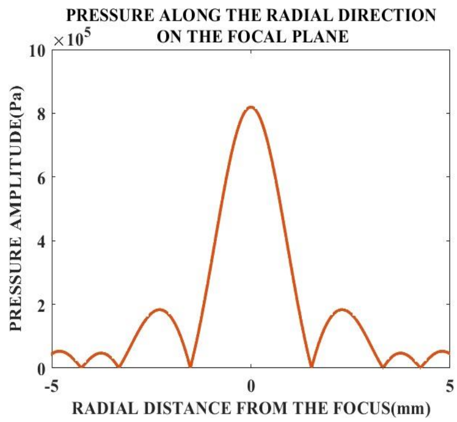
The Domain	Acoustic properties		
	Attenuation coefficient of water $\alpha\ (\frac{Np}{m/MHz})$	Frequency dependent attenuation coefficient $(\frac{Np}{m})$	Speed $(\frac{m}{s})$
Epidermis	0.15	$\alpha_{epidermis} * f^2$	1566
Papillary dermis	0.15	$\alpha_{epidermis} * f^2$	1566
Reticular dermis	0.15	$\alpha_{reticular\ dermis} * f^2$	1566
Fats	0.15	$\alpha_{fats} * f^2$	1500
Glands	0.4	$\alpha_{gland} * f^2$	1545
Breast muscles	0.4	$\alpha_{breast\ tissue} * f^2$	1545
Tumor	8.55	$\alpha_{tumor} * f^2$	1550
Water	0.025	$\alpha_{water} * f^2$	1522

4.2 Initial observations

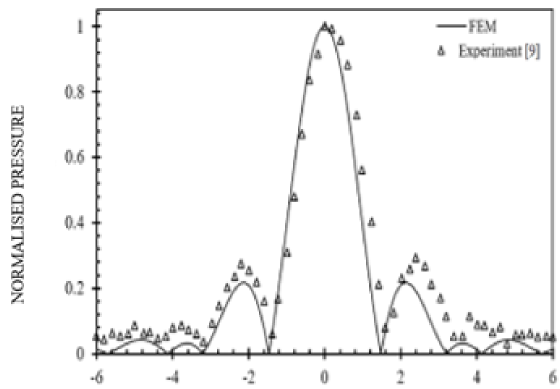
As highly focused energy at a restrained and precise area causes local vibration. It can observed from profile plots figure (4.1) that in the radial direction from the focal point within the lesion (r-axis), pressure is more focused and oscillates with greater frequency in the proposed model than that proposed by the model in [1]. This is as a result of the higher pressure built-up in the proposed model. This high pressure built in the proposed model would cause higher local vibrations of the cancer lesion and hence their mechanical ablation by cavitation. It can also be seen that, the model built in this work matched perfectly with the reference model from the literature in figure 4.1(c) after undertaking simulations with similar conditions as in the literature figure 4.1(b). This confirms the effectiveness, accuracy and validity of the future results the will be obtained by using the designed in this work.



(a)



(b)



(c)

Figure 4.1: The normalized pressure profiles in the focal plane in (a) Proposed model (b) Reference model (c) Reference model from literature [9].

In this chapter, it has been shown that the proposed model is valid and could be used for further studies by confronting its performance to that of an existing model. The parameters used here for comparison were the pressure profiles of both models. A clear agreement in both profiles can be seen, with an advantage in the proposed model being that there is more focusing and pressure concentration at the focal point compared to that of the existing model.

