Design and Analysis of Multimodal Piezoelectric Ultrasound Transducer for Cancer Cells Bursting

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Annex A

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DEDICATION

I would like to dedicate my thesis to my parents, siblings and dearest friends, who have always been supporting me and motivating me to study. I would like to express my gratitude to my parents who have always believed in me and encouraged me to work hard in the completion of this thesis. All the hard work, time, and understanding I have received from them have been very inspiring and I am grateful for it.

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ABSTRACT:

Cancer research has been a significant concern for researchers globally owing to the tremendous loss of life caused by various kinds of cancer cells. Traditional cancer treatments, such as chemotherapy, can have severe adverse impacts on the human body. Ultrasound bursting is a unique technique that produces powerful, short-duration ultrasound pulses. When such pulses are focused on specific target cells, they can cause localized effects such as cavitation, acoustic streaming, and thermal ablation. This study suggests a new multi-modal piezoelectric ultrasonic transducer design for the bursting of many types of cancer cells. The design consists of three dual-band piezoelectric ultrasound transducers that generate resonance frequencies of 80, 120, 150, 180, 250, and 300 kHz that have been carefully selected for various types of cancer cells. The generated resonance frequencies will resonate with cancer cells and burst them when resonance-induced vibrational energy increases a certain limit. The design and analysis of the transducer were carried out in COMSOL Multiphysics and the results show focused ultrasounds with a maximum sound pressure level of 200 dB a biocompatible piezoelectric material is required for direct contact with biological tissues without causing harm or inducing adverse reactions while also having low acoustic impedance and impedance matching with the human tissue is required for this purpose.

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CHAPTER 1: Introduction

Cancer cells develop uncontrolled and rapidly, producing malignant tumors and infecting neighboring tissues. Cancer can potentially circulate to other regions of the human body via the lymphatic system or the distribution. During chemotherapy, cancer cells acquire multidrug resistance (MDR), which is a major impediment to cancer treatment. Prostate cancer and breast cancer are most widespread invasive cancer forms in men and women, respectively. They account for the majority of the projected new cancer cases detected in 2022[1]. Although these cancer types arise in two distinct organs with distinct structures and functions, both organs require gonadal hormones for growth, so their tumors are hormone-dependent and have significant characteristics. Despite the different conventional therapies now in use, there is continuing research for alternative ways of therapy with fewer side effects.[2]. Currently, the most common cancer treatment procedures include surgery, radiosurgery, radiation, chemotherapy, and immunotherapy. Unfortunately, the employment of these strategies is not always beneficial, owing to side effects that impact even normal cells, causing oncologists to limit the same therapy that was chosen. [3], [4], [5], [6], [7], [8], [9].

Ultrasound resonance is a promising technique that could selectively destroy cancer cells whereas leaving healthy cells unscathed. The technique involves using low-intensity pulses of ultrasound waves to oscillate the nucleolus membrane of a cancer cell to the point of bursting. The natural frequency gap between healthy and cancerous cells means that the method should leave healthy cells unharmed while non-invasively annihilating the diseased cancer cells. [10]. This technique is still in its early stages, but early in vitro, studies have disclosed sound waves pulsed at a specific frequency can successfully destroy cancer cells while leaving healthy cells intact. The research is still introductory and has not been tested in a live animal or human, and as such there are several key challenges to address [11]. The research by [12] Shows that there is a gap in the so-called resonant expansion rates of cancerous and healthy cells. That gap imply that a thoroughly tuned sound wave could, in assumption, cause the cell membranes of cancerous cells to oscillate to the point that they burst while leaving healthy cells intact.

The solution to generating such carefully tuned ultrasound waves lies in a piezoelectric ultrasound transducer. Piezoelectric ultrasound transducers are devices that convert electrical energy into mechanical vibrations and vice versa, based on the piezoelectric effect. Ultrasound transducers input alternating current (AC) across piezoelectric material to output ultrasound and vice versa, and typically use piezoelectric or capacitive transducers to produce or receive ultrasound. Piezoelectric crystals can transform their volumes and shapes in response to a voltage being applied and can convert electric currents into ultrasounds [13].

1.1. Ultrasound Technology

In the last decades, ultrasound technology has already greatly improved, and it is now a commonplace diagnostic imaging technology in hospitals around the world. High-frequency sound wave technology creates internal body structure images and is hugely important in the diagnosis and monitoring of a broad spectrum of conditions. Ultrasounds, however, do not use ionizing radiations such as CT scans or MRIs, which is much acceptable for patients, especially pregnant women and young children. [14]. Nowadays, ultrasound is being utilized in almost all medical specialties, from obstetrics and cardiology to musculoskeletal imaging and emergency medicine.

In this review, different ultrasound technologies and their applications in hospitals and the contributions that have been made by developing novel ultrasound technologies in transforming patient care will be considered. Portable ultrasound devices, 3D and 4D ultrasound technology, elastography, contrast-enhanced ultrasound, and artificial intelligence (AI) integrations that improve the diagnosis will be discussed. Through this highlighting of these developments, we can better understand the here and now, and the here and future, of ultrasound in the clinical context.

1.2. Key Applications of Ultrasound Technology

1.2.1. Obstetrics and Gynaecology

- **Fetal Imaging Ultrasound**: Although the development of fetal imaging and health monitoring techniques have vastly improved, ultrasound remains the primary imaging technique for monitoring fetal development, diagnosing congenital abnormalities, and evaluating fetal health in real-time. Both 2D and advanced 3D/4D ultrasounds are used to visualize details of the inside of a human body [15].
- **Gynaecological Health**: Ultrasound also plays an important role in diagnosing uterine fibroids, ovarian cysts, and various other reproductive health issues [16].

They are more diagnostic than abdominal ultrasounds because they come closer to the reproductive organs.

Figure 1: Fetal Ultrasound

1.2.2. Cardiology

- **Echocardiography:** This type of ultrasound is very important to look at how the heart structures and functions. It enables cardiac performance assessment, the diagnosis of heart valve diseases, determination of the ejection fraction and the myocardium or the pericardium abnormality [17].
- **Portable Echo Devices:** Pulse echo devices are extremely useful in the emergency department and intensive care unit (ICU), where patients do not have to be hurried to the radiology department for a quick heart assessment.

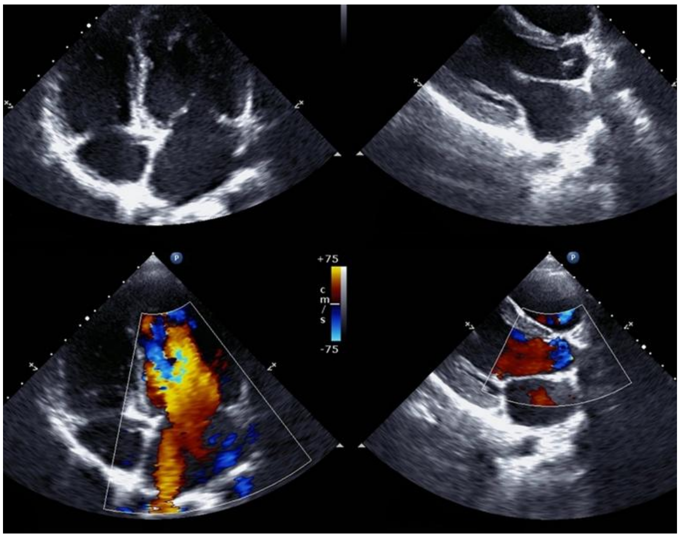


Figure 2: Echocardiogram

1.2.3. Musculoskeletal Imaging

- **Soft Tissue and Joint Evaluation:** Musculoskeletal ultrasound [18] Is used for the diagnosis of issues with tendons, muscles, ligaments, and nerves. In addition, it is used to help guide procedures such as injections or aspirations, which makes it in indispensable orthopaedic and sports medicine.
- **Portable Devices for Bedside Assessment:** Such devices are of utmost importance in emergency rooms, where doctors can evaluate injuries and plan treatment much faster than traditional methods.

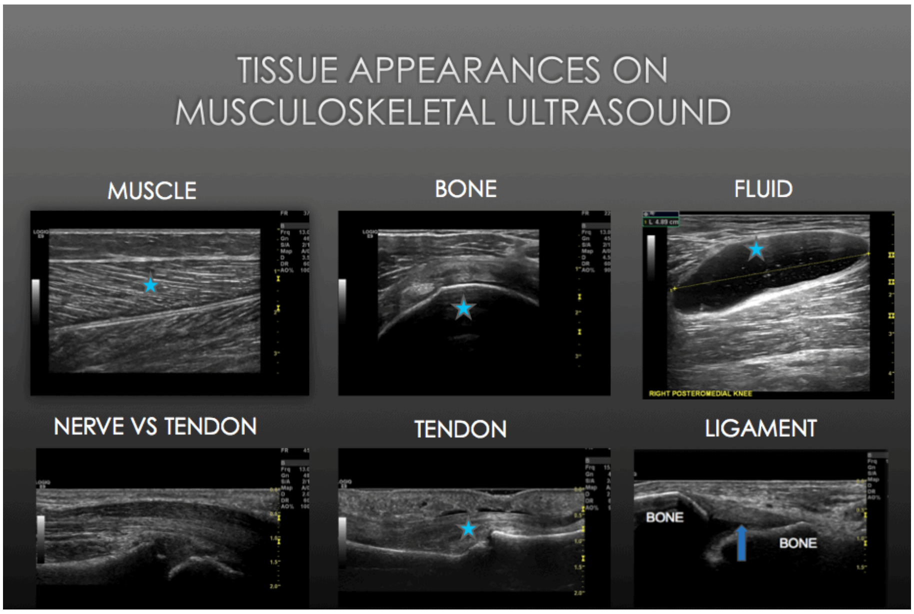


Figure 3: Musculoskeletal Imaging

1.2.4. Emergency Medicine

- **Point-of-Care Ultrasound (POCUS):** Point-of-care ultrasound (POCUS) has become a must-have in emergency departments, allowing clinicians to rapidly assess internal injuries, bleeding, and other primary life-threatening conditions. In trauma cases, cardiac arrest situations, abdominal pain assessments, and others, POCUS can give the medical staff important information.

1.2.5. Oncology

- **Elastography for Tumour Detection:** Elastography, which measures tissue stiffness, is used to differentiate benign from malignant tumors, especially in the breast, liver, and thyroid. Elastography can provide additional information about tissue elasticity and thereby decrease the frequency of invasive biopsies [19].
- **Contrast-Enhanced Ultrasound (CEUS):** This technique is being used increasingly to see blood flow in tutors and distinguish cancerous from non-cancerous tissue, which is non-invasive and cost-effective than CT or MRI scans.

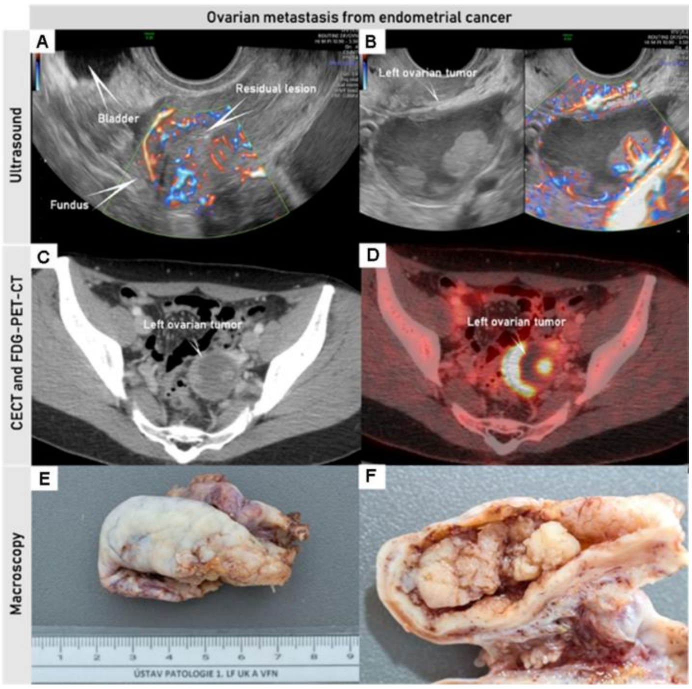


Figure 4: Ultrasound Imaging of endometrioid cancer

In recent years, artificial intelligence (AI) integration into ultrasound technology has allowed it to become one of the most revolutionary areas in the field. With the help of AI, the image can be interpreted by the algorithm to detect some very subtle abnormalities that our eyes might not notice in case. Another use of AI can be automated measurements, for example, fetal biometrics or cardiac dimensioning, reducing variability consistent with results and increasing the reliability of diagnoses. In a busy hospital setting where radiologists as well as technicians work under a high volume of cases every day, this automation can be particularly useful [20]. Other than diagnostics, AI is being used to power ultrasound systems and has shown great potential for telemedicine applications like remote image analysis that can help clinicians of underserved or rural regions in real-time through high-level diagnostic support to healthcare providers. Using AI could potentially decrease human error and increase diagnostic accuracy, allowing for more consistent outcomes regardless of which hospital department she's in, and potentially increase high-quality imaging within areas with less access to high-quality resources.

Despite these noteworthy advancements in the field of ultrasound, several difficulties remain in carrying out the latest ultrasound technologies across hospitals and clinics [21]. Cost can be said to be a primary concern in the implementation of any solution. The latest machines and features like 3D/4D, elastography, contrast, or AI-enhanced machines, are expensive. Hospitals, especially in non-developed regions find it difficult to make large initial expenses and recurrent costs of maintenance. Even today, portable and handheld wireless ultrasound systems and equipment are available at a comparatively low cost, yet high-end machines with more features and functions are still not affordable to many healthcare organizations. Also, many of these new technologies are designed to force clinicians to receive certain training to make optimal use of these new technologies. For example, while 3D and 4D images provide improvement in visual representation, the machines are complex and take a while to understand and when mastered they need a specialized operator to get the correct results which makes it necessary for hospitals to spend money on training programs to help their staff to use the machines effectively. Furthermore, by adding AI assistance for the analysis of ultrasound images, its speed and, accordingly, accuracy have almost certainly increased, although it introduced new problems associated with the approval of such equipment. The advancement of AI devices happens at an enormous pace, and this means that devices with the features have to undergo huge testing so that they can be approved to meet safety standards and effectiveness in the market. Another challenge of regulatory bodies is that they are unable to competently regulate the rate of innovation and thus delay in approving tools that could be of immense benefit in practice. They also require regulations because, while they utilize artificial intelligence in diagnosing their patients, the automated decisions made still require supervision to prevent wrong interpretation of results as no AI model is 100% accurate.

The anticipated future of ultrasound technology points toward this trend of miniaturization and increased utilization of AI for diagnosis. With miniaturization, such devices will be made available, portable even in outpatient care, away from hospitals. Wearable ultrasound could one day replace constant monitoring in critical care units and allow for tracking of patient status changing over time through cloud data with little inconvenience to the patient. Further advances in ultrasound technology are inevitable since the field can continue to gain superior and progressive applications as a safer, faster, and more accurate diagnostic tool in many medical applications. For example, such enhancements as the additional imaging features, AI incorporation, and better mobility can turn ultrasound into not only an essential diagnostic tool at hospitals but also at outpatient clinics, in rural areas, and in-home care settings. At the same time, hospitals will have to think about the advantages and disadvantages of these technologies along with implications for costs, training, regulations, and more importantly patient alignment

1.3. Ultrasound in Cancer Therapy

There are growing applications of ultrasound technology in the treatment of cancer as a therapy tool or in cancer diagnoses. Diagnostic ultrasound in combination with CEUS and elastography is used to diagnose and stage tumors, as well as to assess the results of treatment without performing invasive procedures. [22]. For instance, elastography allows us to determine whether the tumor is benign or malignant by evaluating the tissue's stiffness the information that it provides reduces the demand for biopsy which immensely increases the danger to human life. Ultrasound is also being researched in therapeutic uses other than diagnosis, most notably in cancer therapy, where high-intensity focused ultrasound (HIFU) and low-intensity focused ultrasound (LIFU) are utilized for different types of cancer cells [23]. HIFU targets tumors with powerful sound waves to heat the cancer cells and burst them out while leaving the surrounding tissues intact; thus, it affords a minimally invasive treatment as opposed to surgery or radiation. This precise targeted delivery is less likely to damage the surrounding unconcerned tissues and therefore HIFU is well suited for cancers that are located in areas close to critical parts of the human body. [24]. Ultrasound technology has a diagnostic and a therapeutic side as well, and with its help, procedures applicable to cancer treatment become more efficient, while patients' experience is enhanced throughout their treatment stages.

Ultrasound-induced microbubble therapy is another new area of research in selective cancer therapy and drug delivery. [25]. This strategy employs fine gas-filled microbubbles together with ultrasounds to improve the efficiency and distribution of therapeutic agents to the tumor-affected region. It is with these microbubbles that can be injected into the bloodstream that, when the focused ultrasound waves reach their intended location, they cause the microbubbles to oscillate and expand. This oscillation improves the capillary penetrability in a tumor so that the blood-tumor barrier of cancer cells is temporarily interrupted to allow therapeutic agents or a gene of interest to access cancer cells more easily. Rather, the microbubbles can be collapsed at higher ultrasound intensity and it generates localized forces, useful in breaking the tumor cell membrane. [26]. This technique has several feasible benefits over traditional cancer therapy. For instance, ultrasound-induced microbubble therapy can deliver a small concentration of drugs directly to the tumor sites and this relaxes the requirement for a large quantity of the drug that would normally have it circulate within the bloodstream hence increasing the side effects on the human body. Also, since the approach uses ultrasound to activate the microbubbles, the clinicians can well define the site and time of drug delivery thus increasing safety and efficacy. Current research works are seeking to establish if this therapy is ideal for intractable tumors that are hard to get to, say in the brain because of the blood-brain barrier that hinders drugs from getting in. Researchers are also exploring the synergistic application of microbubble-enhanced ultrasound with immunotherapies, wherein the mechanical actions of the microbubbles augment an immunological response to tumor cells. Being used experimentally at the moment, ultrasound-triggered microbubble therapy has the potential to become a breakthrough targeted treatment that can minimally invasion change the landscape of cancer therapy by improving the delivery of medications, minimizing side effects as well and boosting the efficacy of treatments.

1.3.1. Ultrasound Resonance Therapy

Studies into the usage of ultrasound resonance to selectively target and kill cancerous cells without affecting the normal ones without destruction are being regarded as an advanced replacement for cancer treatment in the form of acoustic or ultrasonic cancer therapy. This treatment takes advantage of some fundamental differences in the properties of cancer cells as compared to normal cells. This is because cancer cells have altered mechanical properties including densities and stiffness, and variations of the cell membrane are widespread making it easier to apply varied frequencies and intensity of ultrasound waves. When using ultrasound, it is possible to only excite the cancer cells' biomolecules at the resonant frequencies. In this way, the cancer cells would either burst or be forced into apoptosis, while not affecting the normal cells in the vicinity [27].

