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Ultrasound radiation force transport of drugs in tumors

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Medical Technology
Submission date: June 2013
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Contents

Abstract

Chemotherapy effectiveness not only depends on drug penetration extent in target tissues or tumor cells, but also depends on drug suppression extent by the normal tissues and cells. Ultrasound acts as an important role to meet this requirement in drug delivery of chemotherapy in recent years. The popular methods are micro bubbles and HIFU (high intensity focused ultrasound). In this thesis, we developed a method using ultrasound radiation force to “push” the drug penetrate into tumor cells.

The capillaries' walls in tumor are different from normal capillaries' ones. The space between cells of tumor capillary wall is quite big due to the aggressive growing. So drug can easily leak to interstitium and reach the pressure low difference besides capillaries wall. Which implicates that drug cannot travel too far from the blood vessel, only few tumor cells close to the blood vessels are exposed to the drug.

Our study is addressing this issue. In our experiment, the tumor is placed at the focus of transducer and the radiation force in focus will build the bigger difference pressure besides capillaries walls and “push” the drug from capillaries into tumor cells. But the radiation force must be controlled not too high to burn out the tumor. So in order to produce suitable radiation force or intensity in focus to improve drug transport, transducer simulation and design is the first important . In this thesis, many parameters of transducer such as center frequency, aperture size, beamwidth, depth of focus and so on are simulated. Transducer efficiency, thermal effect were measured. In the experiment, their combinational effect was applied.

Ultrasonix 4DL14-5/38 probe, Sonix MDP scanner, software Forwardsim[1], hydrophone, thermal meter were used in this project. Center frequency, aperture size, beamwidth, depth of focus and ultrasound field are simulated by Forwardsim[1]. This software is quite powerful and developed mainly by Johannes Kvam and can simulate transducer ultrasound field in many aspects. Transducer efficiency was measured by hydrophone. Heating effect was measured with thermal meter and thermal camera.

A final experiment conditions are decided based on the simulation and measurement results:8MHz center frequency, 14.4mm*5mm aperture size, 10 cycles

pulse length, 18V input power, 10KHz PRF (pulse repeat frequency) , 10 minutes therapy time and so on(see table 4.3) .

The experiment was carried on 7 mice being anesthetized and injected with drug or nanoparticles. Plastic glove filled with water was used as propagation medium. We observed tumor imaging from scanner and confirm the tumor was located in focus. Afterwards we exerted ten minutes ultrasound radiation therapy on tumor. At last tumor was excised from mice and froze in N2 liquid. The frozen sections with a thickness of 5 um were mounted on glass slide for microscopy observation.

The experiment results matches very well with the simulation and measurement results.

Acknowledgments

The research work presented in this thesis is carried out at the Department of Circulation and Medical Imaging at Norwegian University of Science and Technology 2013.

I would like to express my gratitude to professor Bjørn Angelsen who lead the research work and give me very patient and meticulous explanation for the related knowledge and many questions I met.

I would also like to thank Johannes Kvam who developed Forwardsim and helped me to use it in endless patience and always kind to answer my questions.

Furthermore, I wish to express my thankfulness to all my colleagues at this project group : Siv Eggen, Larenus de Bruijn.

And finally I thank Petros Tesfamichael Ymane shared some measurement results to me. During the process, we discussed how to carry out the experiments and have done many valued measurements.

Chapter 1 Introduction

Tumor can be classified into benign and malignant ones. Malignant tumor is called cancer that is a kind of diseases and is characterized by cell aggressive growth out of control.

Prostate is a gland of men's reproductive system. Prostate tumor is a form of cancer that develops in the prostate. The cancer cells can spread from the prostate to other parts of the body, especially to the bones and lymph nodes. Men in fifty age easily get prostate cancer and it is the sixth leading death cancer [3].

The treatment method for prostate cancer generally are surgery, radiation therapy, hormonal therapy and chemotherapy [3]. Ultrasound radiation force used for prostate tumor treatment is a new branch in last ten years.

Three advantages of ultrasound are attributed to the wide application of ultrasound. The first is the ultrasound treating can increase blood flow thereby speed up the healing process. The second is ultrasound could cause less pain when it is used for the reduction of swelling and edema. The third is ultrasound treatment will not lead to any strain and any scar to tissue.