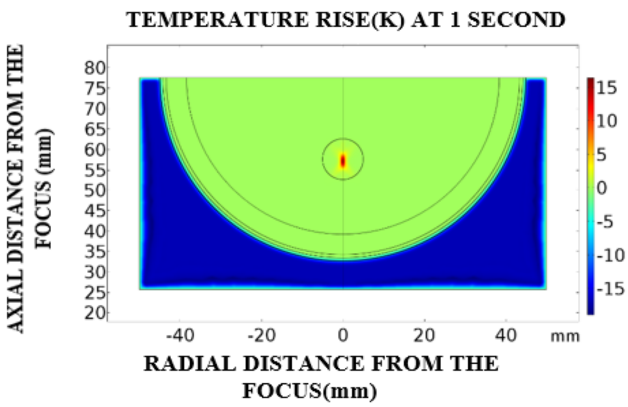
Chapter 5

RESULTS

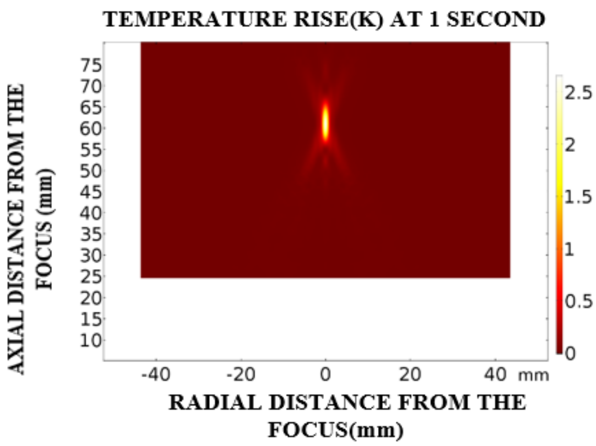
Several steps have been taken In order to properly visualize the performance of the proposed model. These include comparing the results obtained from simulating the proposed model to that of an existing model. These comparisons are broken down into two broad sections corresponding to the qualitative results that focus on the results obtained at the focal point and the quantitative results that focus on the simulation environments of the setups.

5.1. Qualitative Results

This involves the analysis of the results obtained at a restrained area (focal point). These results could be extended to other parts by a simple position change of the transducer.



(a)

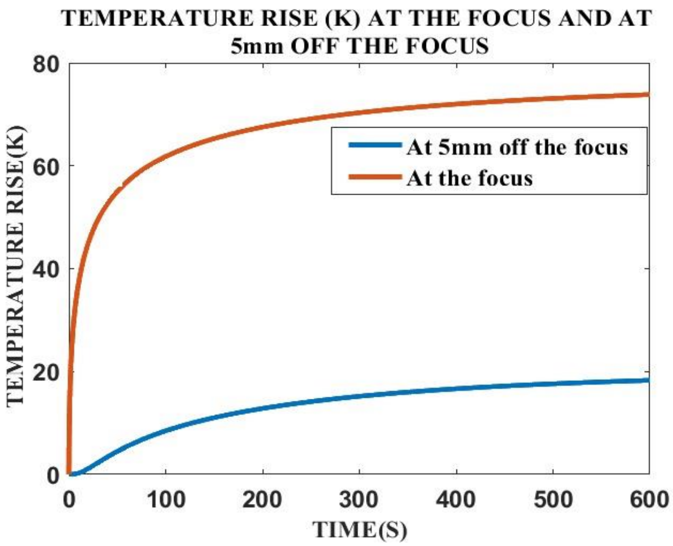


(b)

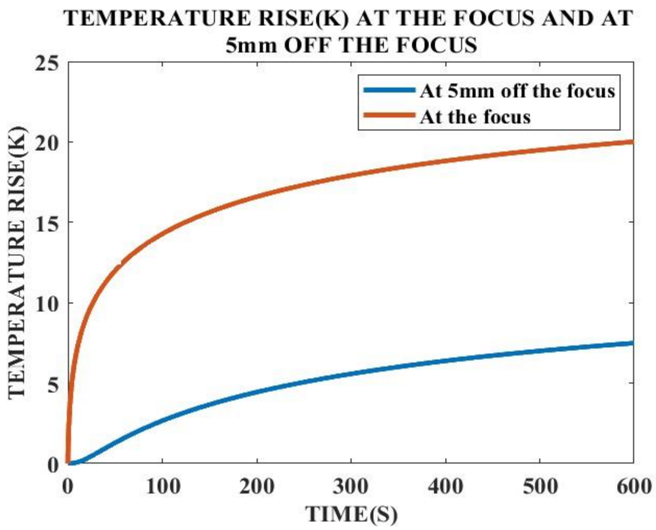
Figure 5.1: Temperature rise (ΔT) at 1 second in (a) proposed model and (b) Reference model.