This selectivity is due to a 'spectral gap' meaning a range of frequencies that homes in the cancer cells not on normal cells. Many researchers have discovered that cancer cells have a unique frequency at which they vibrate and it is a physical cell, it can burst on resonance when it reaches certain extremes. [12]. For instance, in some studies, they employed low-intensity focused ultrasound or applied high-frequency ultrasonic waves to determine the vibration frequencies of the tumor cells of the various types of cancer. [28]. These frequencies of sound can create effects such as cavitation that involves the development of millions of microscopic bubbles in the environment of the cancer cell. This can generate mechanical forces so powerful that they can tear apart the cancer cells' cell membranes and clear their intracellular structures, thus killing the cancer cells. Cancer cells are endowed with unique mechanical characteristics and therefore there is a spectral gap when ultrasound frequencies are applied leading to researchers tuning ultrasound parameters to exact selective cell destruction. Within such resonance frequency range of cancer cells, they vibrate and are destroyed, normal cells which have different resonance frequencies do not get affected. Such a conclusion is at least partly attributed to variations in membrane stiffness and cytoskeleton characteristics distinguishing cancerous cells from normal ones. Furthermore, Tumour cells are generally softer and have different cytoskeleton architecture than normal cells. [29], making them more susceptible to oscillation and rupture at certain frequencies.

The research is still being conducted on this new subject and subsequent investigations are concerned with determining the most effective frequency bands, amplitudes, and duration of pulses that destroy cancerous cells without harming healthy tissue. Because of the disparity in the structure of cancer cells depending on the type of cancer, various cancer cells also have different resonance frequencies and numerous clinical trials are now ongoing to identify whether it is possible to create personalized ultrasound treatments for specific types of cancer. This method could in the future be used in place of surgery and have lesser side effects to the body as compared to surgery like chemotherapy or radiation. In general, it can be noted that research into ultrasound resonance as a selective therapy is still at a very early stage and remains mainly experimental. It may result in a completely new procedure to mediate cancer cell multiplication and spreading without having to use invasive methods that would increase patient prognosis and give oncologists a new weapon against cancer cells.

1.4. Piezoelectric Ultrasound Transducers

Piezoelectric ultrasound transducers are an important division within the medical imaging and therapy domain as they employ the features of piezoelectric materials that can transmute electrical energy into mechanical sound and vice versa. When voltage is applied, the piezoelectric material found in the transducer is set to high-frequency vibrations to produce ultrasonic waves. The most commonly used piezoelectric materials are PZT (Lead zirconate titanate) ceramics. These waves can pass through the body and influence the tissues, which can explain the versatility of ultrasound equipment. Interestingly, as with diagnostically useful ultrasound, these sound waves bounce off all structures throughout the body back to the transducer, which then processes the said electrical signals into images. The ultrasound waves can also transfer the heat to the cells if their frequency matches with the cells. It has therefore turned out to be one of the safest ways to make use of ultrasound technology among the many ways in many fields such as obstetrics, cardiology as well and abdominal imaging. Apart from imaging, piezoelectric ultrasound transducers have numerous therapeutic benefits: High-Intensity Focused Ultrasound (HIFU) for therapy of cancer. [30]. HIFU uses a transducer that directs focused sound waves that cause the temperature of the cancerous tissue to rise to levels that will cause coagulative death to the tumor cells. This is realized by directing therapeutic pesticides densely in the affected area without causing damage to the adjacent healthy tissue. The advantages of HIFU have made the treatment popular in the treatment of cancer diseases such as prostate and liver cancer. Thus, the avoidance of risks associated with surgical operations is one of the advantages of demonstrating high effectiveness and comfort, including shorter time needed for the rehabilitation of patients and fewer complications after the HIFU treatment in oncology. The piezoelectric transducers therefore play a central role in producing these focused high-intensity waves since the quality and stability of the frequencies produced by such transducers determine the reliability of HIFU treatments.

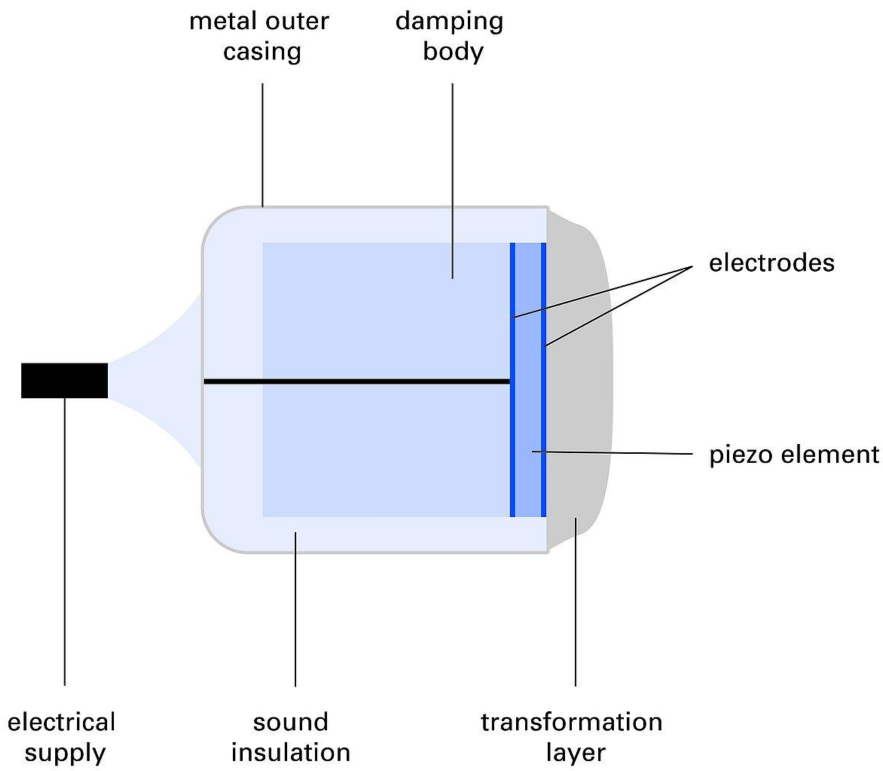


Figure 5: Component of a Piezoelectric Ultrasound Transducer

Another advanced application of piezoelectric ultrasound transducers in cancer therapy comprises ultrasound-induced cavitation and microbubble technology [31]. Microbubbles are small spheres containing gas and can be introduced into the circulatory system, upon their reach to the tumor area, several types of waves are generated by the transducer causing them to rupture. The stimulus applied in this case causes the microbubbles to expand and contract, and at some point, they can do so violently in a process called cavitation. This action creates strong mechanical forces that can cause the membranes of adjacent cancer cells to break which increases the absorptivity of the cells to drug therapy. Thus, not only is the cancer cell direct destruction achieved by ultrasound-assisted microbubble therapy, but drug delivery is also improved and targeted mainly at the disease focus point. This concept of mechanical disruption combined with improved drug delivery through enhanced diffusion is also being studied as a way of increasing the efficacy of chemotherapy and minimizing side effects from high doses of cancer-fighting drugs.

Possibly the most interesting aspect of ultrasound cancer therapy is the accessibility of targeted destruction of the cancer cells depending on physical properties. Cancer tissues are denser, stiffer, and possess different structural compositions than normal ones, therefore, respond to distinct US frequencies. It has been for this reason that researchers have conducted experiments to apply piezoelectric transducers in order to produce certain frequencies known as US frequencies that induce the cancer cells to vibrate strenuously resulting in cell destruction or cancer cell apoptosis [12], [23], [27]. The fact is that there is a potential to change the frequency to reach one resonating with the cancer cells, but not with the healthy cells so that less harm is done to the body. This idea, known as 'selective resonance,' still remains experimental, where the principle of cancer cell destruction is based on the mechanical weaknesses of these cells. Specifically piezoelectric ultrasound transducers are also advancing in the field of targeted drug delivery, which is critical in oncology, which requires drugs to be delivered with much accuracy to the tumor sites. The shortcoming of traditional chemotherapy is that drugs are spread all over the body and harm the malignant and normal cells thus causing side effects. However, when the drug-loaded microbubbles are combined with ultrasound it is possible to release such drugs at the tumor site in a controlled manner. With the help of ultrasound, the microbubbles make the encapsulated drugs become available for the tumor and the rest of the body does not receive a high concentration of medication. This ultrasound-mediated approach has even more potential when used with piezoelectric transducers, and has shown remarkable potential in enhancing chemotherapeutic and gene therapeutic treatments by making doses more targeted, thus decreasing side effects.

Although piezoelectric ultrasound transducers show promise in cancer therapy, difficulties still exist. The mechanical properties of each type of cancer cell are somewhat distinct and that gets to the reason of establishing all the relevant resonant frequency cycles and possibly enough differences in various patients. Moreover, although microbubble cavitation and selective resonance are potential solutions for drug delivery, their ability to damage healthy tissue in the surrounding area must no longer happen inadvertently. Therefore, current research explores how transducer technology can be optimized; in other words, how it can be modified so that frequencies and intensities can be changed in the instant of the operation in response to the target area. Increasing the efficiency of such transducers and imparting them the ability to adapt to the tumor's character can bring about improvements in cancer treatment that are specific to the profile of the tumor. These therapeutic progress are driven by piezoelectric ultrasound transducers which are at the center of the transition of ultrasound from simple diagnostic imaging technology to an innovative tool in anti-cancer warfare. Thanks to the possibility of selective frequency and power control, these transducers can provide highly specific, nondestructive treatments that can redefine oncology as a field. However, as long as the technology of ultrasound cancer therapy is improving in the future, piezoelectric transducers may contribute to a new pattern of development for medical treatment: precision medicine for patients, which can reduce side effects and increase treatment efficiency. Work on this front to improve and broaden the application of piezoelectric ultrasound technology goes on in parallel, with each advancement that it produces, making cancer remedy or treatment, safer, more exact, and less intrusive in the medical field.

1.5. Types of Piezoelectric Ultrasound Transducers

1.5.1. Linear Array Transducers

The linear array transducers consist of piezoelectric elements arranged in a straight line, which is scanned in the elevation direction so as to generate ultrasound waves for imaging. This formation gives improved quality images, particularly when used to investigate structures that are nearer the surface. Linear transducer arrays are suitable for vascular, musculoskeletal, and small organ lesions/ pathologies as in the thyroid and breast. [32], [33]. Their aptitude to produce detailed images of structures close to the skin makes them indispensable in specific diagnostic contexts where precision is essential.

1.5.2. Curved (Convex) Array Transducers

Curved array transducers, also referred to as convex transducers consist of a series of piezoelectric elements whose arrangement is curved in the direction of the array so that the ultrasound waves emitted fan out and deliver a wider field of view. This wide-angle makes them ideal when imaging larger as well as deeper structures, especially in the abdomen and the pregnant female pelvis. Convex transducers are commonly utilized when examining organs including the liver, kidney, and fetus during pregnancy owing to their deeper tissue penetration and broader imaging.

1.5.3. Phased Array Transducers

Phased array transducers are made up of multiple piezoelectric elements, which activate in order to achieve electronic beam steering and focusing. This design allows the production of rapidly updating and high frame rate images with a low field of view, which can provide deeper penetration into the body. Phased array transducers are most suitable for cardiac applications, in particular echocardiography, because real-time imagery of the moving organ is essential for precise analysis of the heart’s performance, blood circulation, and condition of valves.

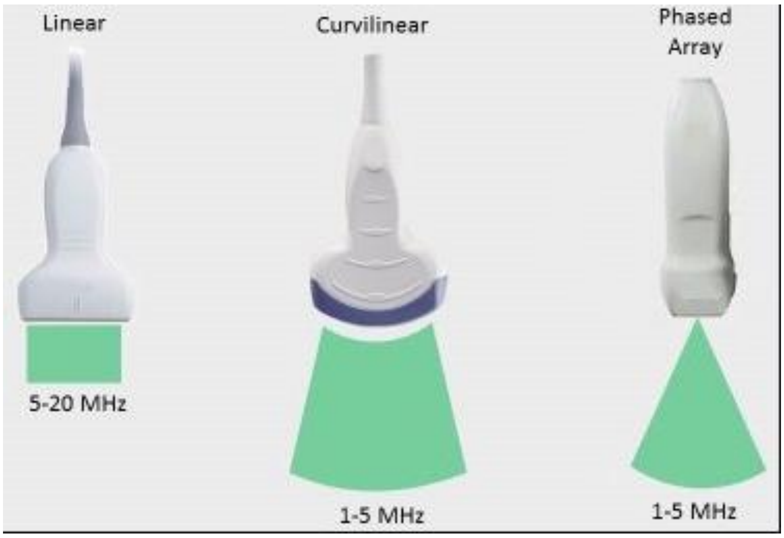


Figure 6: Linear vs Curved vs Phased Array Transducers

1.5.4. Endocavity Transducers

Endocavity transducers are unique types of transducers that are intended and used to be placed inside the human body for inspecting the inside or interior part of the human body. These transducers are employed in transvaginal, transrectal, and transesophageal ultrasonic examinations using a small probe with piezoelectric elements. Endocavity transducers provide high spatial resolution in structures that cannot easily be visualized externally, which is used in gynecological, prostate, and gastrointestinal imaging.

1.5.5. High-Intensity Focused Ultrasound (HIFU) Transducers

High-Intensity Focused Ultrasound (HIFU) transducers are intended for therapeutic rather than diagnostic intentions. These transducers focus ultrasound energy on a precise area within the body to raise tissue temperatures and ablate (destroy) targeted cells, commonly used in cancer treatments such as prostate and liver cancer. HIFU transducers offer a non-invasive alternative to surgery, utilizing focused energy to target and destroy tumor cells while sparing surrounding tissues. HIFU treatment is also beneficial for the de-aging of skin. The deeper layers of the skin are essentially injured/damaged and the body repairs the micro injuries by producing more collagen and elastin through HIFU.

Figure 7: HIFU Treatment for De-aging

1.5.6. Low-Intensity Focused Ultrasound (LIFU) Transducers

Low-Intensity Focused Ultrasound (LIFU) transducers are designed to deliver targeted, low-intensity ultrasound energy to specific areas within the body for therapeutic purposes. Unlike High-Intensity Focused Ultrasound (HIFU), which uses high energy to ablate tissue, LIFU applies lower energy levels, making it suitable for neuromodulation, drug delivery enhancement, and even blood-brain barrier modulation. In cancer therapy, LIFU transducers are used experimentally to aid in targeted drug delivery by temporarily increasing the permeability of blood vessels around a tumor, allowing chemotherapy drugs to enter more effectively. [34]. LIFU is also being studied in neurological applications, where it has the potential for non-invasive brain stimulation to treat conditions like epilepsy and depression. Its ability to focus ultrasound power accurately and control the grade of intensity makes LIFU a hopeful tool in non-invasive therapy and precision medicine.

1.5.7. Intravascular Ultrasound (IVUS) Transducers

IVUS transducers are miniaturized transducers that are placed on a probe and can therefore be progressed into the blood vessels to obtain high-resolution images from within the vascular system. The main applications of Optical coherence tomography (OCT) are in cardiology for determining morphological characteristics of the internal layer of coronary arteries, the amount of atherosclerotic plaque, the state of arterial walls, and blood circulation. IVUS transducers give useful data to be used in directing mediatory cardiology processes such as the deployment of stents.

1.6. Structure of piezoelectric ultrasound transducer

Whenever one is constructing a piezoelectric ultrasound transducer, four principal components are usually used, all of which have been created to enhance the conversion of electrical energy into mechanical energy or vice versa. These components include:

1.6.1. Piezoelectric Material

Piezoelectric materials [35], [36], [37], [38]Are fundamental to ultrasound transducers, determining their efficiency, sensitivity, bandwidth, and versatility. Continuous advancements in piezoelectric materials focus on optimizing their mechanical, electrical, and thermal properties to meet the growing demands of various applications. A high-performance piezoelectric material has the following properties:

- **Piezoelectric Coefficient (d33)**: Indicates the efficiency of electric-to-mechanical energy conversion.
- **Electromechanical Coupling Coefficient (k):** Measures energy transfer efficiency between electrical and mechanical systems.
- **Acoustic Impedance**: Matching this to the transmission medium improves energy transfer.
- **Dielectric Constant**: Affects the material's response to an electric field.
- **Mechanical Strength**: Ensures durability under high-stress operations.
- **Thermal Stability**: Critical for high-intensity or continuous-wave applications.

Commonly used piezoelectric materials are as follows:

- **Piezoelectric ceramics:** These are the most widely used materials in ultrasound transducers due to their high piezoelectric coefficients, excellent durability, and ability to be manufactured in diverse shapes and sizes. The most commonly employed ceramic is **lead zirconate titanate (PZT)**, known for its strong electromechanical coupling and thermal stability. Variants of PZT are modified with dopants such as lanthanum or strontium to enhance specific properties like sensitivity, operational bandwidth, or thermal resistance.
- **Piezoelectric polymers:** Polymers like **polyvinylidene fluoride (PVDF)** and its copolymers, are increasingly used in applications where flexibility, low acoustic

impedance, and biocompatibility are required. Unlike ceramics, polymers are lightweight and can conform to curved surfaces, making them ideal for wearable sensors, medical imaging, and implantable devices. Although their piezoelectric coefficients are lower compared to ceramics, advancements in processing techniques, such as stretching and poling, have improved their performance.

- **Composite materials:** These combine the advantages of ceramics and polymers, offering a balance between sensitivity, bandwidth, and flexibility. A typical structure is the **1-3 composite**, where piezoelectric ceramic pillars are embedded in a polymer matrix. This design reduces the overall acoustic impedance, making it easier to match with biological tissues, while retaining the high piezoelectric efficiency of ceramics.
- **Single-crystal piezoelectric:** Materials such as **lead magnesium niobate-lead titanate (PMN-PT)** and **lead indium niobate-lead magnesium niobate-lead titanate (PIN-PMN-PT)**, offer superior piezoelectric and electromechanical characteristics compared to ceramics. These materials exhibit much higher piezoelectric coefficients (d33) and coupling efficiencies, making them ideal for high-performance applications like medical imaging and therapeutic ultrasound.

The selection of piezoelectric material significantly influences the performance and application scope of ultrasound transducers. Ceramics like PZT dominate due to their high efficiency and versatility, while polymers like PVDF cater to flexible and biocompatible applications. Composites offer a balanced solution, and single crystals deliver unmatched precision for high-performance needs. As research progresses, emerging materials and hybrid designs promise to expand the capabilities of piezoelectric ultrasound transducers, addressing challenges like environmental sustainability, cost reduction, and enhanced functionality.

1.6.2. Electrodes

Electrodes in piezoelectric ultrasound transducers are vital for establishing the electric field needed to activate the piezoelectric effect. Common materials include gold and silver for their excellent conductivity and stability, while platinum is used in high-durability applications like biomedical implants. Copper offers affordability but requires protective coatings to prevent oxidation. Thin-film electrodes are frequently used for their uniformity in high-frequency devices, while patterned electrodes enable precise control in array transducers. Advanced designs incorporate dual-layer or composite electrodes combining metals with conductive polymers for enhanced flexibility and performance. The choice of electrode material and configuration significantly impacts the transducer's efficiency and durability.