Based on acoustic propagation effect in attenuating media, ultrasound radiation force is first used as tissue imaging. In recent years, the relative high power ultrasound radiation force was used as breaking up stony deposits or tissue, such as kidney stones and gallstones, into fragments small enough to be passed from the body without undue difficulty. This process is known as lithotripsy [4] .Ultrasound radiation force can also be used in ablating tumors or other tissue non-invasively. This is accomplished by using a technique known as High Intensity Focused Ultrasound (HIFU).

Another important application of ultrasound radiation force is to enhance the delivery and activity of drugs in targeted area. The roll of ultrasound radiation force in this application is a trigger which improves the chemotherapy drug deliver into tumor cells. In other words, this method can enhance drug uptake. Our study is addressed on this application. Prostate tumor is the object tumor we treated on.

The capillaries' walls in tumor are different from normal capillaries. The space between cells of tumor capillaries' wall is rather bigger due to the aggressive growing

compared to the normal capillaries. So drug can leak easily to interstitium and cause quickly the low pressure difference besides capillaries wall. So drug cannot travel far from the blood vessel. Therefore, only few tumor cells close to the blood vessel are exposed to the drug.

If a beam is focused on small size area on a target tissue, the power per area becomes very large. The large force changes the pressure difference the vessel and "push" the drug is used to build into the tumor cells. On the other hand, the energy will also be absorbed by tissue to "melt" drug-containing liposomes.

Ultrasound radiation force onto a small volume ΔV can be written in the form as below:

$$\Delta F = \frac{\delta_e I}{c} \Delta V$$

ΔF is radiation force, δ_e is the extinction cross section. c is ultrasound velocity. I is intensity. So radiation force is proportional to intensity .If a bigger radiaton force is required,then a high intensity is needed. The high intensity is available when the beam area is small. It means the elevation beamwidth and azimuth beamwidth should be small. Beamwidth is related with aperture size, focus and frequency. In order to get small beamwidth, many parameters of transducer such as center frequency, aperture size, beamwidth, depth of focus and so on are simulated or measured.

But the radiation force cannot be too high to burning out the tumor. Controlling the radiation force or intensity in focus in suitable value is important task. Therefore transducer simulation and design was done first.

Ultrasonix 4DL14-5/38 probe, Sonix MDP scanner, software Forwardsim [1], hydrophone, thermal meter and thermal camera were used in this project.

Chapter2 Theory

2.1 Ultrasound Radiation Force

Ultrasound is plane longitudinal pressure wave through mediums with frequency greater than the upper limit of the human hearing ranging. The ultrasound wave can be reflected, refracted, focused and absorbed. Ultrasound wave actual movement is represented as medium is compressed and expanded. So ultrasound could act physically upon biomolecules and cells. Ultrasound wave is absorbed little by water and other tissues. Therefore, ultrasound wave can transmit energy into cells[5].

Here we give the analysis of ultrasound motion and get the radiation force equation .

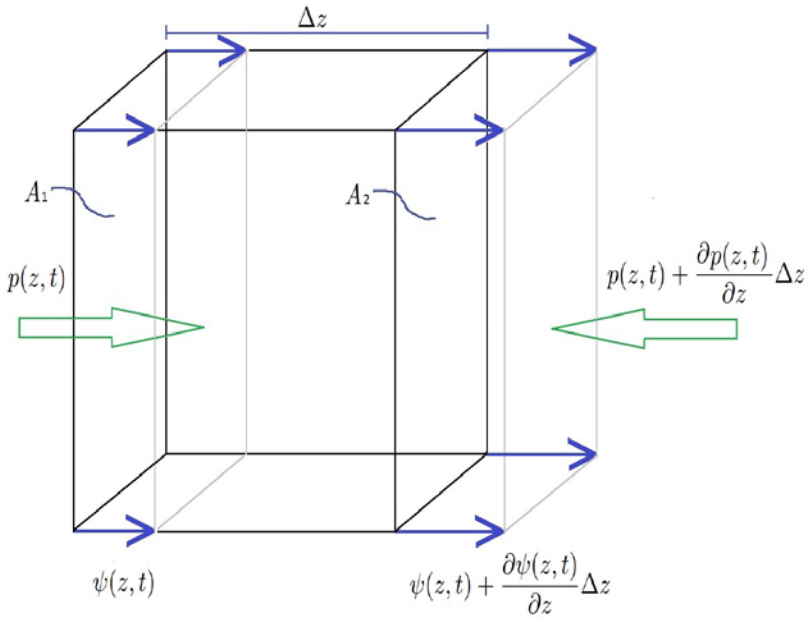


Figure 2.1 Volume change of a thin element of material causes by the wave motion [6]