5.1.1 Temperatures achieved at the focus

At one second of insonation, higher temperature (up to 50°C) was obtained at the focus with less outward radiation in the radial direction (more focusing) compared to the reference model with just 20°C attained. These results favor the better targeted ablation of cancerous lesions. Figure 5.1 shows the profiles of the temperature rise ($\Delta T = T - T_0$) vs time for both models. Where T0 is the body temperature (37°C) and T is the temperature at any time t. The focus is seen to have moved from a cigar-shape to an elliptical-shape showing more focusing.



(a)

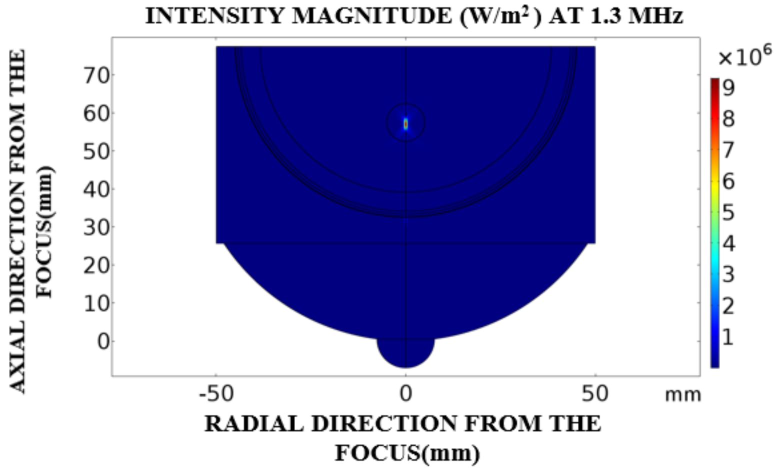


(b)

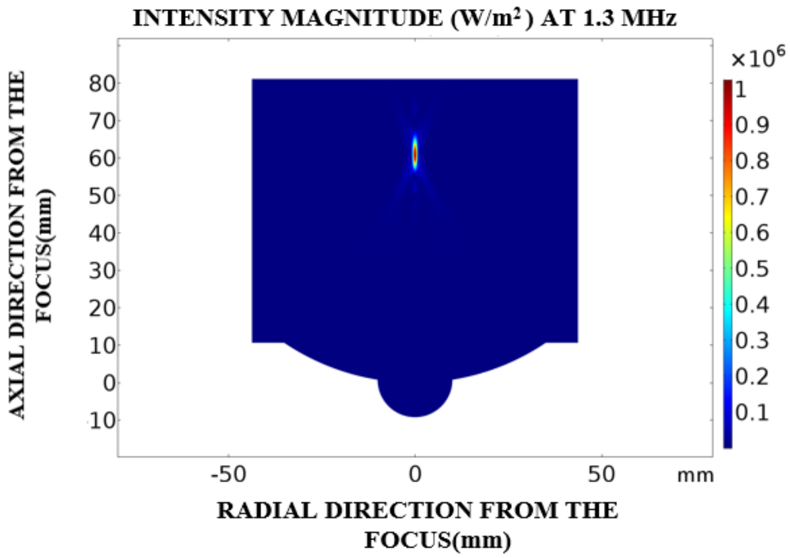
Figure 5.2: Temperature rise (ΔT) per unite time, along the radial direction in (a) Proposed model (b) Reference model.

5.1.2 The Temperature rate at the Focus

The increase of temperature per unit time increase at the focus in the proposed model was more than four times that for the model in [1].The proposed model reached ablation temperature of $T_1 = 62^0$C at 100s compared to that in [1] reaching $T_2 = 14^0$C in 100s at the focus. This fast rate of temperature buildup at a small area, favors the quick change of positions to target other regions, hence saving therapeutic time and ensuring patients comfort during the process. Figure 5.2 shows the plots of the temperature rise (ΔT) vs time of our model and that in [1] at the focus and at a radial distance of 5mm off the focus.



(a)



(b)

Figure 5.3: Pressure intensity profile in (a) Proposed model (b) Reference mode.