1.6.3. Backing Material

The backing material is placed behind the piezoelectric element to:

- Dampen vibrations for short pulses.
- Reduce ringing and improve axial resolution in imaging applications. Common materials include tungsten-filled epoxy or rubber, which provide impedance matching and effective damping [39].

1.6.4. Matching Layers

Matching layers are used on the front surface to bridge the acoustic impedance mismatch between the piezoelectric material and the medium (e.g., tissue, water, or air). Multiple matching layers may be used to optimize energy transmission. Their thickness is often designed to be a quarter-wavelength for maximum efficiency.

1.6.5. Acoustic Lens

For focused ultrasound applications, an acoustic lens is added to the front of the transducer. These lenses shape and concentrate the beam, improving spatial resolution.

1.7. Impedance Matching and its Role

Impedance matching is a critical aspect of designing piezoelectric ultrasound transducers (PUTs) [40], significantly influencing their performance in transmitting and receiving ultrasonic energy. Energy transfer from the transducer through the surrounding medium to the electronic circuitry of the system is only possible when the acoustical and electrical properties of the two mediums match. Where impedance matching is not achieved, power is reflected or absorbed at boundaries hence the sensitivity, bandwidth, and overall efficiency of the transducer are jeopardized. This discourse specifically focuses on the fundamental notion of impedance matching, obstruction, and its solutions in connection with piezoelectric ultrasound transducers as well as its viability in different applications.

Impedance is the resistance against the flow of energy through an electrical as well as an acoustical circuit. In the context of piezoelectric ultrasound transducers, there are two primary types of impedance to consider: electrical impedance which is associated with the connection between the transducer and the electronics that drive or receive the signal, and acoustical impedance – the connection between the transducer and the environment in which it works (air, water or tissues). The goal of impedance matching is to minimize mismatches at these interfaces to ensure maximal energy transfer.

- **Electrical Impedance Matching**: This involves such things as the matching of the impedance of the driving circuit to the input impedance of the transducer. They can cause unplanned directions to power flow and signal to be directed where it is not required.
- **Acoustic Impedance Matching**: This type of matching requires the impedance of the piezoelectric material to be compatible with that of the transfer medium. Large differences in acoustic impedance cause significant reflection of ultrasonic waves, diminishing the transducer's effectiveness.

1.7.1. Challenges in Impedance Matching

Achieving optimal impedance matching for piezoelectric ultrasound transducers poses several challenges:

- **Wide Impedance Gaps**: Piezoelectric materials, such as ceramics (e.g., PZT), typically have high acoustic impedances ranging from 20-30 MRayl, whereas biological tissues or water have much lower impedances (1-2 MRayl). Bridging this gap is crucial but technically demanding. A few piezoelectric materials like PVDF have lower impedances (2-4 MRayl).
- **Frequency Dependency**: Both electrical and acoustic impedance are frequency-dependent. This makes achieving uniform impedance matching across a broad frequency range complex, particularly in broadband applications.
- **Thermal and Mechanical Stability**: Materials used for impedance matching must maintain performance under varying thermal and mechanical conditions, especially in high-power or therapeutic ultrasound applications.
- **Physical Constraints**: Matching layers and circuit components must be compact, lightweight, and integrated seamlessly into the transducer design.

1.7.2. Techniques for Acoustic Impedance Matching

Acoustic impedance matching primarily focuses on improving energy transmit between the piezoelectric material and the medium of propagation. [41]. Common techniques include:

- **Matching Layers:** Matching layers are thin layers of material applied to the front of the piezoelectric element to reduce impedance differences between the transducer and the medium. Each layer is typically designed to have an acoustic impedance value that lies between the transducer and the medium, following a geometric progression. The thickness of each layer is precise and common for the layer thickness is for a wavelength of the working frequency divided by four to ensure that there is constructive interference to enhance transmission gain. Feasible materials for matching layers are ceramics, polymers, and composites for the layers, depending on the application and necessary impedance level.

- **Multiple Matching Layers**: In more difficult applications where high-efficiency coupling is essential, the use of multiple matching layers is made. These layers further decrease the impedance mismatch on multistage analysis and improve the energy transfer. The thickness and the nature of such layers depend on the number of layers necessary, which makes it more bulky to calculate and produce.

- **Surface Treatments**: Surface coatings or treatments e.g. applying a thin polymer film that can act as fundamental matching layer for low-frequency applications.

1.7.3. Techniques for Electrical Impedance Matching

Electrical impedance matching focuses on ensuring efficient power transfer between the transducer and its driving electronics. [42]. Common methods include:

- **Matching Networks**: Electrical matching networks incorporate inductors, capacitors, and resistive circuit elements that suit the impedances of the transducer and the driving circuit. These networks are beneficial in bandwidth-constrained or, as they are commonly referred to, narrowband applications. The design of these networks relies on the operating frequency, bandwidth, and specific transducer properties.
- **Tuning Techniques**: Adjusting the operating frequency to coincide with the transducer's resonance frequency inherently reduces electrical impedance mismatches. This is particularly useful for single-frequency systems.

- **Impedance Compensation Circuits**: Compensation circuits are used to counteract reactive components of the transducer's impedance, ensuring a more purely resistive load for the driving electronics.

1.7.4. Principle of Electric Impedance Matching

Electrical impedance matching aims to minimize reflections at the electrical interface between the driving electronics and the transducer. [43]. Key concepts include:

- **Impedance Reflection Coefficient (Γ)**:

  The impedance reflection coefficient (Γ) quantifies the mismatch between the source and load impedances and determines the proportion of energy reflected back at the interface. It is mathematically defined as:

$$\Gamma = \frac{Z_{load} - Z_{source}}{Z_{load} + Z_{source}}$$

  Where Z_{load} is the input impedance of the transducer, and Z_{source} is the impedance of the driving circuit. An ideal match results in $\Gamma=0$, meaning no energy is reflected, and all the energy from the source is transferred to the load. However, when $\Gamma \approx 1$, high reflection occurs resulting from a significant impedance mismatch, leading to poor energy transfer and degraded performance. In piezoelectric systems, achieving a low reflection coefficient is critical to enhance efficiency and avoid energy losses.

- **Energy Transfer Efficiency**: Achieved by ensuring the source and load impedances are equal, maximizing power transfer.

- **Bandwidth Considerations**: Impedance matching also affects the bandwidth of the system. A wider bandwidth is generally desired for applications such as imaging.

By using ultrasound in the range of 100 kHz and above, several cell operations from single-cells, to acoustic trapping, and during high-resolution mechanotransduction are executed. The transducer used for very high ultrasound will accomplish its goal via focused beam with a large aperture radius for establishment of a very strong acoustic pressure field. Due to the diminished power and duration of pulse, it is also innocuous to live cells. This lower power is obtained only when the loading impedance of the transducer is matched with the driving electronics. The impedance mismatch equation leads to a large part of the electrical energy reflected back to the source of excitation especially with large aperture and very high ultrasonic transducers producing frequencies almost above 100 kHz. The problem arises mostly due to dielectric constant assuming exceedingly high values for piezoelectric materials. Various impedance matching schemes were devised in order to have the characteristics of a wide band operation coupled with high resolution. Most of the matching circuits are devised to function the transducer on its resonant frequency.

1.7.5. Butterworth-Van Dyke (BVD) model for Electric Impedance Matching

The piezoelectric transducer functions as a capacitive load (not a resistive one) at its resonant frequencies. The ultrasonic signal exhibits a phase difference between voltage and current, which affects the resonant effect of the transducer and the power transfer from the power supply. A straightforward method for matching the electric impedance involves adding an inductor in series or parallel with the transducer. However, this approach may introduce complexities in circuit design because of the potential interactions between components. Although it appears simple, the process requires careful consideration of various factors to ensure optimal performance. At series resonance, a shunt inductor with a value $1/(\omega^2 C_0)$ is added. While for parallel resonance, a shunt inductor with value $1/(\omega^2 C_0)+R_a^2 C_0$ is added. Here, C_0 is the capacitance of transducer and $R_a = 4k_t^2 Z_c/[\pi\omega_a C_0(Z_1+Z_2)]$. Where Z_1 and Z_2 are the acoustic impedance of load and backing material, respectively.

A piezoelectric ultrasonic transducer, being an electromechanical element, is treated as an equivalent circuit for electrical impedance-matching network (EIMN) design purposes. The Mason, Redwood, KLM network, and Butterworth-Van Dyke (BVD) models are widely utilized as comparable circuits for piezoelectric ultrasonic transducers. A single-frequency BVD model represents the analogous circuit of a single resonant frequency transducer as shown in Figure 8: Single frequency matching circuit. It consists of a resistor R_{SE} (mechanical and radiation loss) and a clamping capacitor C_0 (equivalent capacitance due to piezoelectric elements and cables, connections, etc.) as connected elements. The other elements capacitor CSE and inductor L_{SE} model the resonant output of the transducer. Such a circuit has power delivered to RSE mimicking the acoustic power emitted when mechanical losses are insignificant. [44]. The impedance is described by series and parallel resonant frequencies. ω_{SE} and ω_{PA}, respectively, as

$$Z_{SE} = \frac{1}{\omega C_0} \frac{(\omega_{\mathrm{SE}}^2 - \omega^2) + j\frac{R_{SE}}{L_{SE}}\omega}{-\frac{R_{SE}}{L_{SE}}\omega + j(\omega_{\mathrm{PA}}^2 - \omega^2)'}$$

where $\omega = 2\pi f$ is the angular frequency, $\omega_{\mathrm{SE}}^2 = 1/(L_{SE}C_{SE})$ and $\omega_{\mathrm{PA}}^2 = (C_{SE} + C_0)/(L_{SE}C_{SE}C_0)$.

An equivalent circuit of a multi-frequency resonant transducer is described by joining multiple single resonant frequency equivalent circuits in parallel.

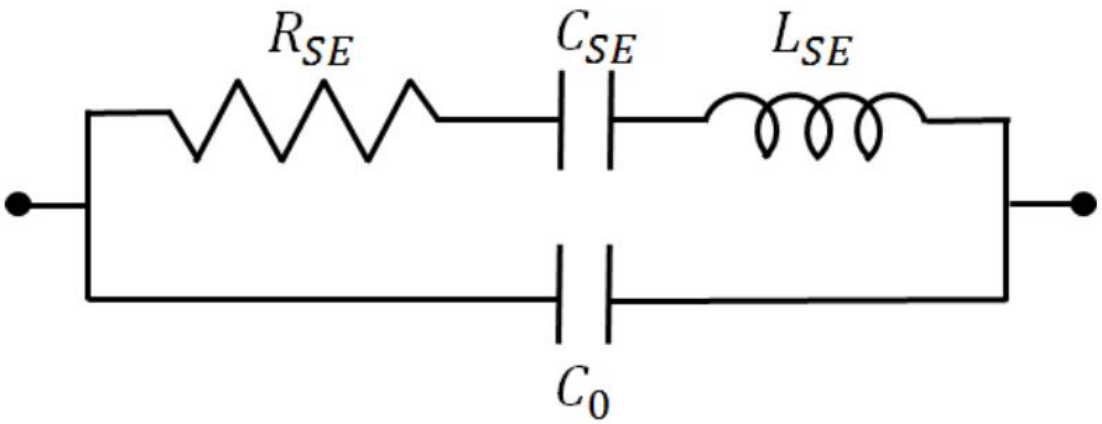


Figure 8: Single frequency matching circuit

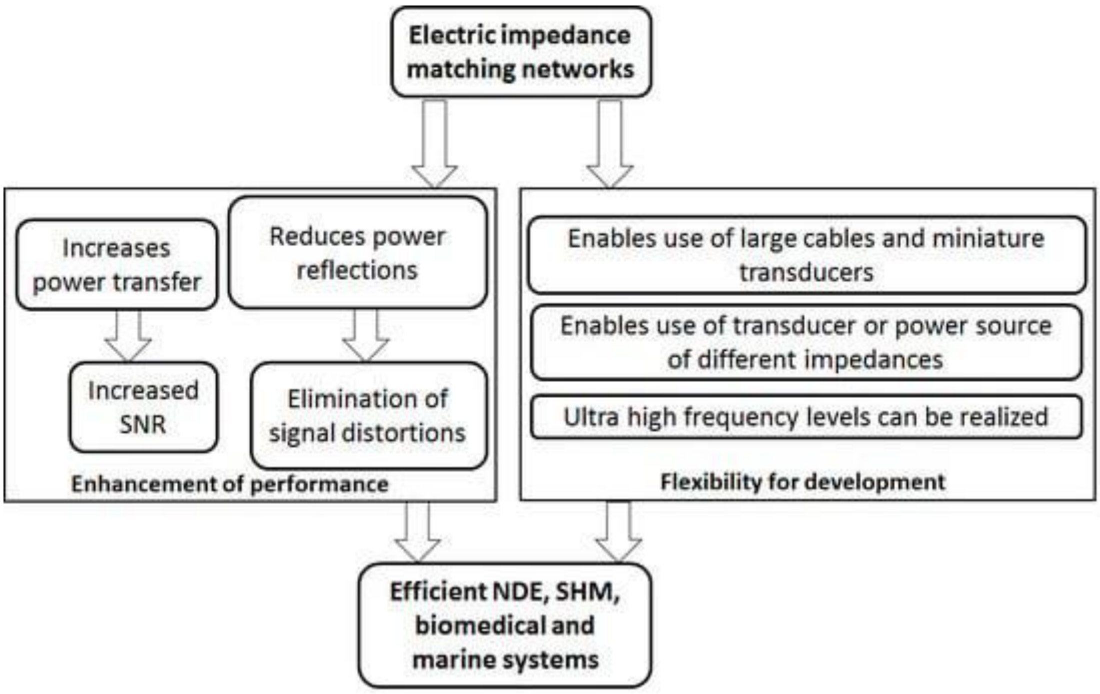


Figure 9: Electrical Impedance Matching Networks

1.7.6. Applications and Importance of Impedance Matching

The importance of impedance matching extends across all applications of piezoelectric ultrasound transducers:

- **Medical Imaging**: In diagnostic imaging, accurate impedance matching improves sensitivity and resolution, ensuring clear, detailed images. Broadband transducers benefit from sophisticated matching techniques to accommodate the wide frequency range required for high-quality imaging.
- **Therapeutic Ultrasound**: For applications like high-intensity focused ultrasound (HIFU), efficient energy transfer ensures sufficient power is delivered to target tissues for ablation. Proper impedance matching reduces the risk of overheating or damaging the transducer.
- **Industrial Non-Destructive Testing (NDT)**: Efficient impedance matching improves the penetration depth of ultrasonic waves in materials, enhancing flaw detection accuracy.
- **Underwater and Sonar Applications**: In underwater systems, where water has a low acoustic impedance, matching layers are critical to minimize reflections and maximize sound propagation.

Impedance matching is a cornerstone of piezoelectric ultrasound transducer design, ensuring efficient energy transfer and optimal performance. By bridging acoustic and electrical impedance mismatches, impedance matching improves sensitivity, bandwidth, and energy efficiency across medical, industrial, and underwater applications. While challenges remain in managing wide impedance gaps and frequency dependencies, ongoing research and innovation continue to enhance the effectiveness and reliability of matching techniques. From advanced matching layers to sophisticated electrical networks, the development of impedance-matching solutions ensures that piezoelectric ultrasound transducers remain indispensable in diverse fields.

CHAPTER 2: Literature Review

Sound waves are a type of energy transfer that occurs during an object's mechanical vibration. Ultrasound is a form of sound wave with a vibration frequency greater than 20 kHz that is hearable by humans [45]. A piezoelectric ultrasound transducer (PUT) is a device for producing shared conversion of mechanical energy and electrical energy. [46]. PUTs are widely used in non-destructive experiment, medical imaging, particle manipulation, etc., and the output of the PUT determines its functional performance and effectiveness in these applications.

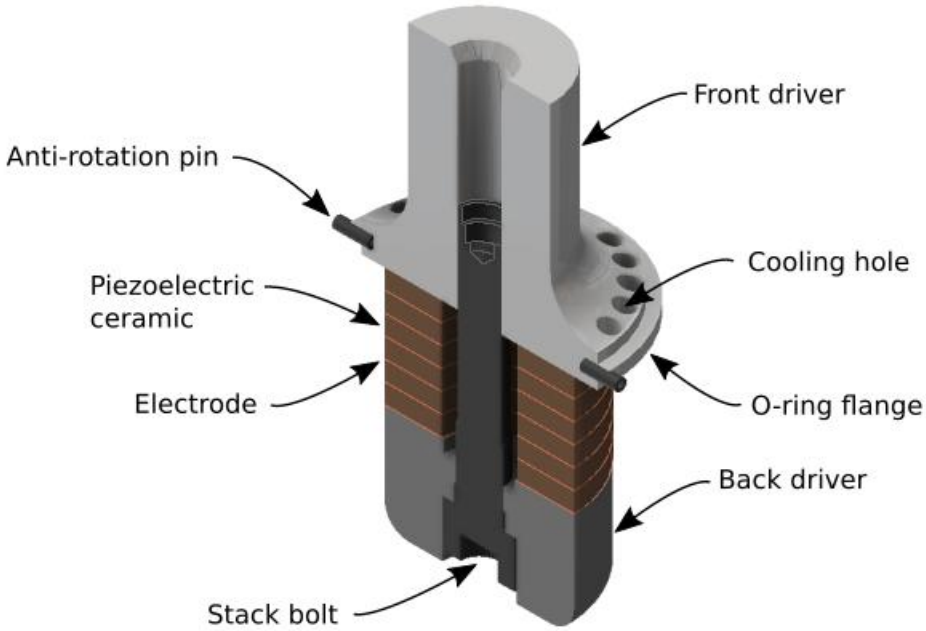


Figure 10: Piezoelectric Ultrasound Transducer

COMSOL Multiphysics (COMSOL Inc., Burlington, MA, USA) is an powerful multi-physical finite element method (FEM) simulation software, being widely utilised in the simulation and design of PUTs due to the accessibility of a wide range of built-in piezoelectric materials archives. [47] Investigated the performance of a standard bending actuator fabricated with lead zirconate titanate (PZT) ceramics and lead magnesium niobate–lead titanate (PMN-PT) material by using COMSOL software. Therefore, A FEM analysis can thoroughly and accurately simulate the multi-physical domains of a PUT, which is advantageous for its optimization, design and fabrication. [48].