Figure 2.1 shows the basic acoustic wave physical phenomenon in a small material medium volume. Acoustic wave propagate in z direction and the medium volume is compressed or expanded periodically during the process. In other words, acoustic wave propagation in medium lead to medium particles vibration front and back near the balance points. A_1 and A_2 are two equilibrium plans. $\psi(z,t)$ is the motion

displacement from equilibrium position. $u(z,t)$ is particle velocity, $p(z,t)$ is acoustic pressure. $\Delta V = \Delta Z \bullet A_1$ is the unstrained volume. δV is the compressed volume.

So the relations are:

$$u(z,t) = \frac{\partial \psi(z,t)}{\partial t} \tag{2.1}$$

$$\Delta V = \Delta Z \bullet A_1 \tag{2.2}$$

$$\delta V = \left\{ \psi(z,t) + \Delta Z \frac{\partial \psi(z,t)}{\partial z} - \psi(z,t) \right\} \bullet A_1 \tag{2.3}$$

Therefor it could get relative volume compression

$$\frac{\delta V}{\Delta V} = \frac{\partial \psi}{\partial z} \tag{2.4}$$

Because the pressure p is expression in a function of the with the relative volume compression $\frac{\delta V}{\Delta V}$:

$$p = f\left(\frac{\delta V}{\Delta V}, \frac{\delta V^{'}}{\Delta V}, ...\right) \approx -\frac{1}{\kappa}\frac{\delta V}{\Delta V} - \mu_B \frac{\delta V^{'}}{\Delta V} \approx -\frac{1}{\kappa}\frac{\partial \psi}{\partial z} \tag{2.5}$$

κ is the bulk or volume compressibility, μ_B is the bulk viscosity,

Insert $u(z,t) = \frac{\partial \psi(z,t)}{\partial t}$ (2.1) to equation (2.5) this equation, another relation can get

$$\frac{\partial p(z,t)}{\partial t} = -\frac{1}{\kappa}\frac{\partial u(z,t)}{\partial z} \tag{2.7}$$

The radiation force between the plane A_1 and A_2 is

$$\Delta F = \left\{ p(z,t) - \left[p(z,t) + \Delta z \frac{\partial p(z,t)}{\partial z} \right] \right\} A_1 \tag{2.8}$$

$$\Delta F = -\frac{\partial p(z,t)}{\partial z} \Delta z A_1 = -\frac{\partial p(z,t)}{\partial z} \Delta V \tag{2.9}$$

When we introduce acoustic radiation intensity I, The intensity (also called power density) of an ultrasonic beam is measured in terms of power carried per cross section area of the beam, typically having units of Watts/cm^2

The definition of I is :

$$I(z,t) = cE = \frac{p^2}{Z_0} \tag{2.10}$$

c is acoustic velocity and E is sum of kinetic energy and potential energy density . Z_0 is characteristic impedance.

We can get the new relation between pressure $p(z,t)$ and intensity I

$$p(z,t) = \frac{I(z,t)}{u(z,t)} \tag{2.11}$$

In Bjørn A.J. Angelsen's book chapter 2 *Plane Waves In Linear Elastic Medium* gave detailed derivation[5].

When the conception of extinction cross section is induced , we can get the radiation force onto a small volume ΔV given by:

$$\Delta F = \frac{\delta_e I}{c} \Delta V \tag{2.12}$$

δ_e is extinction cross section, c is ultrasound velocity. The detailed description in chapter 3.

2.2 Linear array ultrasound Transducer

Ultrasound transducer is a device for converting electronic energy to ultrasound energy. The ultrasound transducer have different names according their different shape. Such as annulus ultrasound transducer, linear array ultrasound transducer and so on.

Linear array ultrasound transducer is the most common type of ultrasound scanners. This kind of transducer has large contact area with object. The piezoelectric element is placed inside the transducer lens [7]. The piezoelectric is divided into many parallel elements along the azimuth direction. See figure 2.2.