5.1.3 The pressure built-up at the focus

At the focal point, a pressure intensity of 5.5 M_W/m^2 (5.5MJ/s/m^2) was achieved in our model against 1.1 M_W/m^2 (1.1MJ/s/m^2) in the that in [1].This high intensity was due to the increase of the effective radiation area (intensity is proportional to the square of the area), the decrease in the area of the aperture (more flux reach the focus) and the Decrease in focal length (due to the increase of the probes curvature).

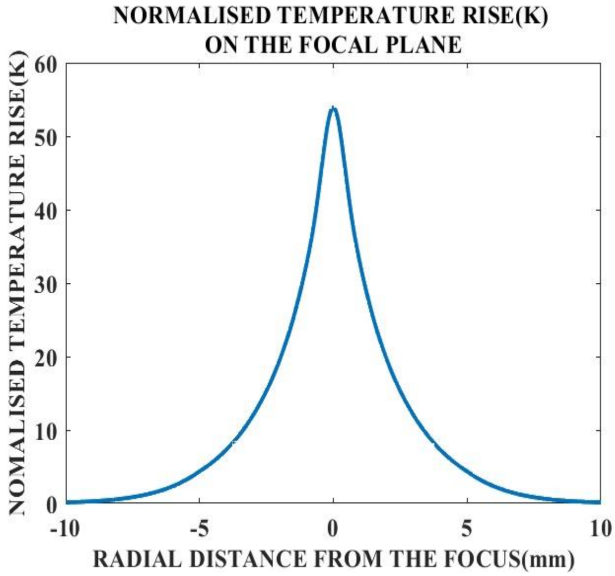
The high pressure buildup associated with proper oscillations could be harnessed in the cavitation process to further ablate the cancerous lesion. Figure 5.3 shows the pressure profiles in both models. It can clearly be seen that a more precise focusing in our model at the focal area in comparison to the cigar-shape obtained in [1].

5. 2. Quantitative Results

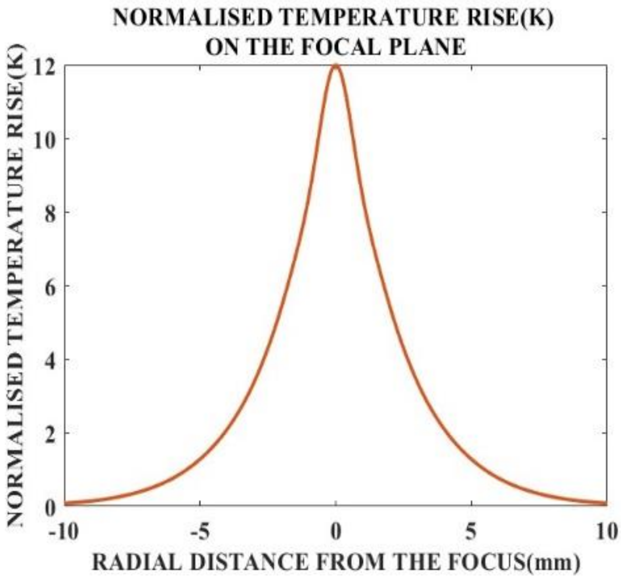
Here, the analysis of the impact of the proposed set up on a larger area at a single dosing was done. The extent to which a probe extended its qualitative properties (at a point) to target more lesions at a single dose, the less time it would take for the therapeutic process hence ensuring the patients safety and comfort in the process.

5.2.1 The Targeted Volume

The targeting of a large volume at optimal therapeutic conditions would save time by avoiding the position change of the probe needed for several dosing. Figure 5.4 compares a 5 minutes insonation in both setups. A targeted-elliptical volume with approximate dimensions of 15.8 mm (along beam axis) × 4 mm (transverse direction) was achieved for the proposed model against the cigar-shape of 11.6 mm (along beam axis) × 2.5 mm (transverse direction) in [1]. The distances were measured from points with an increase of local temperature over 5 degrees above body temperature corresponding to ablation temperatures of more than or equal to 42^0C.