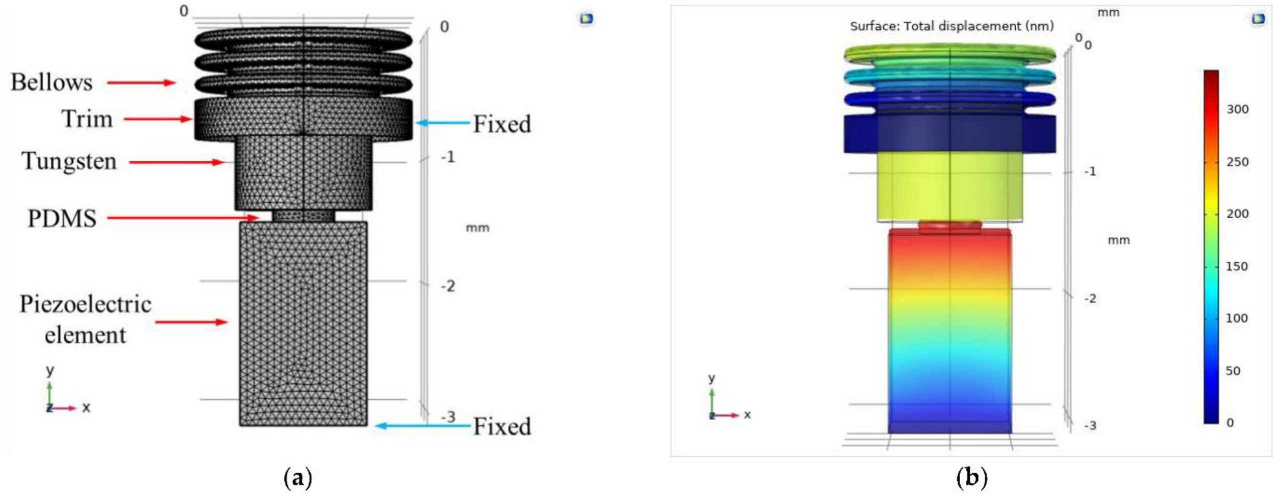


Figure 11: (a) Meshing of PUT in FEM Software (b) FEM Analysis of a PUT

The usage of high-intensity focused ultrasound waves to treat different types of cancer has gained a lot of popularity in the past years due to the fact that it is non-invasive. Ultrasound waves are produced with such a method to raise the temperature of the focused volume to 60°C for a short period of time (1 to 3 seconds). At high frequencies, the penetration depth of microwaves is very trivial. However, at low frequencies, the capability to generate a significant focus is compromised. This fact makes it less beneficial to utilise in microwave devices (Shinohara, 2004), and more research is done on ultrasounds. [49], [50].

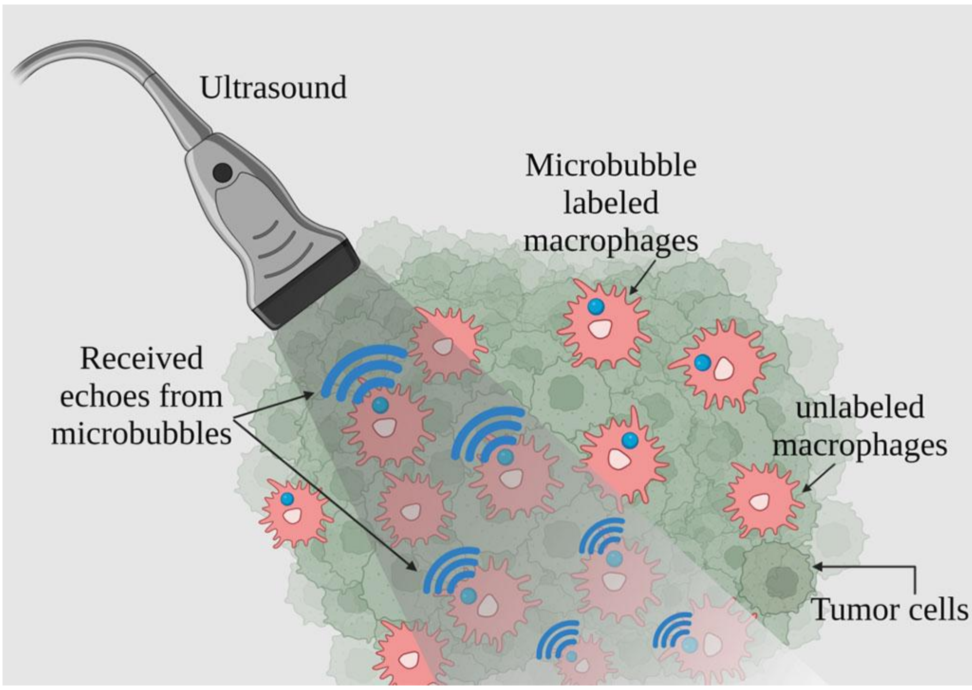


Figure 12: Microbubbles with Ultrasound for Cancer Cells Bursting

Advanced minimally invasive surgery has been carried out for most of the substantial gastrointestinal diseases. However, patients with coagulopathy or unresectable tumors cannot be recovered by existing treatment methods. Moreover, other existent medical devices for focused drug release are larger in size to be applied in gastric endoscopes because the diameter of the biopsy channel is smaller than 3 mm. To tackle this issue, [51] Developed a piezoelectric single crystal ultrasonic transducer (the diameter was only 2.2 mm and the mass was 0.076 g) to generate acoustic waves, which encouraged the drug release in the planned position of the digestive tract by using an endoscope.

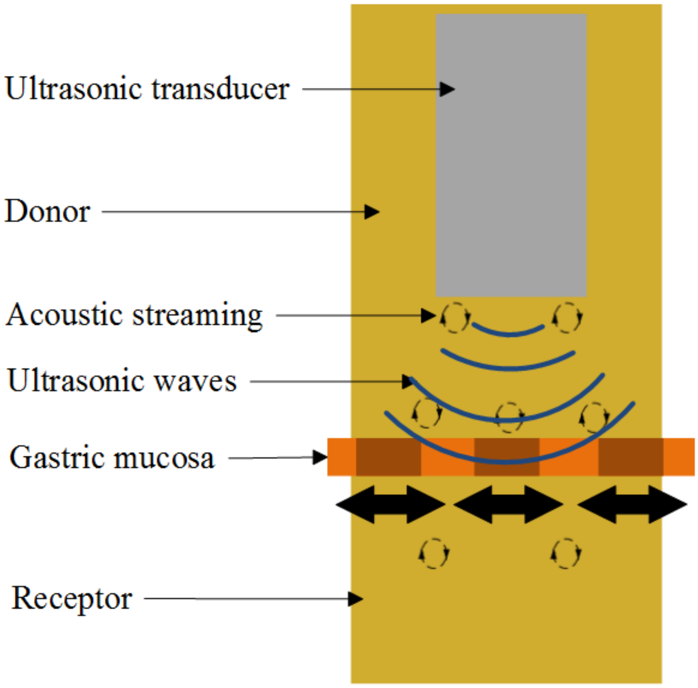


Figure 13: Mechanism of Piezoelectric single crystal ultrasonic transducer

An ultrasonic transducer with a diameter of 2.2 mm is designed based on the PZT excitation, which displays an electromechanical coupling coefficient of 0.36 and a center frequency of 6.9 MHz with a −6-dB bandwidth of 23% was developed. The acoustic field distribution was visualized using the COMSOL FEM simulation software. A 2-D axisymmetric system was used, which is a standard assumption in the calculation of acoustic pressure and streaming. Recently, the combination of ultrasound with microbubbles has also seen developments as a promising strategy to strengthen vascular penetrability, enhancing drug delivery from blood to tissues. [52].

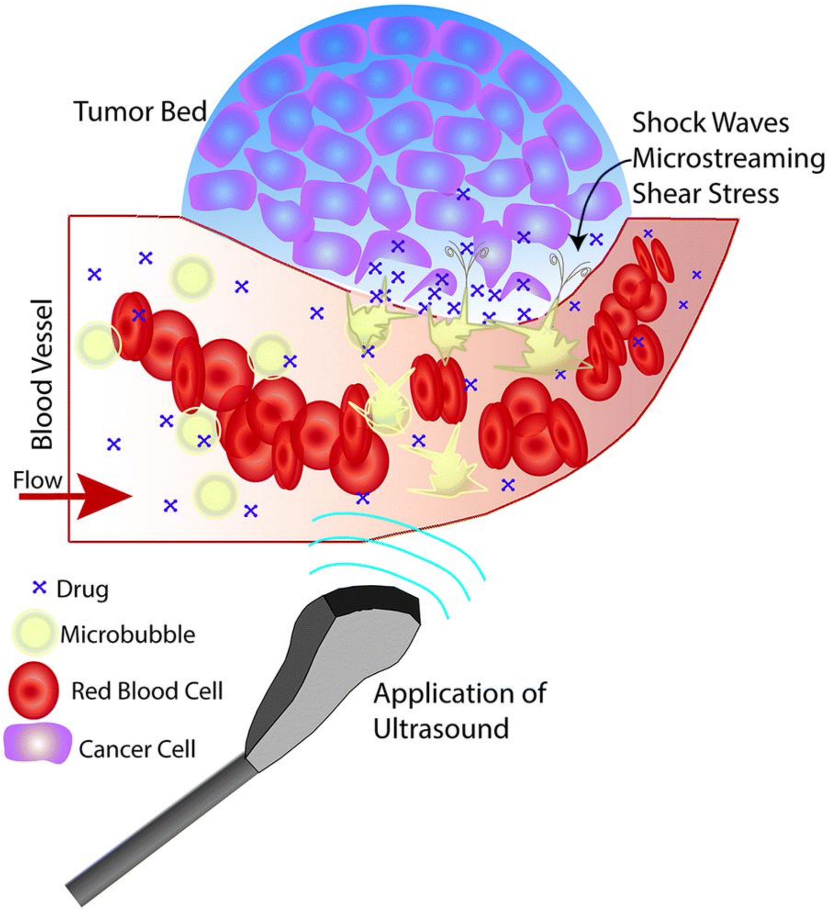


Figure 14: Ultrasound drug delivery system

[12] Their research investigated a method of selectively focusing on cancer cells by means of ultrasound harmonic excitation at their resonance frequency, which is referred to as oncotripsy. The geometrical model of the cells grabs into account the cytoplasm, nucleus, and nucleolus, as well as the plasma membrane and nuclear envelope. Material properties are assorted within a pathophysiological appropriate range. A first modal analysis discloses the presence of a spectral gap amongst the natural frequencies and, most importantly, resonant growth rates of healthy and cancerous cells. The results of the modal analysis are confirmed by simulating the fully nonlinear transient response of healthy and malignant cells at resonance. The fully nonlinear analysis indicates that malignant cells can be selectively lysed using properly regulated ultrasound harmonic stimulation while healthy cells remain intact.

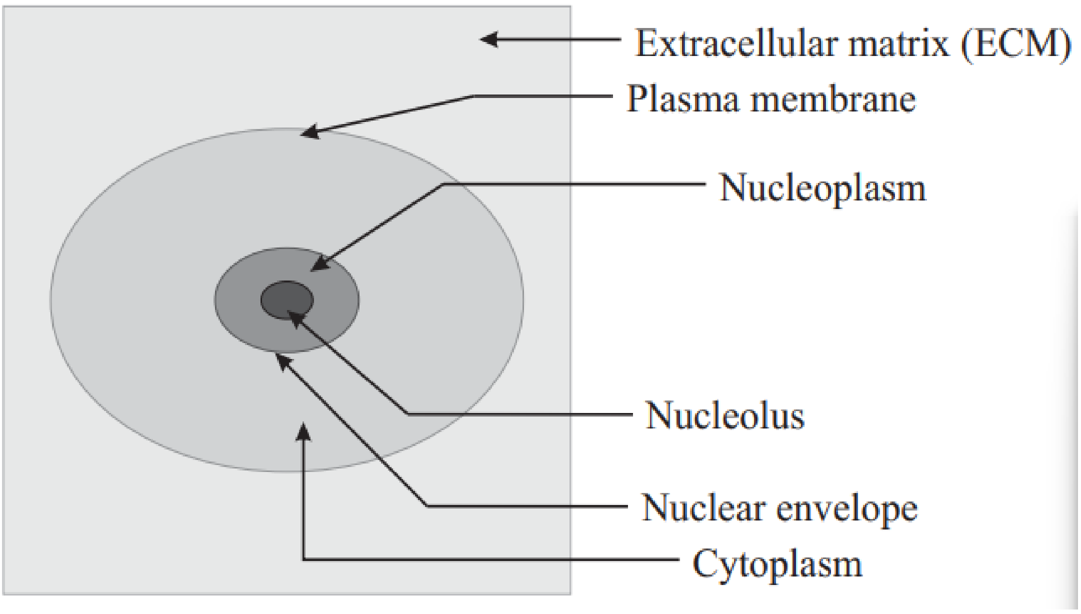


Figure 15: Model for modal analysis

They proposed a novel cancer treatment via the employment of carefully tuned ultrasound pulses in the frequency range of 80 kHz, duration in the range of 70 µs, and power density in the range of 0.8 W/cm2. Such finely tuned ultrasound pulses of variable frequency can be achieved through a piezoelectric ultrasound transducer.

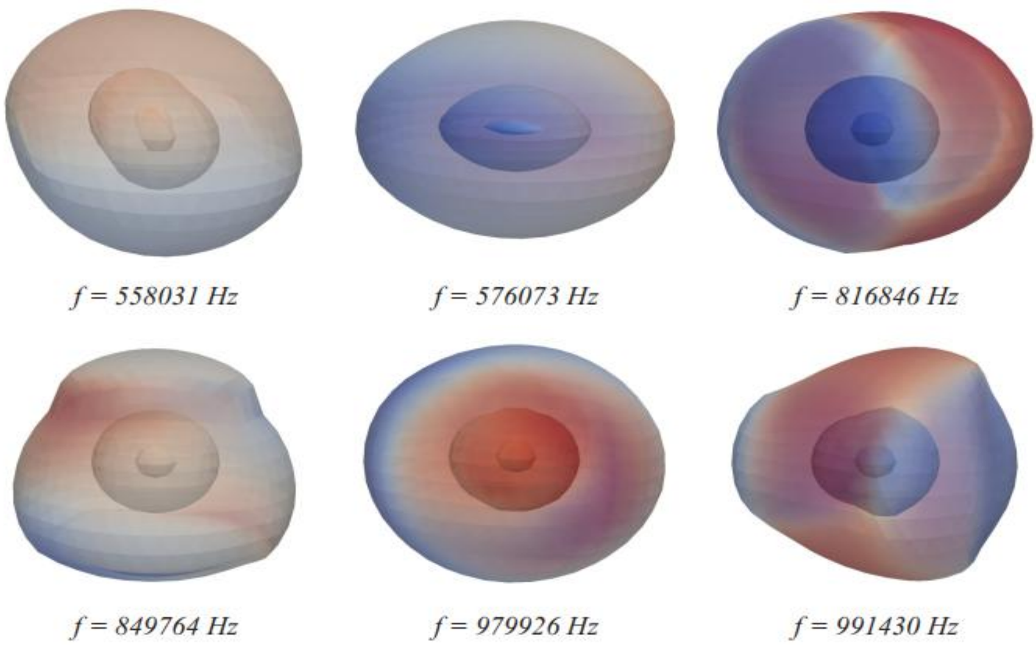


Figure 16: Results of Modal Analysis

Another research was done by [53] Reviewed different research done using Tumor Treating Fields (TTFields), which is a physical treatment that uses frequency range (100–300 kHz) and low-intensity (1–3 V/cm) alternating electric fields to hinder tumors. The study showcased that the cancer cells of different types are vulnerable to frequencies between (100-300kHz), demonstrating a great reduction in cancer cells amount and growth.

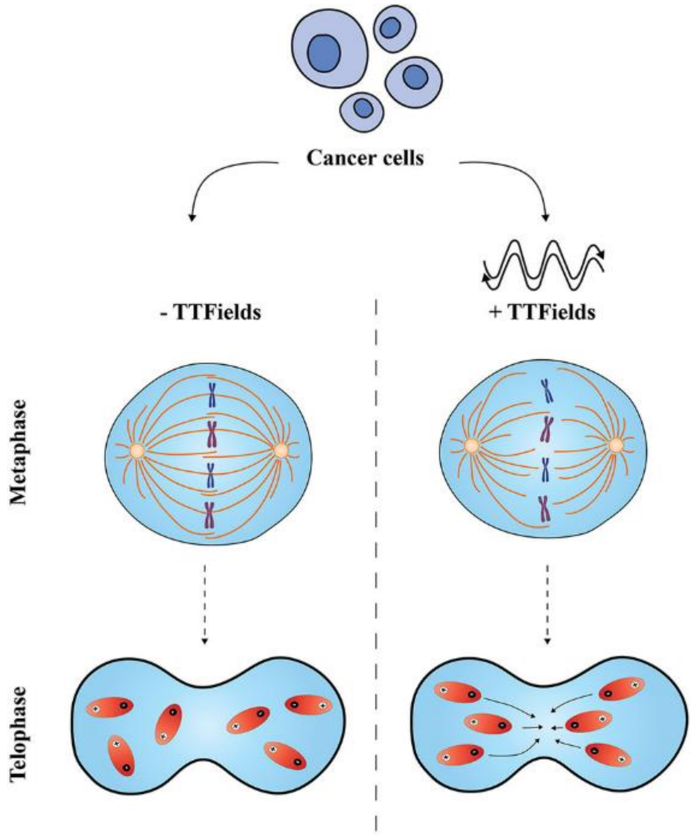


Figure 17: TTFields for Abrutption of Cancer Cells

A similar review by [54] Also provides a range of 100 – 300 kHz for the treatment of cancer and some promising results on cancer cell elimination. A research center by the name of Cancer Research UK has been working on high-intensity focused ultrasound (HIFU) to show promising results.

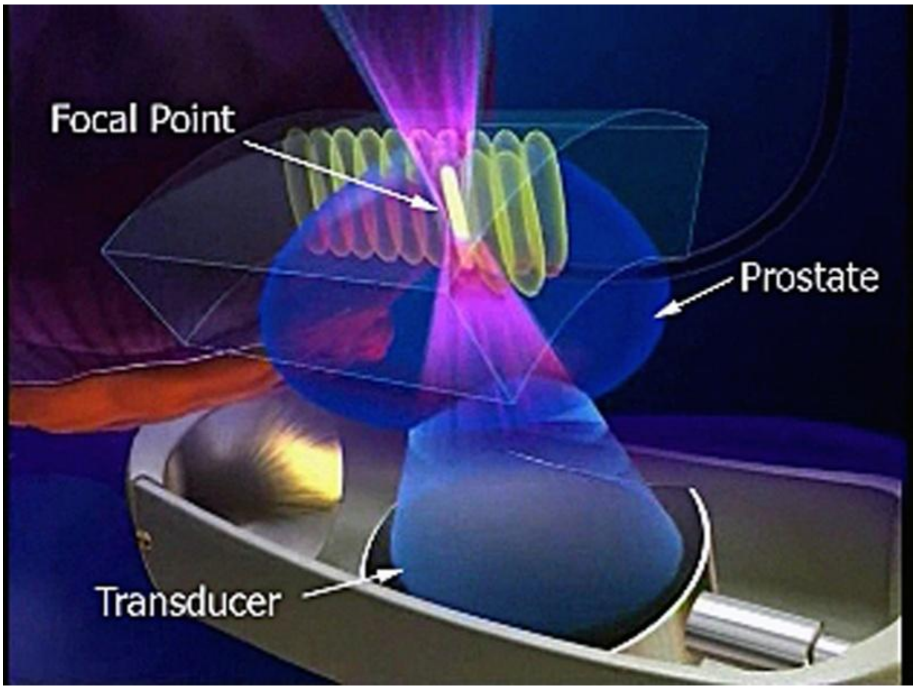


Figure 18: HIFU Prostate Cancer Treatment

A piezoelectric ultrasound transducer was designed by [55] For underwater applications. They described the advancement and characterization of a polyvinylidene difluoride (PVDF) ultrasound transducer to be utilised as a transmitter in underwater wireless communications. The transducer has a beam angle 10° × 70° degrees and a usable frequency band of up to 1 MHz. The transducer was designed using Finite Elements Methods and compared to genuine measurements. Another piezoelectric transducer having a range of 230–380 kHz frequency, a maximum of 168 dB sound pressure using PZT-5A Material was designed by [56]. ANSYS was used for FEM simulation to generate a graph that compared the thickness of the piezoelectric material with resonance frequencies. This is most useful if one requires a specific range of resonance frequencies.