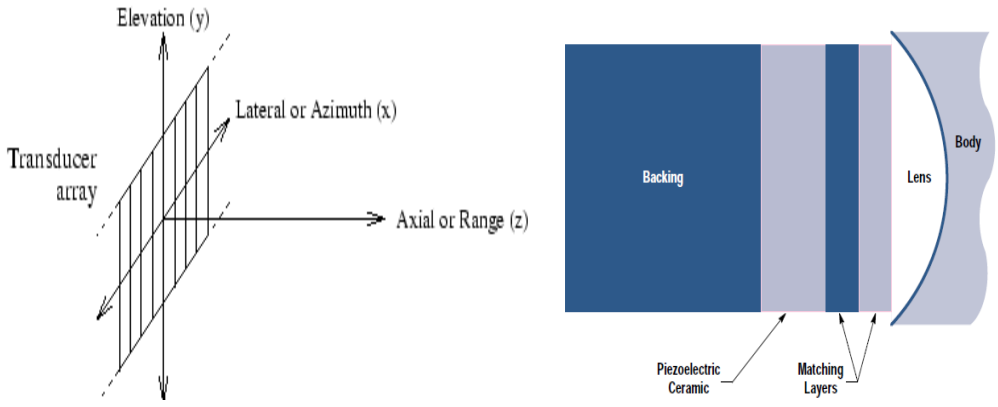


Figure 2.2 Linear array ultrasound Transducer and enlarged of one element [7]

The element structure can see from Figure 2.2. In order to improve tissue impedance coupling, a front matching layer is added to the front face of the piezoelectric[7]. Backing on figure is acoustically absorbing material.

All the elements connected by respective electronic switching which controls if the element should be active or halt. In certain time, only some elements of the transducer is active. The transducer active area transmits ultrasound pulse and to imaging tissue or transmits energy to tissue.

Then the active area repeats along the azimuth direction in certain scan speed. In this way, the scan process is completed. In the imaging transducer, the scan frequency is greater than the flicker frequency of the eye, so we can get a stable picture.

2.2 Prostate tumor

It is well know that the body is made up of many types of cells. These cells grow and are controlled by genetic material (DNA). DNA keeps the body healthy. When the control process goes wrong, the genetic material (DNA) of a cell start producing mutations that affect normal cell growth and division by being damaged. And these mutated cells form a mass of tissue called tumor.

In the experiment, the radiation force are effected on prostate tumor. The tumor were grew on mice of 6 weeks old for one month.

So here give some simple introduction about prostate tumor.

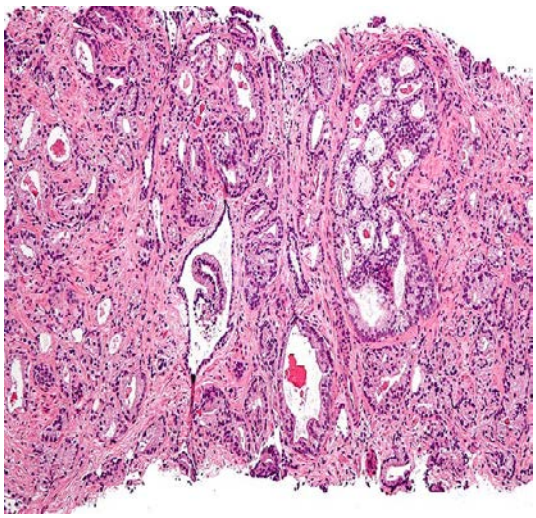


Figure 1.2 Postate tumor cells [8]

Prostate tumor is a type of cancer that affects the prostate gland in men. The prostate is located beneath the bladder, in front of the rectum, and wraps around part of the urethra. According to experts suggestion, the causes and risk factors of prostate tumor is mainly old age, family history and low vegetable diet [8] .Treatment of aggressive prostate cancers may are surgery, radiation ,hormone therapy and chemotherapy. In this experiment, the prostate tumor was implanted on mice which were 6 weeks old .The position was between the hip and the knee.