(a)



(b)

Figure 5.4: The temperature profiles at 50s of sonication in (a) Proposed model (b) Reference model.

5.2.2 The Temperature gradients

The change of temperature per unit change of distance in the radial direction within the lesion was higher in our model than that in [1]. This high temperature gradient enhances cancer ablation thermally by temperature chocks. Figure 5.4 shows the variation of temperature-change (ΔT) vs the increase in radial distance within the lesion. Our model shows a temperature-change gradient more than 2.5 times greater than that proposed in [1] corresponding to a drop of from $\Delta T_2 = 47.5^0C$ to close to $\Delta T_1 = 2^0C$ and from $\Delta T_2 = 18^0C$ to $\Delta T_1 = 2^0C$ respectively, each for an increase in radial distance of 10 mm.

5.2.3 The volume of the degassed water used as coupling material

The reduction in focal length of the acoustic pressure wave had as a direct consequence, the reduction of the thickness of the water bath used for coupling and isolation of the skin from the probe from 25 mm to 10 mm (60% decrease). This would enable the easier manipulation of the probe and the patients comfort during therapy by making the setup less cumbersome.

In this chapter, the simulation results of the non-optimized proposed model have been compared with the results obtained from a previous work done related to the one done in this book. Only few of the most prominent and representative features of the models have been used for comparison but they show an acceptable and noticeable existing different between the models.

Chapter 6

THE PERFORMANCE ANALYSIS OF THE PROPOSED MODEL

The performance of the proposed model in breast cancer therapy is checked in this chapter. To begin with, the setup is first optimized by the trial and error method to find out the optimal operating transducer frequency on which depend the other tissue properties like the attenuation confident. Then the response of the setup to changes of some properties like attenuation coefficients and thermal conductivities of both the tissues and degassed water-coupler is studied. This is the sensitivity check of the model.

6.1. Optimization of the operating conditions of the proposed model

To find the optimal operating condition of the proposed model, the frequency of the transducer and the initial water condition as the optimization parameter were selected. Frequency was selected because three other parameters depend on it. These are; the intensity of the transducer, the attenuation coefficient and thermal conductivity of the tissue. Optimization was measured by the percentage of damage to healthy tissues to the tumor size as the result of the variation of these parameters and the time of insonation. The smaller the insonation time and percentage of healthy tissue damaged, the better the combination of the parameters values of frequency and initial water temperature. The proposed model was simulated for a constant time of 50s for frequencies of 1MHz, 1.1 MHz, 1.2 MHz,1.3 MHz and 1.4 MHz each with initial water temperature varying from 20 ºC to 45ºC at the step of 5 ºC.

Below 1 MHz good qualitative properties of the model were found but still not all the tumor was ablated. Above 1.5 MHz, the attenuation coefficient of the tissue which is frequency dependent became so high and the ultrasound wave became least penetrating so as to reach the tumor. This caused the entire tumor not to be ablated. From our model simulation, we found out that a consolidated frequency value of 1.3 MHz at an initial water temperature of 20 ºC was found to cause less damage on healthy tissues around the tumor, as shown on figure 6.1.

Table 3: Optimization data at 4nm displacement amplitude and 50s sonication

Transducer Frequency(MHz)	Percentage normal tissue damage at					
	20°C	25°C	30°C	35°C	40°C	45°C
1	---	----	----	0.023	0.036	0.075
1.1	---	---	---	0.026	0.051	0.081
1.2	---	0.024	0.036	0.052	0.073	0.11
1.3	0.021	0.032	0.048	0.065	0.09	0.113
1.4	---	---	0.055	0.073	0.095	0.12