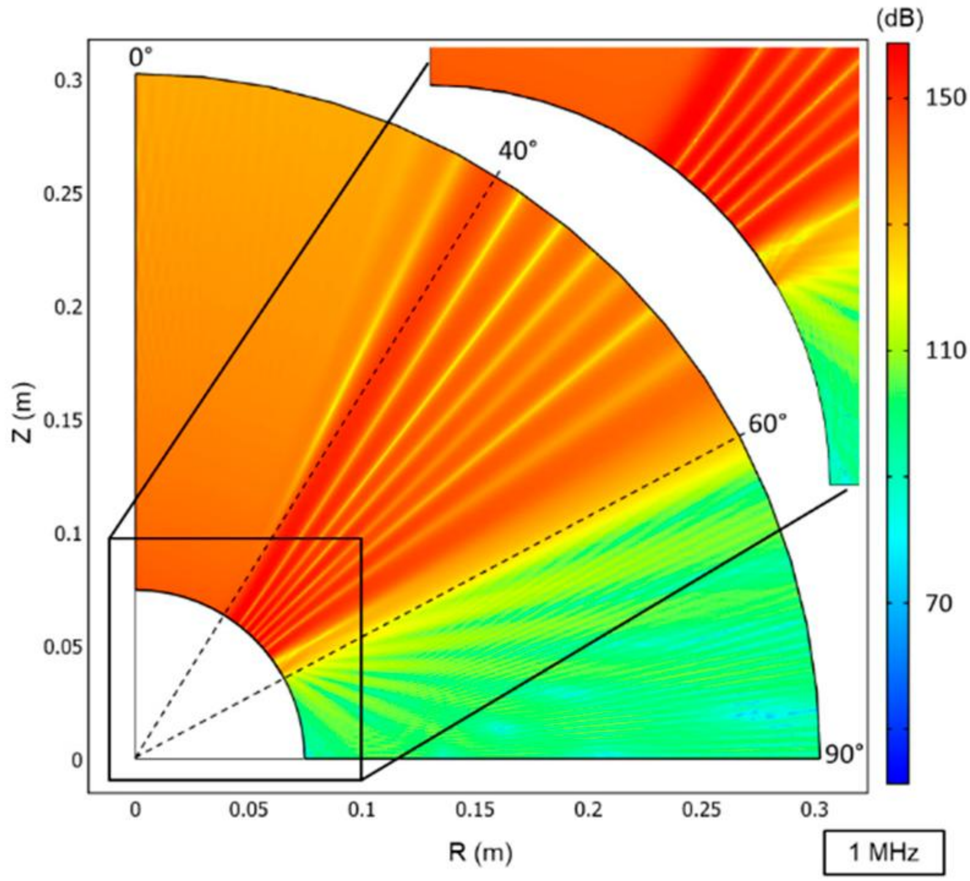


Figure 19: Wideband and Wide beam ultrasound transducer

From the literature, although several works have been done on piezoelectric transducers, the work related to cancer treatment using piezoelectric ultrasound transducers is scarce and the use of a portable, small-size, biocompatible, low-cost piezoelectric-based ultrasound transducer has not been found in any prior research.

Traditional cancer treatment methods like chemotherapy often come with severe side effects. However, it is also apparent from the literature that the cancer cells have a different frequency (80kHz – 300kHz) from the healthy cells (37 kHz spectral gap). This paper focuses on a novel approach to potentially destroy cancer cells with minimal harm to healthy cells. The approach utilizes ultrasound-induced cell bursting, specifically targeting a unique vulnerability of cancer cells. Cancer cells often have weaker cell membranes compared to healthy cells. [12]. By applying ultrasound waves at specific frequencies, we aim to induce resonance within these cancer cells, causing them to vibrate and ultimately burst. This would eliminate the cancerous cells while leaving healthy tissues largely unaffected.

A review of materials, structural designs, and current challenges explores the innovative realm of wearable ultrasound technology, emphasizing its transformative potential in medical diagnostics and therapy. The study discusses how advanced materials like piezoelectric polymers (e.g., PVDF) and composites enable the creation of lightweight and flexible devices, suitable for curved surfaces and continuous health monitoring. Structural designs integrate thin, stretchable substrates with flexible electrodes, employing precise acoustic matching layers to optimize signal transmission and resolution. Applications range from non-invasive tracking of vital parameters such as cardiac activity and blood flow to therapeutic uses like drug delivery and tissue stimulation. Despite their promise, wearable ultrasound systems face challenges, including durability under repeated deformation, thermal management, cost-effective manufacturing, and impedance mismatches that hinder optimal performance.

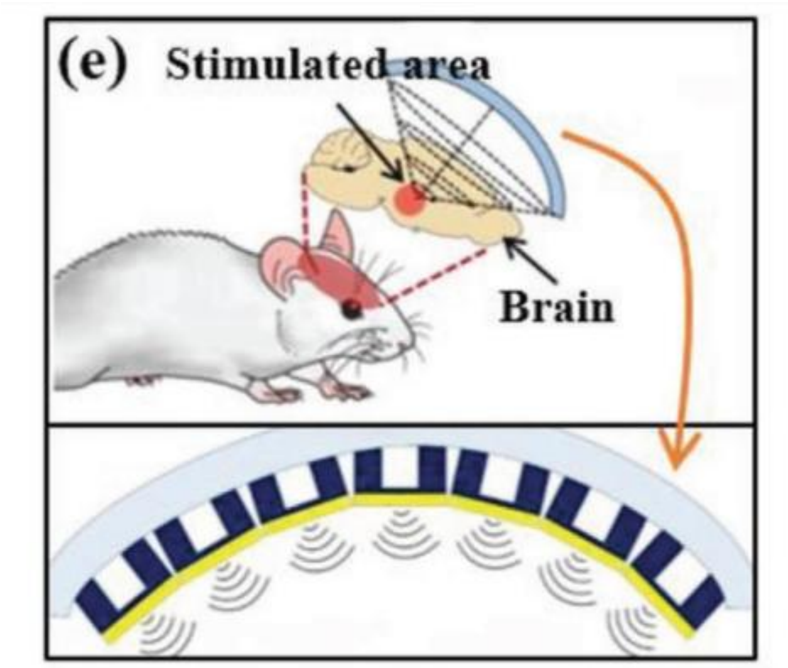


Figure 20: Brain stimulation of a mouse

3.1. Capacitive vs Piezoelectric Ultrasound Transducers

3.1.1. Capacitive Ultrasound Transducer

Capacitive Ultrasonic Transducer (CUT) is regarded a feasible alternative to conventional piezoelectric transducers, offering wide bandwidth, large batch production, and higher frequency. As illustrated in Figure 21: Schematic of Capacitive Ultrasound Transducer, A vacuum cavity divides the structure's two parallel plates. A vacuum cavity separates the thin, flexible conducting top plate—the vibrating and moving membrane—from the bottom electrode, also known as the fixed silicon substrate. An electrostatic force is generated between the top and bottom electrodes when a DC bias voltage is employed to them. This force shifts the capacitance of the CUT by drawing the top electrode closer to the bottom electrode. A mechanical restoring force is generated against the downward motion because of the membrane's rigidity. When an alternating voltage is applied on top of the DC bias voltage during a transmission mode, the top membrane begins to vibrate, producing ultrasonic. When in receiver mode, the top membrane is struck by the target tissue's reflected ultrasonic. The capacitance and output change as a function of the membrane's deflection. It can be transformed into information that can be used for additional processing.

Figure 21: Schematic of Capacitive Ultrasound Transducer

3.1.2. Piezoelectric Ultrasound Transducer

The Piezoelectric Ultrasonic Transducer (PUT) is a potential device that addresses the constraints of conventional piezoelectric transducers in having a bulk construction. PUT is based on the flexural mode of operation, which addresses and lowers the high acoustic impedance, in contrast to traditional transducers. The thin piezoelectric film that sits between the top and bottom electrodes makes up the PUT's structure. A silicon substrate serves as the mounting surface for both the electrodes and the piezoelectric film. The piezo material vibrates, or squeezes and expands, when an AC signal is applied to the electrodes. Ultrasound is the product of this process. Furthermore, PUT does not need a hole or cavity to produce ultrasonic, which removes the PUT's drawbacks that CUT has.

Compared to Capacitive ultrasound transducers [57] piezoelectric ultrasound transducers have a larger ultrasound output, lower bias voltage, and larger detectable range [58]. The Piezoelectric ultrasound transducers unlike capacitive transducers do not require a gap or a cavity to generate ultrasound. Piezoelectric ultrasonic transducers can transmit and detect soundwaves up to very high frequencies in the Megahertz range and are used in medical and industrial applications [59]. Therefore, a piezoelectric ultrasound transducer is a promising solution to generate variable frequency ultrasounds for resonance with cancer cells and such ultrasound resonance is an exciting area of research that could revolutionize cancer treatment. However, more research is needed before it can be used as an effective treatment for humans. Ultrasonic transducers rely on both piezoelectric and capacitive technology; however, their approaches to handling dynamic (fluctuating) vs static signals differ. Dynamic signal processing is a strong suit for piezoelectric transducers. Their intrinsic capacity to translate abrupt voltage fluctuations into physical deformation makes them perfect for producing and receiving oscillating ultrasonic waves. However, extremely dynamic signals are often not the best fit for capacitive transducers. Ultrasound causes quick pressure fluctuations, which can cause non-linear reactions and signal distortion. The dynamic properties of piezoelectric transducers and the static properties of capacitive transducers are combined in a hybrid device known as a piezo-capacitive transducer. It is utilized when both static and dynamic signals need to be accommodated.

As our application is highly dynamic, a piezoelectric transducer is the ideal option. Therefore, this paper showcases the design and analysis of a piezoelectric ultrasound transducer having a range of 80 kHz – 300 kHz for cancer cells bursting. Instead of using a single piezoelectric transducer, we propose a design that utilizes six distinct resonance frequencies. This multimodal approach aims to increase the efficacy of cell bursting by targeting a broader range of resonance frequencies targeting multiple types of cancer cells and providing a greater sound pressure. PVDF is the primary ultrasound-generating material due to its low acoustic impedance and impedance matching with human tissue.

Chapter 3: Methodology

In this thesis, the piezoelectric ultrasound transducer is designed using Polyvinylidene fluoride (PVDF).

3.2. Material Selection

Ultrasound Transducers generally use Lead Zirconate Titanate (PZT) due to its high piezoelectric coefficient and Barium Titanate (BaTiO3) due to its good sensitivity and affordability but with slightly lower piezoelectric coefficient than PZT. Although Polyvinylidene difluoride (PVDF) is not frequently used for an ultrasound transducer, however, due to its flexibility and lightweight, it is ideal for applications demanding adaptability to curved surfaces but it offers a lower piezoelectric coefficient. Other materials not often used such as PZT-epoxy composites, lithium niobate (LiNbO3), etc. Among all the mentioned materials, Lead is known to cause cancer (ATSDR, 2020), and Barium compounds are known to cause high blood pressure, airway irritation, and damage to the liver, spleen, and bone marrow (Agency for Toxic Substances and Disease Registry (US), 2007), and Lithium is known to can cause loss of appetite, nausea, vomiting, diarrhea, and abdominal pain (Australia, 2023). However, PVDF is the only non-harmful, biocompatible, and flexible/lightweight material among the most commonly used piezoelectric materials (Laroche et al., 1995). One of the elements influencing the structure's resonance frequency is the composition of the various layers. The thickness, radius, and material characteristics of the piezo layer are the most crucial components of the PUT construction. First, the electromechanical coupling (k) of the PMUT and the acoustic impedance are determined by the material parameters, including the piezoelectric, dielectric, and elastic constants of the piezo layer. Because of their high conductivity, metals including aluminium, platinum, and chromium are chosen for electrodes. Since silicon is widely accessible and reasonably priced, it is the material of choice for building the substrate, however we require damping as we're stacking multiple piezoelectric transducers on a single substrate, therefore, rubber is a feasible solution to that.

3.1.1. Acoustic Impedance

One important parameter for ultrasound transducers is acoustic impedance (Z), which is a physical property of tissue. It describes how much resistance an ultrasound beam encounters as it passes through a tissue given by Equation (1). It is defined as:

$$Z = d * c \tag{1}$$

Where d is the density of the tissue in kg/m^3, and c is the velocity of the soundwave transmitted through the tissue medium in m/s.

Therefore, impedance rises as tissue density does. In a similar vein, though less naturally, impedance rises as sound velocity does. At the interfaces of various tissue types, the impact of acoustic impedance in medical ultrasound becomes apparent. The differential in impedance between the two tissues determines whether an ultrasonic wave can pass through one type of tissue and into another. The sound is reflected if the difference is significant. Therefore, a term known as Impedance Matching is important for achieving low acoustic impedance so that the ultrasound can reach the cancer cells in the body to burst them. This acoustic impedance matching is crucial for the efficient transmission of sound waves with minimal reflection and signal loss. Impedance matching matters primarily when coupling the piezoelectric material with another medium (e.g., tissue, water).

3.1.2. Impedance Matching

According to the research by [60], PVDF film possesses low acoustic impedance (3.3 MRayl), high piezoelectric constant, high dielectric strength, spectacular mechanical characteristics, and most importantly a closely matching acoustic impedance to that of human tissue (approximately 1.6 MRayl). Therefore, resulting in a lower percentage of wave reflected. PVDF exhibits a wide bandwidth, allowing it to transmit and receive ultrasound waves across a broad range of frequencies. For cancer cells bursting, PVDF is the most suitable for direct contact with biological tissues without causing harm or inducing adverse reactions. PVDF is also durable, flexible, and resistant to chemicals and moisture, ensuring the longevity and reliability of the transducer. Thus, without any coating material applied, or in case of coating failure, PVDF is all around the most effective and applicable for our case or in general biomedical devices. However, if we go towards coating the piezoelectric material with some biocompatible materials such as Polydimethylsiloxane (PDMS), Hydroxyapatite (HA), Poly(ethylene glycol), (PEG)-based hydrogels, etc., then the same result can be obtained if the acoustic impedance of the materials results in impedance matching with the human tissue. PDMS has an acoustic impedance of 1 MRayl and has been used for impedance matching with water and is a great option but due to the high acoustic impedance of PZT (33 MRayl) [55], which results in losses. Furthermore, as per our literature review, no work has been reported on the other biocompatible coating materials. Therefore, this work focuses on using PVDF (3.3 MRayl) material without any coating as it is bio-friendly as well as low acoustic impedance matching that of human tissue.

3.1.3. Working of the PUT

Figure 22 Shows the working of the designed ultrasound transducer for the purpose of cancer cells bursting of various types. The frequency selection for different types of cancer cells is extremely important for resonance, and ultimately bursting of cancer cells.

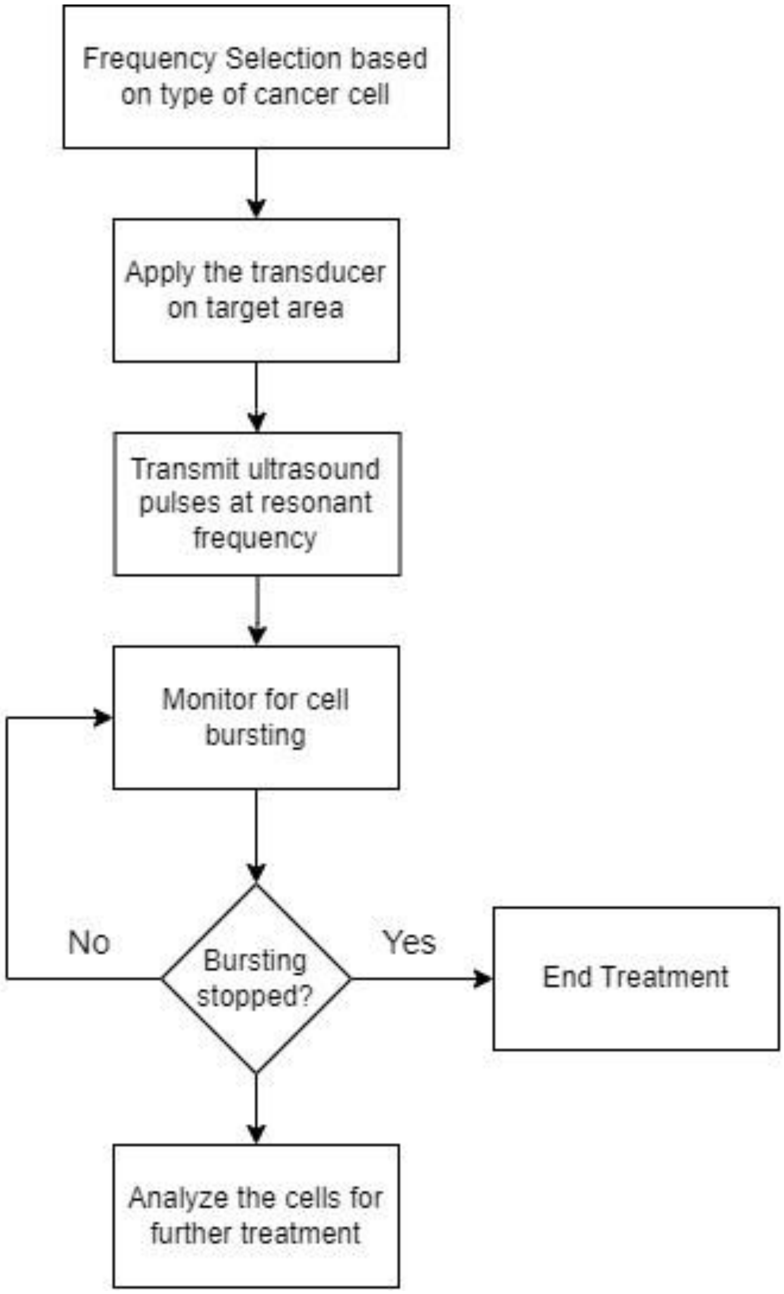


Figure 22: Working of the Piezoelectric Ultrasound Transducer

3.1.4. Modes of Vibration of a Piezoelectric Material

Piezoelectric ultrasound transducers exhibit different vibration modes that define their functional characteristics, with radial mode and thickness mode being two of the most significant. Both modes arise due to the piezoelectric effect, where mechanical vibrations are generated by an alternating electric field. These vibrations propagate as ultrasound waves and are key to applications in medical imaging, industrial nondestructive testing, and therapeutic devices. Understanding the distinctions between radial and thickness modes, as well as their implications for design and operation, provides insights into optimizing piezoelectric transducers for specific tasks. [61].