2.3 The extracellular matrix (ECM) and tumor micro enviroment (TME)

Extracellular matrix (ECM)

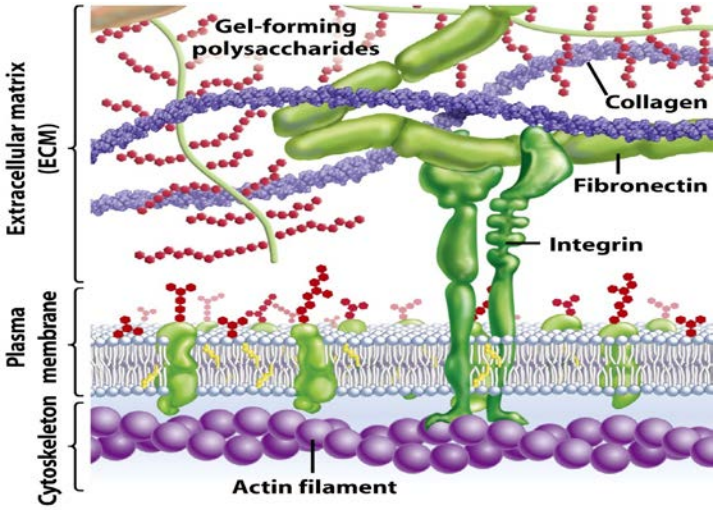


Figure 1.2 Structure of the extracellular matrix [9]

ECM is a network of proteins surrounding cells, also called interstitium. It was long believed that functions mainly as providing support, segregating tissues from one another, and regulating intercellular communication. In addition, ECM also regulates cells' dynamic behavior. [9]

Tumor micro enviroment (TME)

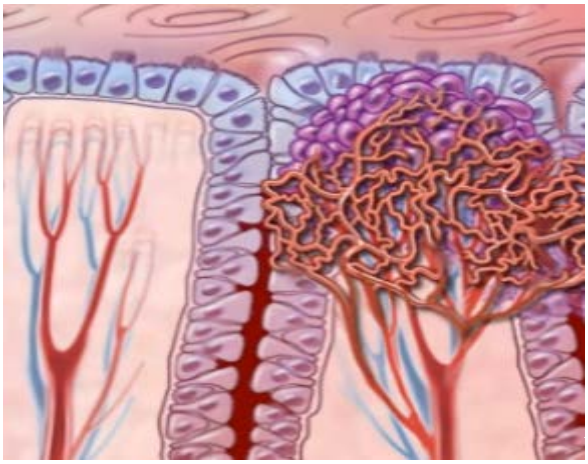


Figure 1.3 normal vascular (left) and tumor vascular(right) [10]

The tumor microenvironment (TME) is composed of cells, soluble factors, signaling molecules, extracellular matrix, and mechanical cues that can promote neoplastic transformation, support tumor growth and invasion, protect the tumor from host immunity, foster therapeutic resistance, and provide niches for dormant metastases to thrive.

The tumor vessel is irregular, disorganized due to the tumor aggressive growth (see Figure 1.3). So the endothelial cells have large spacing, which make it possible to leak and diffuse larger molecules. So some drugs particles could pass tumor vessel but not pass normal tissue [11].

2.4 Nanoparticles and Immunofluorescence

Nanoparticles

Nanoparticles are method for cancer drug delivery in recent years. These particles allow subtle modification to bind cancer cell membranes, microenvironment, cytoplasmic or nuclear receptor sites. The size of nanoparticles can pass through the big holes in the tumor vasculature and access tumor cell directly but cannot enter the normal cells. Nanoparticles has property of high payload, so nanoparticles are utilized as the aid of delivering medicines in chemotherapy. As we have talked TME in 1.3, tumor vasculature is known to be tortuous, chaotic, and leaky. These properties enhance the permeability and retention effect of vasculature. Nanoparticles can enter into the tumor through the leaky vessel and deliver higher doses of drugs with lower

systemic toxicity. It could overcome the limitations of poor drug solubility and nonspecificity and is more effective at treating tumors in mice .The nanoparticle used in this experiment is made of liposomes with average diameter of 90nm and containing cytotoxic drug [12].

Immunofluorescence

Immunofluorescence is emission light by a special substance that has absorbed light or other electromagnetic radiation. Immunofluorescence technique is used in this experiment for labeling of blood vessels in vitro and in vivo. It causes a large number of fluorescent objects so the functional vessels are stained .In this way, we can easily get visualization of the distribution of the target molecule and analyze of the distribution of doxorubicin in the tumor tissue [13].

Chapter 3 Research Methods

In this section, we will discuss how to use ultrasound radiation force to realize drug transportation in tumor.

Ultrasound radiation force could be utilized for increasing the drug transport from capillaries towards the tumors. In other words, ultrasound radiation force can be focused in an interested area and push the drug particles to penetrate deeply into tissue or tumor cells without affecting the surrounding tissue.