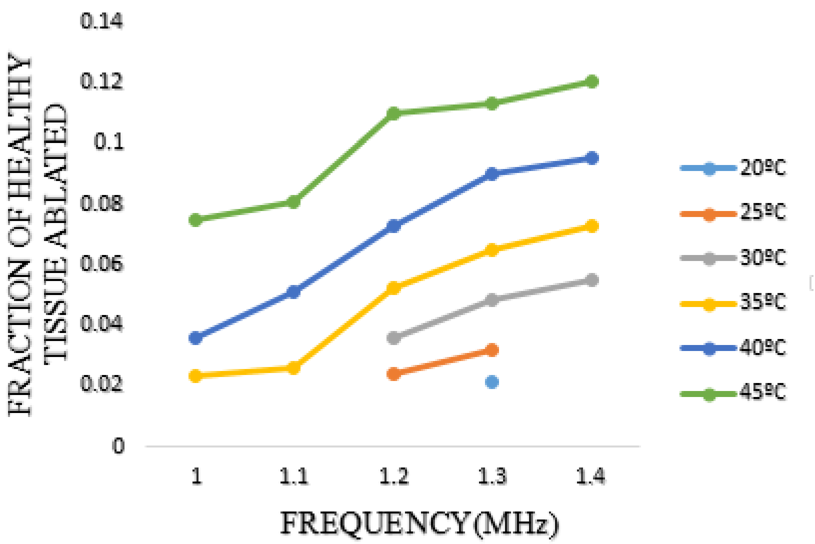


Figure 6.1: the fraction of healthy tissue damaged to the size of the tumor (here 10mm diameter) at the same time of simulation of 50s for various frequencies.

6.2 Sensitivity analysis

After having optimized the proposed model, parameters to which it was most sensitive were searched for. The parameters were varied by ±10% and ±20% for a total of five values each including the central value. These variations were measured by their impact on the average tumor temperature. Many parameters were kept constant and a focus was laid only on the most important ones. These are the absorption coefficient, thermal conductivity, density, and the specific heat capacity of water and tissue. Our central values were those yielding the optimized condition as found in figure 6.1.

Amongst the parameters for both water and tissue that were chosen for the sensitivity check, it was found that all the parameters of water as well as the specific heat capacity and density of the tumor caused little or no change (around ±0.5 ºC) to average tumor temperature, hence less sensitivity. The parameters of concern were then found out to be the thermal conductivity and absorption coefficient of the tissue that caused variations between 2-3 º C of the average tumor temperature. Tissue parameters affect sensitivity more than water parameters because the tissues (especially the tumor) are more conductive and denser hence attenuate acoustic more, while water is less conductive and less attenuation occurs in water due to its low density and low absorption coefficient.

The surface intensity of the transducer is also an important parameter to consider during sensitivity check. It was kept constant during the sensitivity check of water and tissue parameters. The frequency of the transducer is therefore the most important optimizing and sensitive parameter since the surface intensity of the transducer and the attenuation coefficient of the tissue are both depending on transducer frequency. It can be concluded that attenuation coefficient, thermal conductivity and surface intensity (both being frequency dependent) play a large role in breast tumor heating.

In this chapter, the best operating condition for the proposed model has been analyzed via the trial and error optimization technique and found to correspond to an operating frequency of 1.4 MHz, resulting to the minimum healthy tissue damage of 0.021% at an initial water temperature of 20°C. It has also been shown here that, the model is more sensitive to the attenuation coefficient, thermal conductivity and surface intensity (both being frequency dependent), that play a large role in breast tumor heating.

6.3. Tuning of the focal region

The comparative advantage of the proposed model is the possibility of shifting the focal point to other positions within the breast domain with little or no great modification of the skin surface temperature. Ablation results were obtained at an initial water temperature of 20°C and thickness of 10 mm. B-mode US imaging could be used to local the geometric center of the tumor. Based on the position of the geometric center of the tumor, the thickness of the water bath could be adjusted accordingly to enable the acoustic field to target the center of the tumor with little changes made on the water or skin surface temperature.