- **Radial Mode of Vibration:** Radial mode, also known as lateral mode, is characterized by the expansion and contraction of a piezoelectric disc in its planar dimensions (along the radius). In the case of application of an alternating electric field, the material undergoes oscillations in the circumferential direction creating mechanical waves in the lateral plane in the form of ultrasonic waves. This mode operates as a rule at frequencies that are lower than frequencies in the thickness mode and is used in cases where it is necessary to obtain omnidirectional waves or cover an extensive area. In radial mode, the resonant frequency depends mainly on the size of the transducer but is mostly on the diameter of the transducer. Generally speaking, discs with greater radii will hit certain resonant frequencies at lower notes because of the extra mass at their disposal. The radial mode is well suited to such applications as low-frequency underwater sonar, where the ability to transmit sound over a long distance overshadows resolution capabilities. Additionally, radial mode transducers may be applied for vibration evaluation or in mechanical systems where omnidirectional wave excitation may be required. The acoustic impedance in radial mode is comparatively lower than that in thickness mode making these transducers useful in coupling with low-impedance fluids such as air or water.
- **Thickness Mode of Vibration:** In contrast, thickness mode includes the oscillation of the transducer along its thickness, perpendicular to its planar surface [62]. This mode arises out of the use of an oscillating electric field in the direction that is perpendicular to the plane of the piezoelectric element leading to compression across the thickness of this material. Thickness mode transducers in general work at a higher frequency compared to radial mode; the resonant frequency is however dependent on the thickness of the material. For instance, the thin transducers vibrate at high frequencies and are

suitable for use in imaging and detecting defects in the material. Thickness mode is particularly advantageous in applications where highly directive ultrasound beams of high energy density are required. This model is the basis of diagnostic medical ultrasound systems which utilize the high-frequency wave required in the generation of images of soft tissue in the human body. It is also used in therapeutic applications such as high-intensity focused ultrasound surgery (HIFU) for therapeutic application, which requires the energy to be targeted at a specific tissue site. Thickness mode transducers are used in industrial applications for nondestructive testing (NDT) since they can transmit energy to a depth of the material and still be sensitive to fine structural flaws. Matching layers and backing materials are sometimes used with thickness mode transducers so that efficient transfer of energy is allowed and any unwanted vibrations are minimized. Matching layers bridge the acoustic impedance gap between the high-impedance piezoelectric material and the lower-impedance medium, such as human tissue or water, enhancing wave transmission efficiency. The backing layer, usually a highly absorptive material, dampens the transducer’s ringing, ensuring short pulses and improved axial resolution.

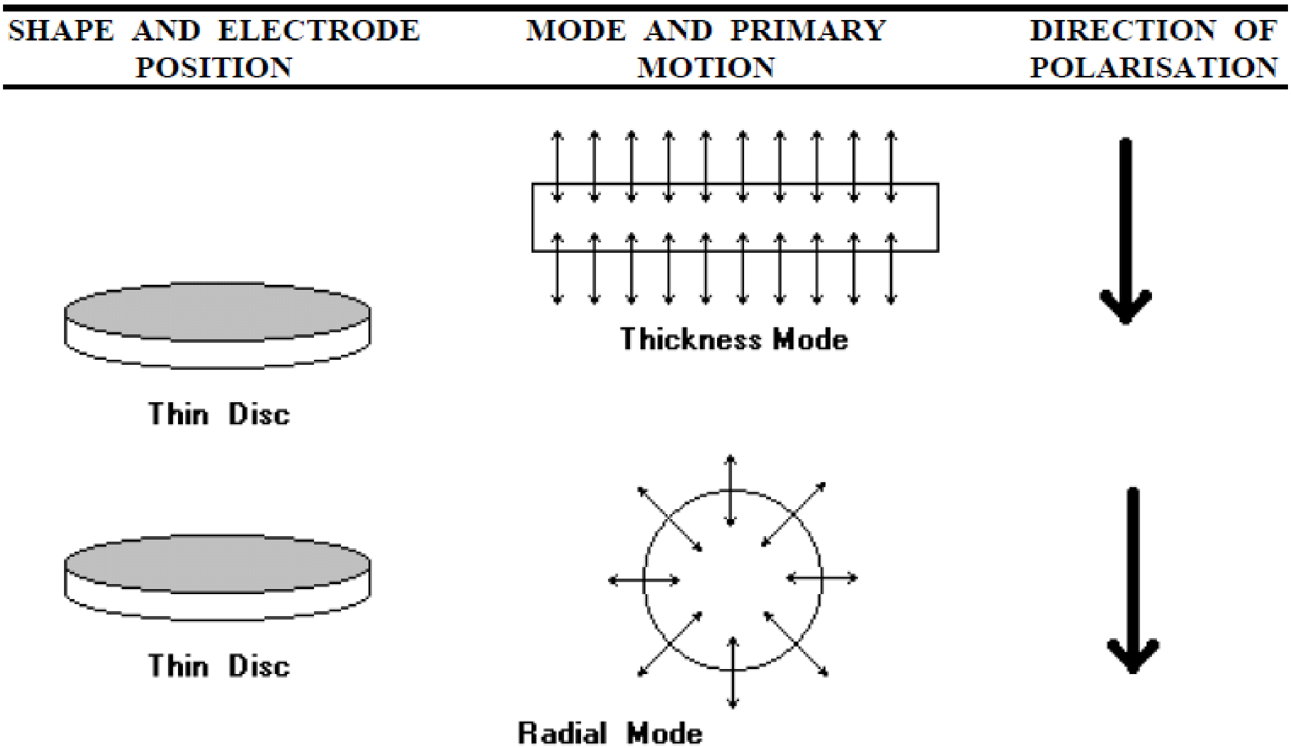


Figure 23: Modes of vibration of a piezoelectric material

For our research, the Radial mode of vibration was selected due to the low acoustic impedance, flexibility, strength, and biocompatibility for direct contact with the human tissue. Following Table 1 Shows the different properties of different materials:

Table 1: Piezoelectric material properties

Material	Piezoelectric Constant D_{33} [pC/N]	Dielectric Constant	Young's Modulus [GPa]	Acoustic Impedance (Z) [MRayl]
PZT-5H [63]	593	3400	63	34.2
PZT-5A [64]	289	1300	90	30
PVDF [65]	20-30	10-12	2-4	2.7 – 4
PMN-T [64]	1500-2500	5000-6000	10-20	37.15
BaTiO3 [64]	190	1500-1700	67	30

3.3. Modelling of Multimodal Piezoelectric Ultrasound Transducer

The geometry of a piezoelectric ultrasound transducer significantly influences its performance, including frequency response, beam pattern, and sensitivity. Common geometries include flat, concave, or spherically focused shapes for single-element transducers, as well as linear, phased, or matrix arrays for multi-element configurations. The thickness of the piezoelectric material dictates the operating frequency, while the lateral dimensions affect beam width and resolution in the case of thickness mode, but our radius is the governing factor for said parameters. Focused transducers use concave geometries to concentrate ultrasound waves, enhancing spatial resolution. Advances in fabrication techniques enable complex geometries, such as annular or ring arrays, for specialized applications in medical imaging, therapy, and industrial inspections.

Multimodal piezoelectric ultrasound transducers are employed to generate ultrasound waves with two different modes of resonance, to improve versatility and application extent. Dual resonance frequency modes in piezoelectric ultrasound transducers are achieved by stacking piezoelectric discs with isolation layers in between. This design enables the transducer to operate efficiently at two different resonance frequencies, one corresponding to the primary vibration of each disc and another resulting from the interplay of stacked layers. The isolation layers play a critical role in avoiding mechanical coupling between discs, allowing independent vibration modes to coexist. This configuration is particularly advantageous for applications requiring multimodal functionality, such as combined imaging and therapeutic ultrasound, as it enhances operational flexibility by providing broader frequency ranges in a single device. It also allows flexible performance, catering to various functional requirements, including frequency optimization and beam shaping, throughout medical and industrial applications. Figure 24 shows the schematic of a Dual Frequency transducer consisting of a low-frequency layer to transmit ultrasonic waves and a high-frequency layer which was for reception [66].

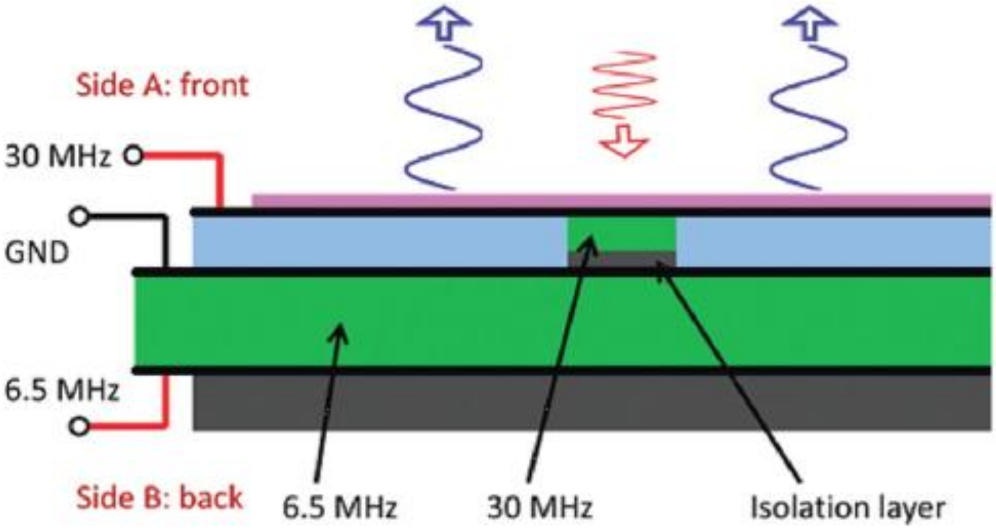
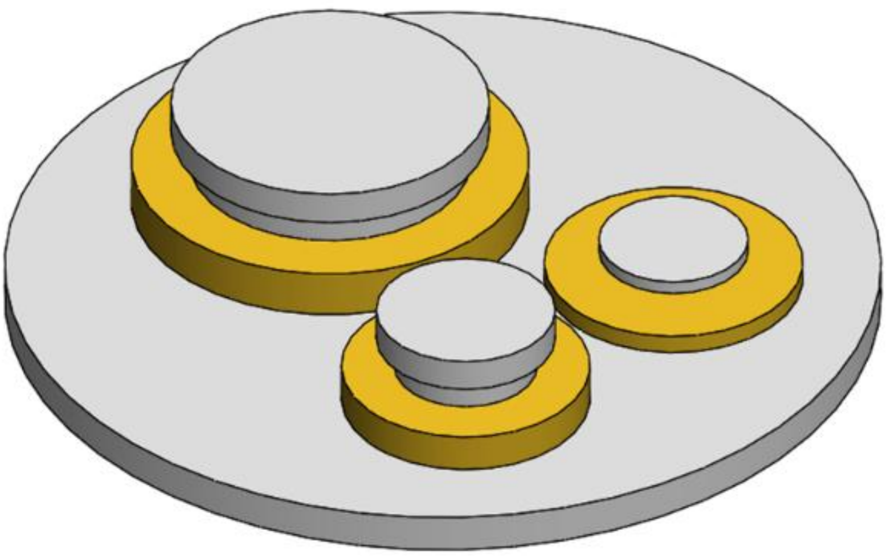
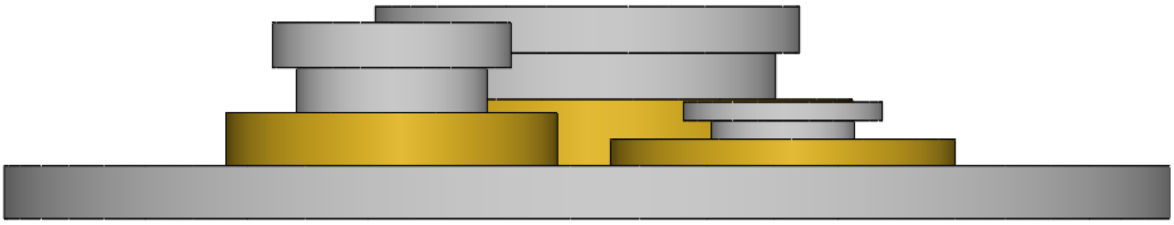


Figure 24: Dual-mode ultrasound transducer

In this thesis, the design consists of three dual-band piezoelectric ultrasound transducers that generate resonance frequencies of 80, 120, 150, 180, 250, and 300 kHz that have been carefully selected for various types of cancer cells. The generated resonance frequencies will resonate with cancer cells and burst them when resonance-induced vibrational energy increases a certain limit.



(a)



(b)

Figure 25: (a) Isometric view of Multimodal Piezoelectric Ultrasound Transducer (b) Front view

The model has two layers of piezoelectric transducer stacked on each other with an isolation layer between them to avoid direct mechanical interaction and potential damage. Such a design has been shown to generate high-pressure waves to excite microbubbles through resonance. A novel multimodal piezoelectric ultrasound transducer designed for bursting cancer cells can offer significant advancements in targeted therapies by leveraging its ability to operate at dual or multiple resonance frequencies. The PUT transmits ultrasounds at the resonance frequencies of the cancer cells to utilize cavitation or mechanical disruption to cause irreversible damage to cancer cells without harming surrounding healthy tissues.

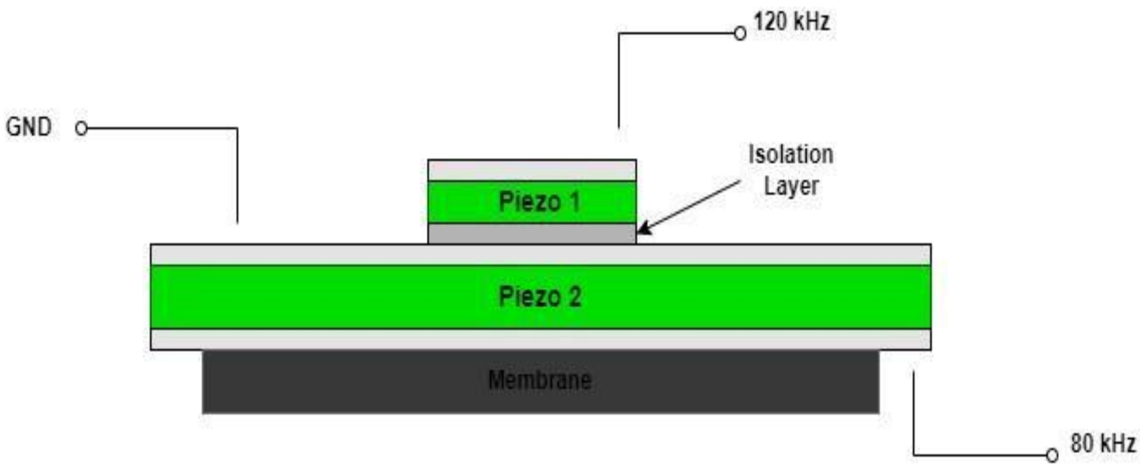


Figure 26: Schematic of Multimodal Piezoelectric Ultrasound Transducer

To generate ultrasound frequencies that resonate with cancer cells, the dimensions of a piezoelectric ultrasound transducer (PUT) in radial mode must be precisely selected. In radial mode, the transducer vibrates circumferentially, with its resonance frequency governed by the material's properties and its radial dimensions. For cancer cell therapies, frequencies are typically tuned to enhance resonance and in turn acoustic cavitation and mechanical oscillation, which are effective at disrupting cancer cell membranes. PVDF allows for ensuring minimal loss of acoustic pressure during wave travel.

Material characteristics such as density and the speed of sound within the piezoelectric material also play crucial roles in determining the exact dimensions needed to achieve the desired resonance frequency. Table 2 Shows the dimensions that have been carefully selected for generating the resonance frequencies. The 3 dual-band PUTs have different dimensions as shown in Figure 25.

Table 2: PUT Dimensions

Parameters	Transducer 1	Transducer 2	Transducer 3
Resonance Frequencies (kHz)	80 / 120	150 / 180 / 200	250 / 300
Radius of Membrane (mm)	20	13	12.5
Radius of 1st PVDF (mm)	14.2	7.2	5.4
Radius of 2nd PVDF (mm)	16	9	7.5
Thickness of Membrane (mm)	2.5	2	1
Thickness of both PVDF disks (mm)	1.75	1.7	0.7

Chapter 4: Results & Discussion

For Finite Element Method (FEM) Implementation, the transducer design is subjected to a FEM simulation, in order to estimate the geometry performance. The designed PUT was implemented in COMSOL Multiphysics software in a 2D axisymmetric plane. COMSOL was selected for this application, due to its abundance of available materials and ease of use. Acoustic-piezoelectric interaction Physics (Frequency Domain) in COMSOL is utilized for simulating the coupled behavior of acoustics, structures, and piezoelectricity. The operation of the PUT relies on the resonant frequency. Therefore, the radius of the piezo layers is optimized to attain the specific resonant frequencies, which is given by Equation (2) [67]

$$f_r = \frac{\gamma_1^2}{2\pi R^3}\sqrt{\frac{D}{\mu}} \tag{2}$$

where $\gamma = 3.19$ for fundamental resonance mode, R is an area of the membrane, D is the flexural rigidity and μ is the mass per given area.

The model uses the built-in acoustic Acoustic-Piezoelectric Interaction and frequency Domain Multiphysics interface, which contains three fundamental physics interfaces: Pressure Acoustics, Solid Mechanics, and Electrostatics. The first one solves the wave equation in the fluid media surrounding the transducer. The latter two are used to model the piezoelectric effect. In the absence of volumetric sound sources, and assuming the pressure varies harmonically in time, the wave equation describing the acoustic pressure distribution is:

$$\nabla.\left(-\frac{1}{\rho_0}\right)(\nabla\rho) - \frac{\omega^2\rho}{\rho_0 c_s^2} = 0 \tag{3}$$

Where ρ_0 is the wave amplitude, $\omega = 2\pi f$ is the angular frequency of the wave and relates the frequency to a full 360o phase shift, c_s is the speed of sound, and p is pressure.

At the interface between the human tissue and the solid domain, the normal component of the structural acceleration of the solid (piezo transducer) boundary is used to drive the human tissue domain. This is described by the following equation:

$$n.\left(\frac{1}{\rho_0}\right)(\nabla\rho) = a_n \tag{4}$$

where a_n is the normal acceleration.

A Spherical Wave Radiation boundary condition is used on the outer surface of the human tissue domain. This helps in implementing the spherical wavefronts that travel outward from the geometric boundary that truncates the human tissue domain with minimal reflection. Additionally, a Far Field Calculation is also set up on the same boundary, which helps to evaluate the pressure and sound pressure level in the far-field limit.

COMSOL Model is shown in Figure 27.