It is well known that drugs in the capillaries can penetrate into the cells interstitium (space between cells) according to the principle of concentration gradient. In tumor the drugs are easier to leak into the tumor interstitium than normal tissue due to the capillaries' imperfect walls. The imperfect walls are resulting from the aggressive growth of the tumors. It means the tumor interstitial fluid has the ability to increase pressure quickly compared to the normal tissue. In other words, the drugs penetrate from the capillaries wall to the tumor interstitium in quiet low pressure (or low concentration gradient). Based on these property and phenomenon, we easily know that this process become like diffusion and it is a slow process. In present chemotherapy mainly utilizes this diffusion property of tumor. Another important thing should mentioned is the normal membranes inhibit the transport of drugs in the forms of large molecules or nanoparticles.

In order to improve the drug transport efficiency from tumor capillaries to interstitium and accelerate the drug penetration process, the ultrasound radiation force is used in the chemotherapy process. The ultrasound radiation force is used for producing driving force and heating drug in this situation.

In order to achieve this purpose, we must precisely control the transducer and make sure which frequency will be used? How large aperture be used? How large input power should supplied to the transducer? How larger pressure could be on the surface of the transducer? And so on.

In this section, I will present how we think about main factors that affect the radiation force or intensity in focus and how we get the condition for the animal experiment. So the transducer design procession is described. Center frequency, aperture size, beamwidth, focus depth, radiation force, heating energy, temperature has been numerically calculated and simulated. The pressure on transducer surface is controlled by controlling the input power. So the transducer elements input impedance and the efficiency of the transducer were measured with hydrophone. Heating energy delivery if also considered, as transducer temperature increased within 10 minutes are measured in temperature meter and temperature cameral. Duty cycle, duration are related with the therapy effect. So they are also considered in this chapter.

3.1 Ultrasound Transducer Design

The first and important work in our experiment is to design the ultrasound transducer. The main idea of the ultrasound transducer design is to realize the determined radiation force and determined temperature on focus. Our design is based on a 1D linear transducer which was made from piezo-composite material. The transducer has 128 elements with size azimuth*elevation (0.3mm*5mm) for element pitch. Using Forwardsim[1], we created 3D numerical model for the transducer and then calculated the performance of the transducer numerically.

3.1.1 Center frequency

The operating frequency of a transducer depends on what application of the transducer will be in. In the operating frequency range the transducer will incite maximum pressure. Generally the operating frequency is not only a single frequency, it's a frequency range. So center frequency is defined as difference between the upper and lower frequencies of which the pulse amplitude is 6db down the maximum amplitude.

In this experiment, ultrasound is propagated in water and tumor tissue. We set the medium parameters such as: tissue absorb coefficient, bulk compressibility, mass density parameters and so on. We use linear array transducer, set the aperture and azimuth ,elevation focus in 25mm, and use the numerical calculation and simulation ,

get the frequency response .See figure 4.1.From the frequency response , the maximum response point will be the center frequency for the transducer.

3.1.2 Aperture size

1D linear transducer with 128 elements in size 0.3mmx 5mm are used in this project. How many elements will be active for transmitting ultrasound pulse depends on radiation force or intensity in focus.

Delivering high doses drug into tumor cells depends on the ultrasound radiation force. With varying the aperture size of the transducer, we get different radiation force or intensity in focus. The radiation force or intensity is related with the focus beamwidth. If beamwidth is small, the energy is centralized. Big aperture size leads to a bigger focus angler and small beamwidth, so it will induce bigger focus energy. But it does not mean that bigger is better. For transducer, there is a threshold value for the aperture. If bigger than its threshold , radiation force or intensity will be constant .So appropriate aperture is chosen by simulation method .

3.1.2 Beamwidth

Beamwidth is an important aspect of ultrasound transducer. It represents how well the beam of ultrasound is focused. In ultrasound transducer, beamwidth includes azimuth beamwidth and elevation beamwidth. Beamwidth also can be divided half power beamwidth(-3dB from the maximum) and quarter power beamwidth (-6dB from the maximum). Beamwidth is the size between the two points of -3dB or-6dB in the main lobe.

The elevation beamwidth measured elevation plane. The azimuth width is measured lateral plane. The elevation size is fixed in 5mm in our project transducer, so the beamwidth mainly depends on azimuth elements switch.