6.4. Patient's safety

The outcome of this work presents the application of a designed US transducer that would be operated at a lower frequency of 1.3MHz. This lower frequency would improve the penetration of the acoustic beam into the breast tissues to easily reach the targeted area with less energy deposited along the path traversed by the beam. It is well known that biological tissue would die when exposed to temperatures of 42°C (which is the threshold of the thermal tolerance of biological tissue) and above. Although a very high energy density is generated by the proposed model, this energy density is localized at a restrained area of consent, where the geometrical center of the tumor is located hence limiting the thermal tolerance of the healthy tissues below the threshold of 42°C. In the work presented here, the breast region traversed by the acoustic beam do not reach 42°C except at the targeted region where the tumor is located. Furthermore, no additional cooling procedure is needed because an initial water temperature of 20°C is applicable that maintains the skin surface temperature below body temperature and also the temperature of the healthy tissue traversed by the beam up to the region where healthy tissues fraction ablation occurs. This fractional tissue ablation is very negligible and would correspond to the volume of healthy tissues removed from the breast during cancer treatment by surgery. A rise of temperature per unit time (s) of 15°C/s was also achieved in the proposed model lying in the safe region of 20^0C/s as proposed by Gail ter Haar [50] for safety in focus ultrasound therapy.

The proposed model creates a very high acoustic intensity within the tumor of 10 mm diameter in a more restrained area than the existing model. This intensity generates a very high energy density within the tumor as analyzed below;

a) At the boundary between the transducer and the degassed water the proposed model generates almost twice the intensity of the existing model. From figure 5.3 (a), the intensity at the boundary of the transducer and degassed water is about $0.2x10^6$ W/m^2 and zero elsewhere. The effective sonication area of the transducer is 7037.47 mm^2. ($7.03717x10^{-3}$ m^2). This yields a power of 1407.4 W. Figure 5.3 (b) shows an intensity at the boundary of the transducer and degassed water to be about $0.1x10^6$ W/m^2 and zero elsewhere The effective sonication area of the transducer is 3534.29 mm^2 (3.53429 $x10^{-3}$ m^2). This yields a power of 353.429 W. This value is about four times less than that of the proposed model.

b) Within the tumor, the intensities in the proposed and existing models are about $9x10^6$ W/m^2 and $1x10^6$ W/m^2 respectively as shown on figure 5.3. These correspond to powers of 9000 W and 1000 W for the proposed and existing models respectively for $1mm^2$ each. In one second and for $1mm^3$ of volume within the lesion, the energy densities of the two models are 9000 J/mm^3 and 1000 J/mm^3 respectively.

It can be seen that the energy density at the center of the tumor creates by the proposed model is about nine times that created by the existing model. This value is said not to affect neighboring healthy cells because the entire generated is contained within the arena of the lesion.

CHAPTER 7

CONCLUSION AND FUTURE WORK

An overview of the work done in this book is presented in this chapter. Due to the lacuna existing in this work, a lot still needs to be done in order to render the research perfect before any clinical trial of the project can be done. This has been mentioned in the future work section and involves the incorporation of the effect of cavitation in tissue ablation, which has not been studied in this work nor in previous related work.

7.1 CONCLUSION

A 2D model of the human breast is presented in this paper for the qualitative characterization of the pressure field and focal point of FUS for an effective ablation of breast lesions. This was done via a computational study using the finite element analysis method in CONSOL to simulate the acoustic wave propagation and heat transfer. The simulations show that the tumor regions are heated above the ablation temperature threshold of 42^0 C at times less than 50s (at focus) and by keeping surface temperatures slightly below 37^0C, hence reducing therapeutic time and ensuring patients' safety respectively. A larger, elliptical more precise focusing with approximate dimensions of 15.8 mm (along beam axis) × 4 mm (transverse direction) was also achieved with pressure intensity reaching 13.5 MW/m^2 at 300s of dosing. It can also be observed that frequency, surface intensity and attenuation were the only sensitive properties of both water and tissues that played a large role in the qualitative characterization of the FUS focal point for the ablation of breast tumors.

7.2 FUTURE WORK

In this work, the computational study applied to generate heat at the focus by the absorption of acoustic energy involved only the non-mechanical mechanism (thermal effect). A future work related to this will be to couple the effects of the mechanical mechanisms (e.g. cavitation) and non-mechanical mechanisms of heat generation to achieve better results and a perfect spherical focus.

Closing up this work, it can be said with a high degree of certainty that, an ultrasound transducer has been designed with its parameters including its operating frequency optimized for tissue heating with specific application in breast cancer therapy, the later that needs to be clinically examined for its future application in the medical domain so as facilitate breast cancer treatment.

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