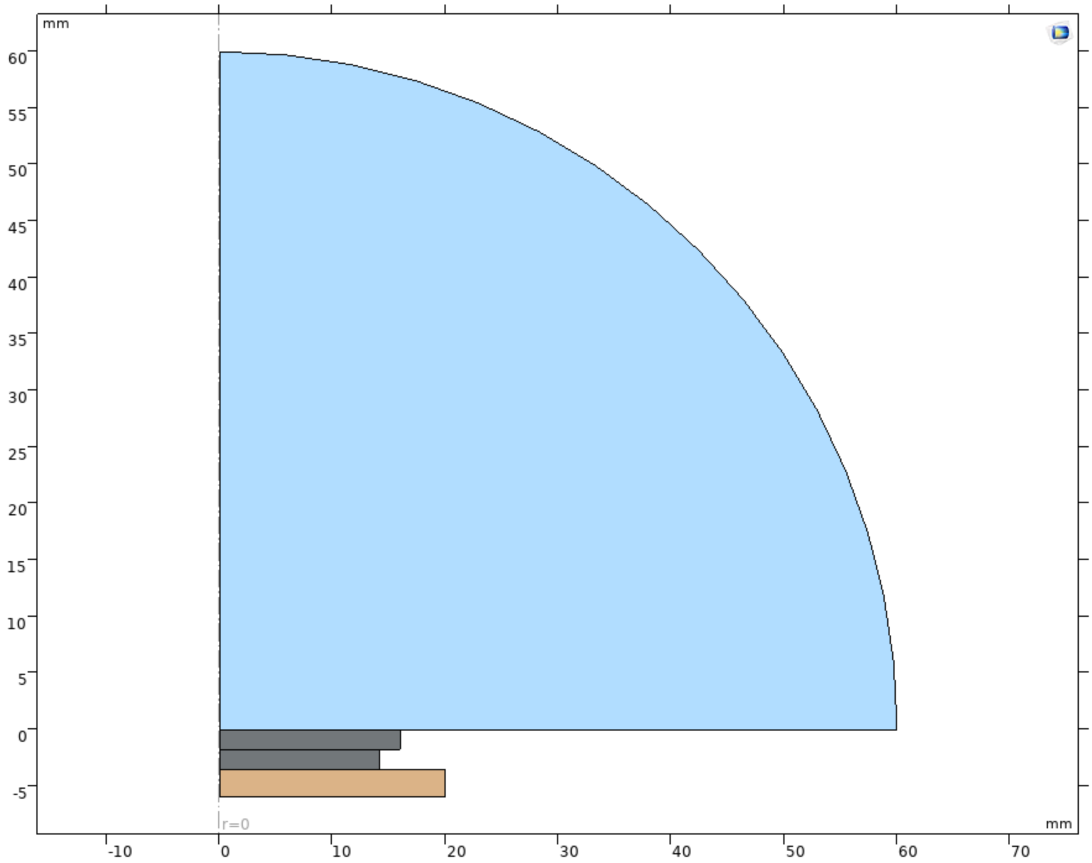


Figure 27: COMSOL Model of PUT

Rectangular Mesh is generated for the piezoelectric material and the membrane, while tetrahedral have been utilized for human tissue as shown in Figure 28.

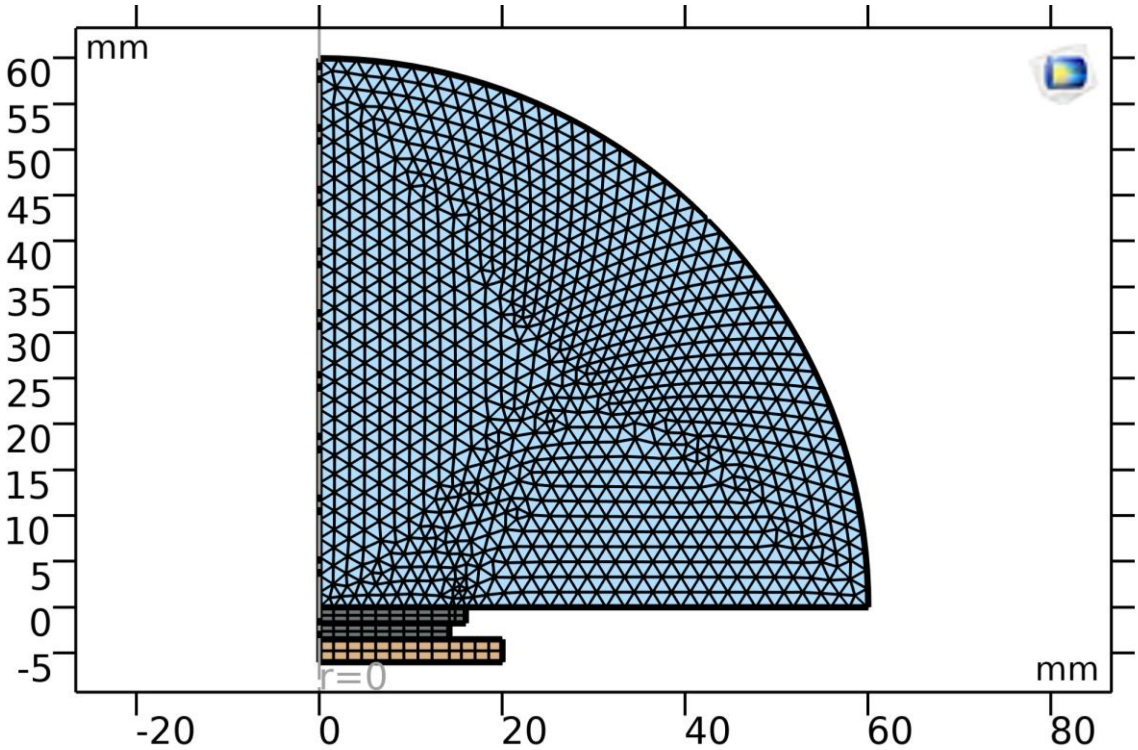


Figure 28: Meshing of PUT in COMSOL

Figure 29 Shows the pressure distribution in the human tissue domain. The transducer has been employed on the skin surface for breast cancer cells, this has been achieved by mimicking the properties of the skin surface for the breast area. The results are expressed as Total Acoustic Pressure as Height expression, showing a maximum of $1x10^5$ Pa acoustic pressure for a frequency of 80 kHz directly in front of the transducer. The high acoustic pressure leads to tissue heating, however, it is not enough to cause any damage to healthy tissue, heating would be with the cancer cells due to resonance, which would cause it to burst, as resonance leads to a significant increase in energy deposition in the target tissue, which causes thermal damage or cavitation. [68].

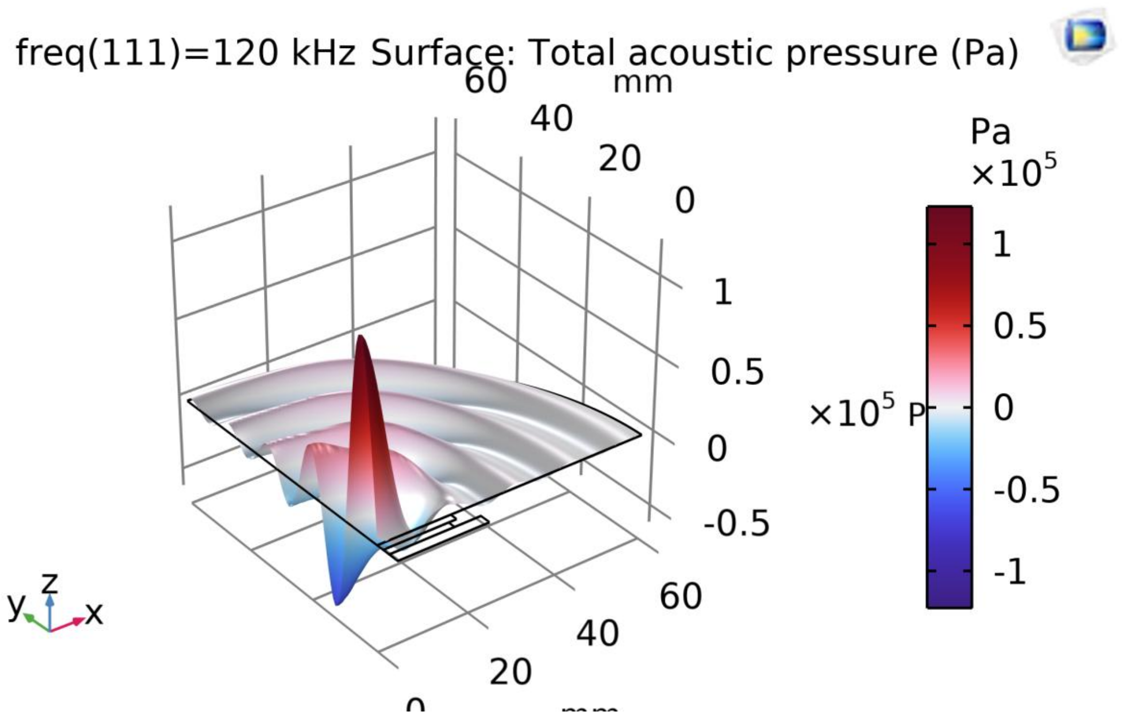
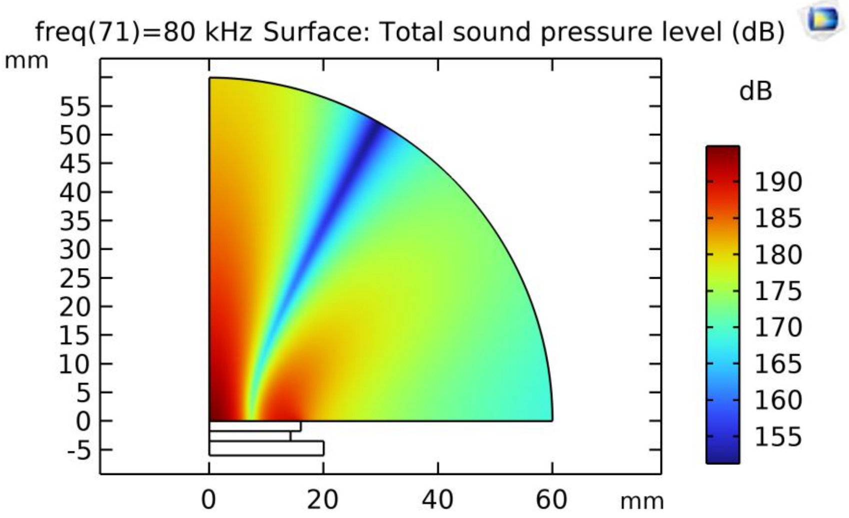
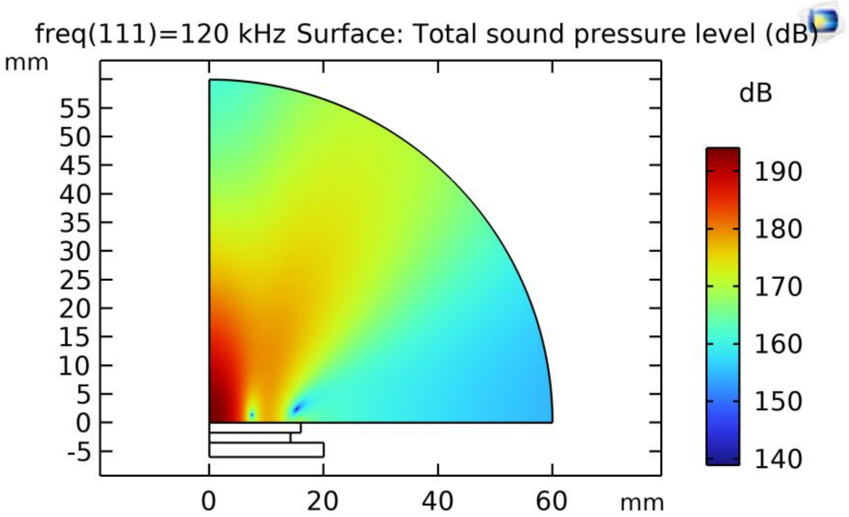


Figure 29: Acoustic Pressure as Height Expression

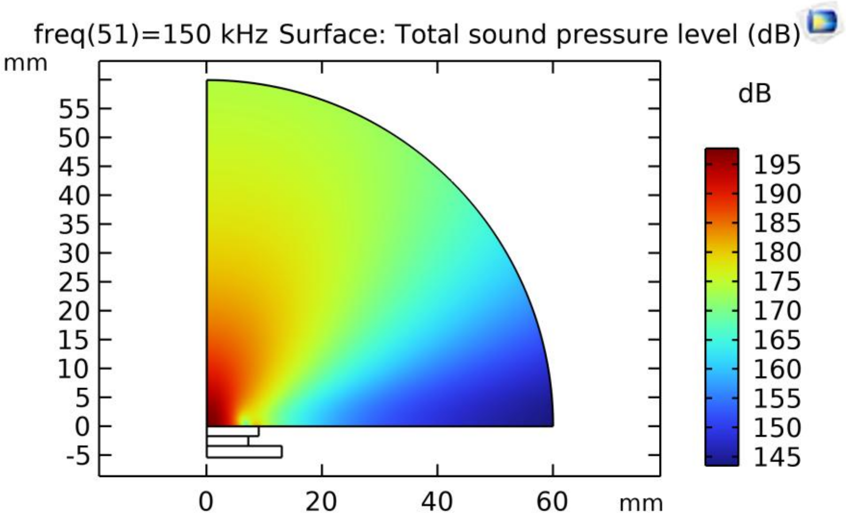
Figure 30 (a)-(g) shows the sound pressure level and distribution in human tissue. The results show that the sound pressure level reaches a maximum of almost 200 dB for all frequencies. The high values of 200 dB for the sound pressure relate to the high energy required for inducing resonance in the cancer cells. However, the fall off of the sound pressure level at different depths can be visualized. The simulation results show that the sound pressure is directed at the center of the transducer and the fall off of sound pressure level is minimised. The sound pressure penetration and uniformity an important factors for the resonance with cancer cells. The small variation in sound pressure level at low frequencies of 80 to 300 kHz at a distance of 4 cm is because of the lower frequency, as it does not result in a significant decline in pressure level with distance [69]


freq(71)=80 kHz Surface: Total sound pressure level (dB)
mm
55 50 45 40 35 30 25 20 15 10 5 0 -5
0 20 40 60
mm
dB
190 185 180 175 170 165 160 155

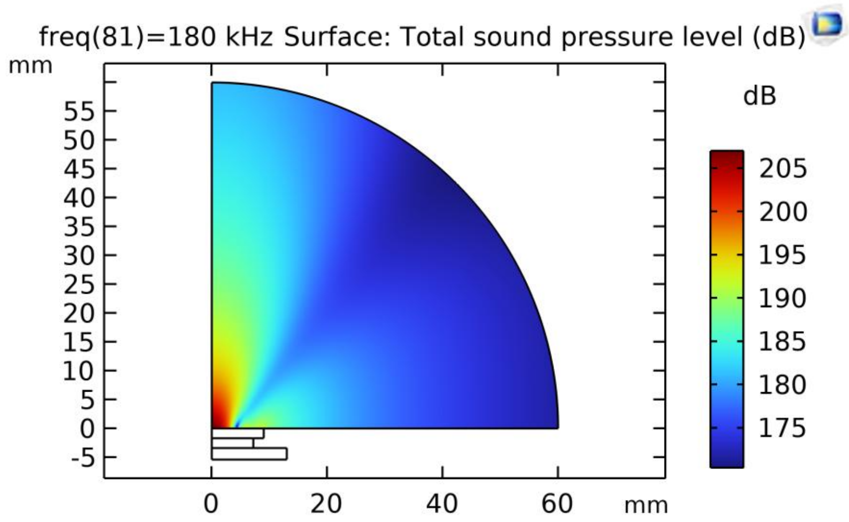
(a)


freq(111)=120 kHz Surface: Total sound pressure level (dB)
mm
55 50 45 40 35 30 25 20 15 10 5 0 -5
0 20 40 60
mm
dB
190 180 170 160 150 140

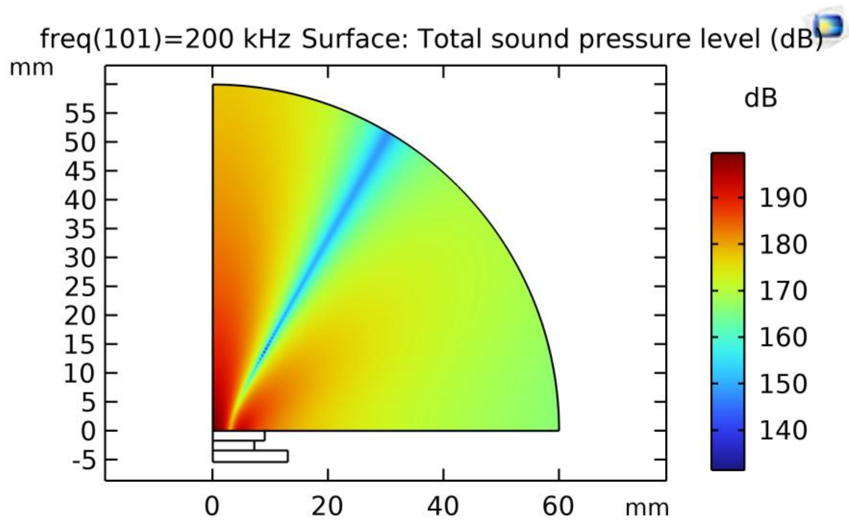
(b)


freq(51)=150 kHz Surface: Total sound pressure level (dB)
mm
55 50 45 40 35 30 25 20 15 10 5 0 -5
0 20 40 60
mm
dB
195 190 185 180 175 170 165 160 155 150 145

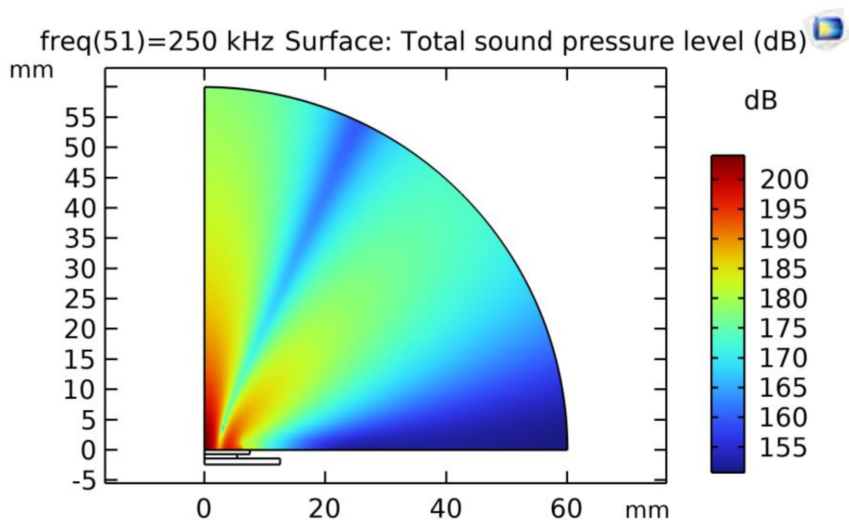
(c)


freq(81)=180 kHz Surface: Total sound pressure level (dB)
mm
55
50
45
40
35
30
25
20
15
10
5
0
-5
0
20
40
60
mm
dB
205
200
195
190
185
180
175