The beam produced by a linear array transducer is shown in Figure 3.1

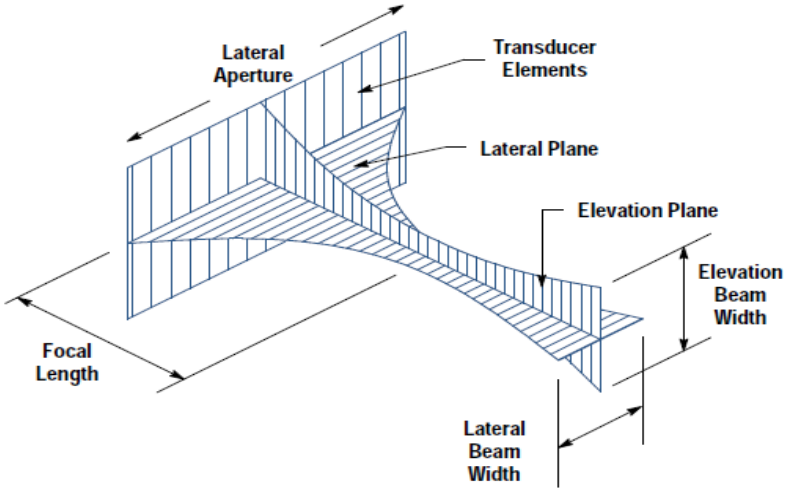


Figure 3.1 Focused Beam ,azimuth and elevation [14]

The beamwidth requirement in high intensity ultrasound transducer for drug transport application is different than the diagnostic imaging. For diagnostic imaging we only emphasize on the resolution. But in drug transport application, we stress on high intensity, radiation force and pressure on transducer on focus.

Beamwidth is related with many factors. In this project, lots of investigations have been conducted to find how the factors affects the beamwidth . These factors include aperture size, center frequency and focus, etc.

3.1.2.1 Analytic expression

Analytic expression of the pressure field in non-absorbing homogeneous medium, from a rectangular aperture in focus is given by [5]:

$$P(\vec{F},\omega) = ik\frac{e^{-ik|F|}}{2\pi|F|}\int_{-D_a/2}^{D_a/2} dx_0 \int_{-D_e/2}^{D_e/2} dy_0 e^{i\frac{k}{|F|}(x_0.x+y_0.y)} \qquad (3.1)$$

The integration expression is:

$$P(\vec{F},\omega) = \frac{ifab}{c|F|}e^{-ik|F|}\sin c(\frac{D_a x}{\lambda|F|})\sin c(\frac{D_e y}{\lambda|F|}) \qquad (3.2)$$

Where P is pressure, F is the focus, D_a is the transducer azimuth width, D_e is the transducer elevation width. From this formula, it could reaches the conclusion: decreasing wavelength (increase frequency), increasing aperture size, decreasing focus could increase pressure and get small beamwidth. In other words, if bigger pressure and narrower beamwidth in focus are expected, higher frequency, shorter focus, bigger aperture should be given.

The narrower beamwidth, the better energy concentration and better directivity could available .

3.1.2.2 Numerical expression

Beamwidth also could be calculated by empirical formulas [5]. $FN = F / D$, FN is F number, F is focus .Here an example is given to show how to use the empirical formulas to calculate the beamwidth. The focus is 25 mm, aperture size $D_a * D_e$ is 15mm*5mm, so

$$FN = F / D = \frac{25mm}{15mm} = 1.6 \tag{3.3}$$

So the azimuth beamwidth D_{Fa} in 3dB can be expressed as

$$D_{Fa} = \lambda FN = \frac{\lambda F}{D_a} = \frac{0.192 * 25}{15} = 0.3mm \tag{3.4}$$

The elevation beamwidth D_{Fa} in 3dB can be expressed as

$$D_{Fe} = \lambda FN = \frac{\lambda F}{D_e} = \frac{0.192 * 25}{5} = 0.96mm \tag{3.5}$$

So the focus area is

$$A_F = D_{Fa}.D_{Fe} = \frac{\lambda^2 F^2}{D_e D_a} = 0.288mm^2 \tag{3.6}$$

If in 12 dB

the azimuth beamwidth D_{Fa} in 12dB can be expressed as

$$D_{Fa}(12dB) = \lambda FN = \frac{2\lambda F}{D_a} = \frac{2 * 0.192 * 25}{15} = 0.6mm \tag{3.7}$$