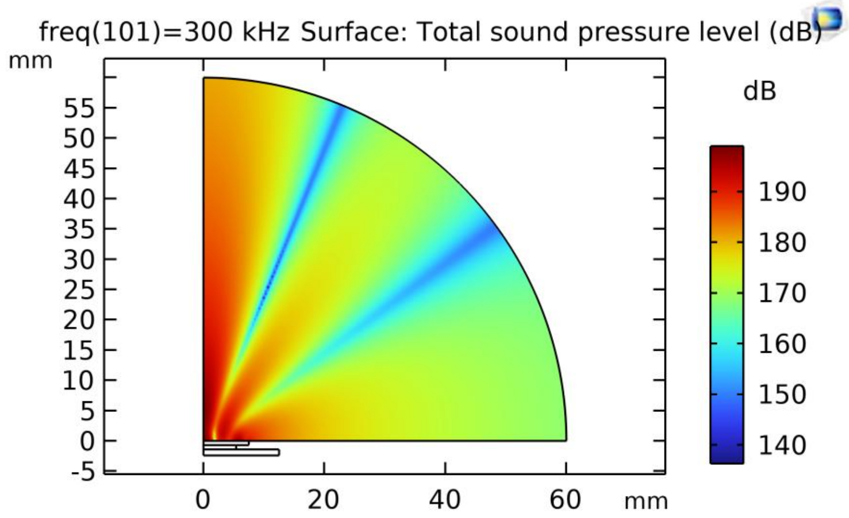
(d)


freq(101)=200 kHz Surface: Total sound pressure level (dB)
mm
55
50
45
40
35
30
25
20
15
10
5
0
-5
0
20
40
60
mm
dB
190
180
170
160
150
140

(e)


freq(51)=250 kHz Surface: Total sound pressure level (dB)
mm
55
50
45
40
35
30
25
20
15
10
5
0
-5
0
20
40
60
mm
dB
200
195
190
185
180
175
170
165
160
155

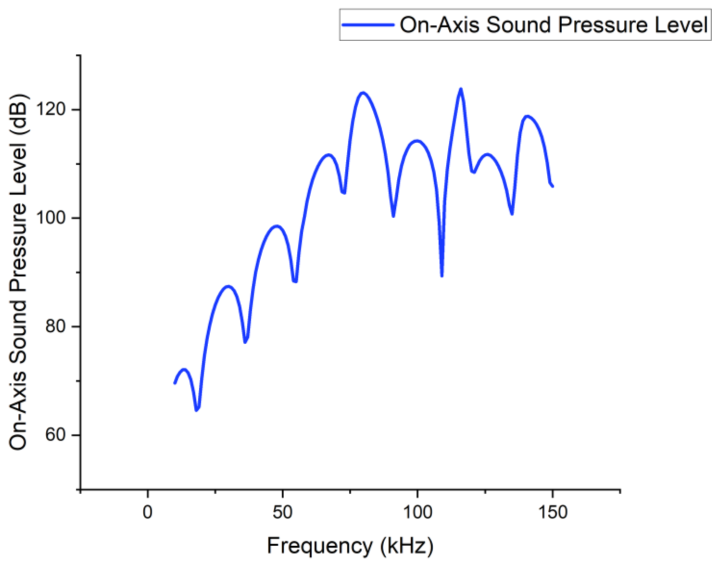
(f)



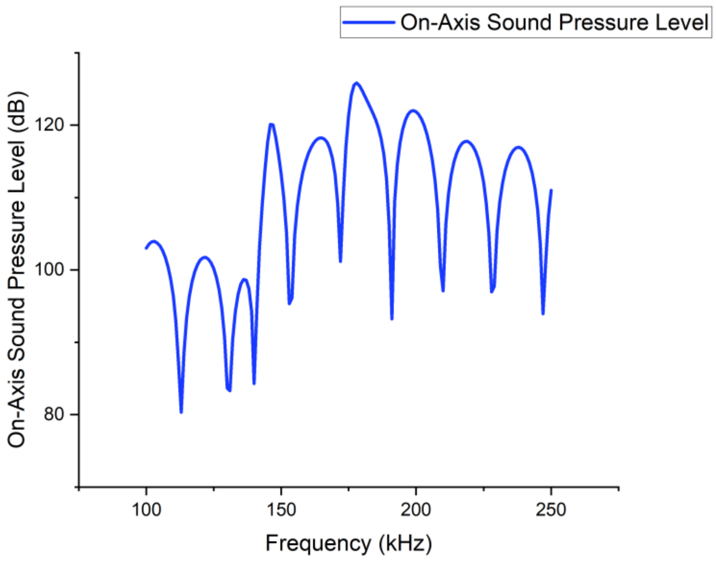
(g)

Figure 30: Sound Pressure Level (SPL) (a) SPL at 80 kHz (b) SPL at 120 kHz (c) SPL at 150 kHz (d) SPL at 180 kHz (e) SPL at 200 kHz (f) SPL at 250 kHz (g) SPL at 300 kHz

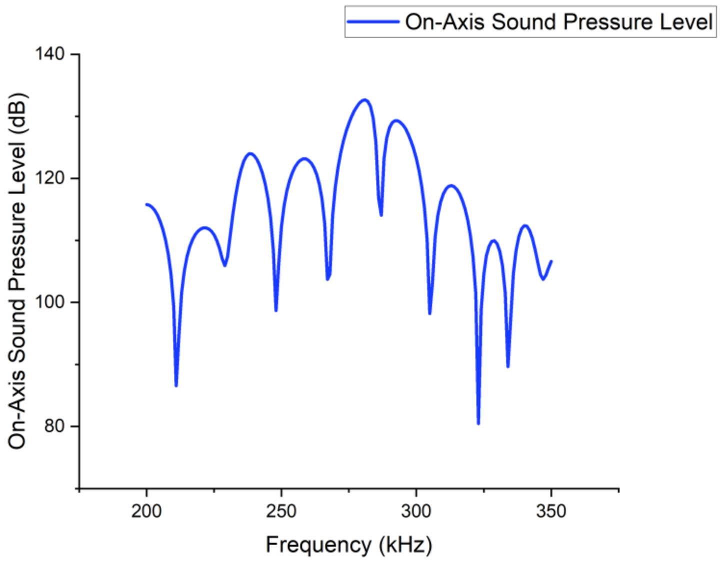
Figure 31 (a) – (c) shows the on-axis sound pressure level at 4 cm. The depth value of 4 cm has been chosen due to the average of cancer cells present at a depth of 4 cm or below the human skin. The sound pressure of around 120 dB on average is recorded for the frequencies 80, 120, 150, 180, 200, 250, and 300 kHz. This high value of sound pressure is required for cancer cell excitation to be achieved.



(a)



(b)



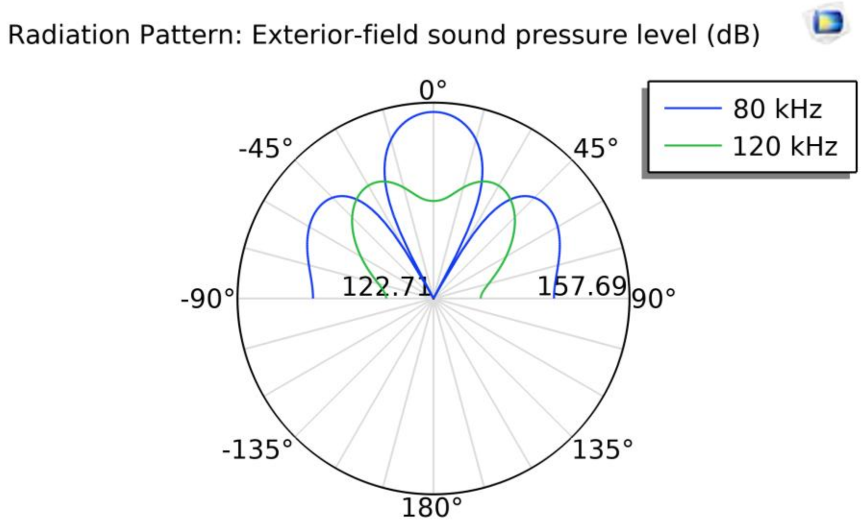
(c)

Figure 31: On-axis sound pressure level 4 cm (a) Pressure at 80, 120 kHz (b) Pressure at 150, 180, 200 kHz (c) Pressure at 250, 300 kHz

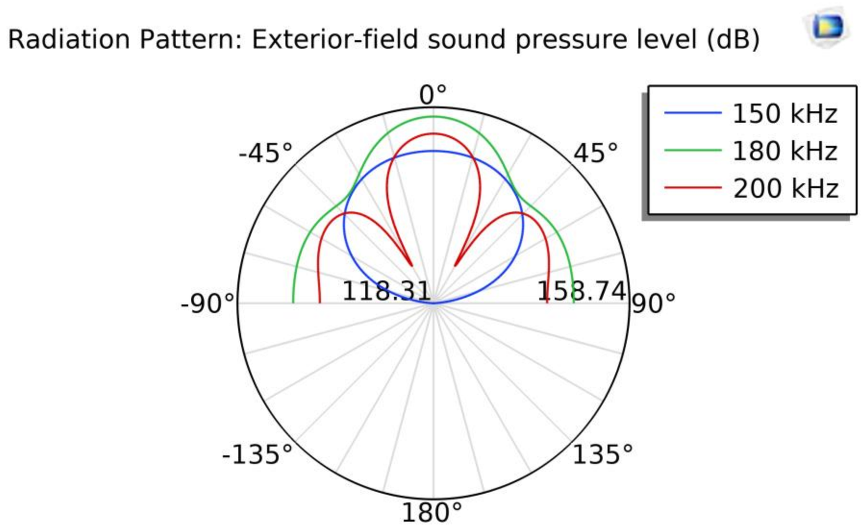
Figure 32 (a)-(c) shows the exterior-field sound pressure level for the different frequencies mentioned. This provides information about the intensity and directivity of the ultrasound beam generated by the transducer. The radiation pattern shows that the ultrasounds are focused directly in front of the ultrasound transducer for all the frequencies. The Z-axis was defined as the 0° axis and R axis the 90°. The focused beam at 80 kHz showcases the need for our design as more focused ultrasound is required for cancer cells bursting as per literature [12], [53] and the increased sound pressure (120-200 dB) is also required for cancer cells bursting has been achieved. The maximum force that the piezoelectric element can apply to the medium is obtained by equation 3 [70] as follows:

$$F = d_{33}\frac{A_p}{S_{33}^E t_p}v \tag{5}$$

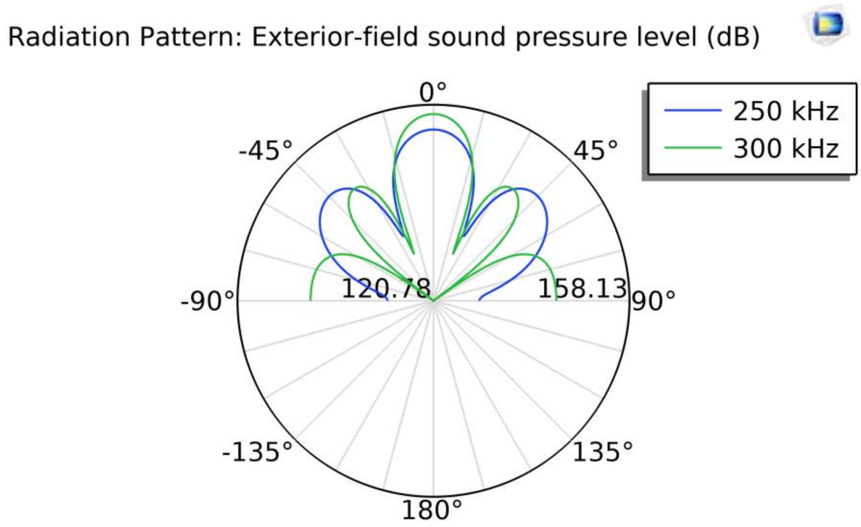
Where d_{33} is the coupling coefficient, A_p is the surface area of the piezoelectric element, S_{33}^E is the elastic compliance coefficient, t_p is the thickness of a single layer, and v is the applied voltage.



(a)



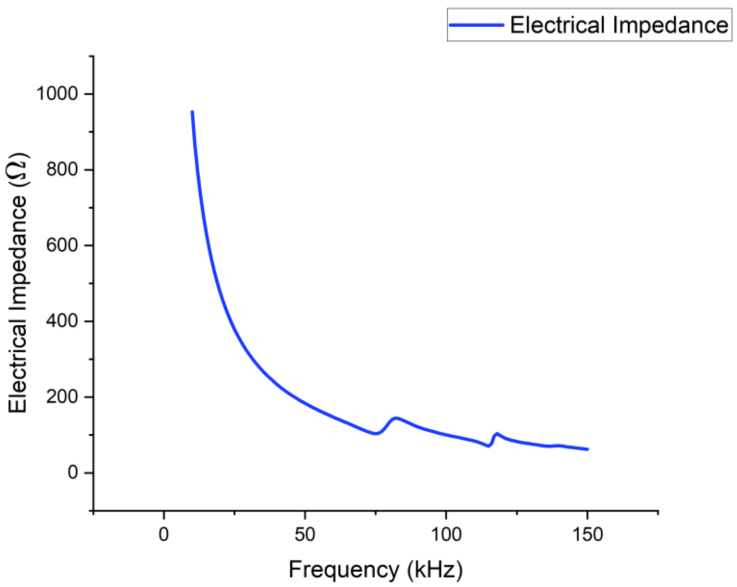
(b)



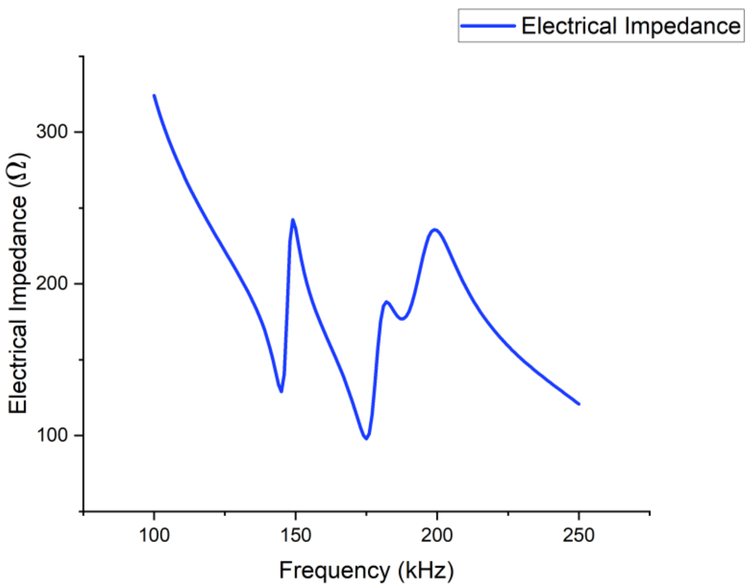
(c)

Figure 32: Exterior-field sound pressure level (a) at 80, 120 kHz (b) at 150, 180, 200 kHz (c) at 250, 300 kHz

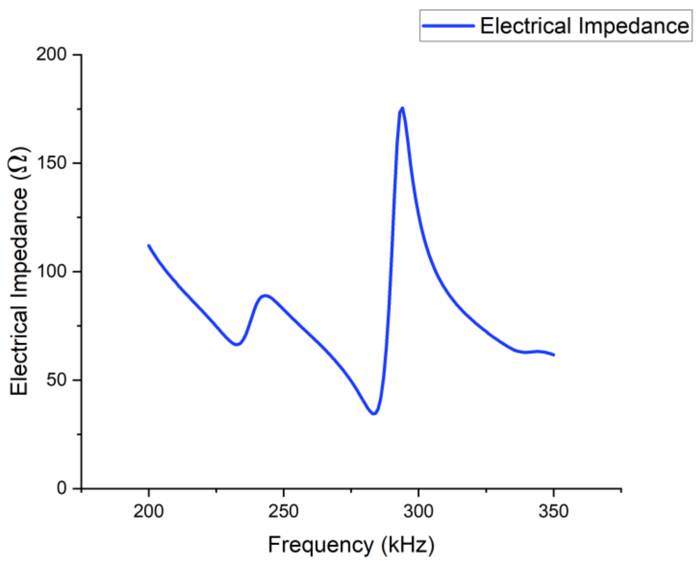
Figure 33 Shows the electrical impedance changes at different frequencies. By analyzing the changes in electrical impedance, we can see that around 80, 120, 150, 180, 200, 250, and 300 kHz are the resonance frequencies that have been carefully selected for maximum acoustic and sound pressure for cancer cells bursting at resonance.



(a)



(b)



(c)

Figure 33: Electrical Impedance vs Frequency (a) at 80, 120 kHz (b) at 150, 180, 200 kHz (c) at 250, 300 kHz

Therefore, a novel design for a multimodal ultrasound transducer having 6 modes of resonance is designed for the application of cancer cells bursting using PVDF as the piezoelectric material.

Chapter 5: Conclusion and Future Works

The present work describes the design and analysis of a multimodal and focused PVDF ultrasound transducer and its application in cancer cell bursting. The transducer has been designed to operate on resonance frequencies of 80, 120, 150, 180, 200, 250, and 300 kHz that have been carefully selected for different types of cancer cells through the literature for a maximum sound pressure level of 200 dB as per Acoustic-Piezoelectric Interaction Physics in COMSOL Multiphysics. This enables interaction between the ultrasound waves and the cancer cells in such a manner that the membranes of the cells are exposed to cancer which has an effect of bursting the cells much more as compared to normal cells. The geometries of the focused ultrasound transducers have also been modified for direct focusing of the tissue region containing tumor cells with the added feature of providing reproducibility. The findings also indicate the allocation of the ultrasound energy at the center of the transducer. Design of the piezoelectric ultrasound transducer which will further be used in medical trials will be completed in the next stage of the research to validate the usefulness of the design developed in terms of its practicability.

As described the emerging multimodal, focal PVDF ultrasound transducers require clinical trials to establish safety and effectiveness in real-life scenarios as a part of future work. These trials will be aimed at determining the effectiveness of differentiating cells of cancer colonies and healthy tissues. More efforts are required in focusing on the resonance frequencies of various cell types to diagnose and treat the diseases at maximum value and utility. Hybrid composites as new classifications of piezoelectric materials may provide greater compliance and biocompatibility. Combining them with ultrasound or MRI imaging modalities will enable better aiming and tracking during the treatment process. Following these avenues would encourage miniaturization and portability allowing for the complimentary use of these devices with less invasive methods or for wearing. Furthermore, coupling these transducers with drug delivery or photodynamic therapies may also result in better outcomes. Using AI systems for automation allowing for modification to treatment in real time and optimization would further increase the performance of ultrasound transducers and clinical versatility for targeted therapy.

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