The elevation beamwidth D_{Fa} in 12dB can be expressed as

$$D_{Fe}(12dB) = \lambda FN = \frac{2\lambda F}{D_e} = \frac{2*0.192*25}{5} = 1.92mm \quad (3.8)$$

So the focus area in 12 dB is

$$A_F(12dB) = D_{Fa}.D_{Fe} = \frac{2^2\lambda^2F^2}{D_eD_a} = 1.152mm^2 \quad (3.9)$$

The depth of focus in azimuth

$$L_{Fa}(1dB) = 2D_{Fa}(12dB)FN = 2*0.6*1.6 = 1.92mm \quad (3.10)$$

The depth of focus in elevation

$$L_{Fe}(1dB) = 2D_{Fe}(12dB)FN = 2*1.92*5 = 19.2mm \quad (3.11)$$

3.1.2.3 Forwardsim beamwidth simulation

We also use software simulation method to calculate the beamwidth .In chapter 4 gives detailed simulation or calculation results .

3.2 Duty cycle and Pulse repetition frequency

Duty cycle is the product of the pulse duration and pulse repetition frequency, equal to the pulse power applied per second .

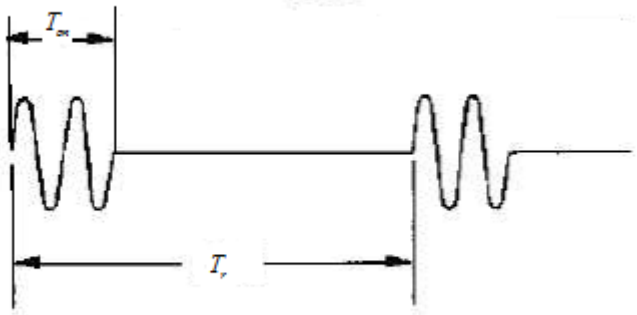


Figure 3.2 duty cycle schematic

From Figure 3.2 we know the duty cycle D can be expressed

$$D = \frac{T_{on}}{T_r} \quad (3.12)$$

In this Figure , we also give the definition of pulse repetition frequency (PRF),it is the number of pulses per time unit.

$$PRF = \frac{1}{T_r} \tag{3.13}$$

Pulse duty cycle is related with the energy supply and duration of exposure.

3.3 Duration of exposure

Duration of exposure plays important role in ultrasound therapy. Too long exposure duration will induce cell lesion and damaging. Too low exposure duration can not achieve expected radiation force, intensity and temperature. In this experiment, we hope to get quite high intensity on the focus. But with the limitation of transducer thermal effect, the high input voltage cannot be allowed. We considered to improve PRF and pulse cycle to achieve the energy on focus. In order to get the appropriate input voltage, we measured the impedance, efficiency and temperature. Then we follow the previous experience and medical experts recommendation [15], we decided the total therapy time (duration of exposure) is 10minutes.

3.4 Wave equation with extinction cross section

In order to describe the radiation force, intensity and pressure propagation in absorbing material, we induce the concept of extinction cross section which also called attenuation cross section. The extinction cross-section σ_e , is a hypothetical area describing the likelihood of ultrasound radiation scattered and absorbed by the medium. σ_e multiplied by the ultrasound wave intensity incident on the object gives the total amount radiant that scattered and absorbed by the medium [16].

The definition of the extinction cross section is $\sigma_e = \sigma_s + \sigma_a$, σ_s is scattering extinction cross section, σ_a is absorbing extinction cross section.

Based on the definition of extinction cross-section and the theory in chapter 2 ,we get the radiation force in scattering and absorbing medium is expressed :

$$\Delta F = \frac{\sigma_e(\omega) I}{c} \Delta V \tag{3.16}$$

Where I is averaged intensity across one oscillation and could be expressed :

$$I = \frac{P^2}{2Z_0} \tag{3.17}$$

P is pressure and Z_0 is characteristic impedance. σ_0 is extinction cross section of acoustic intensity, and the expression in frequency domain is

$$\sigma_e(\omega) = \sigma_s(\omega) + \sigma_a(\omega) = \sigma_{a0}((\frac{\omega}{\omega_0})^a + \sigma_{r0}(\frac{\omega}{\omega_0})^b),$$

$$a = 2-4, b = 1-1.5 \tag{3.18}$$

σ_s is scattering extinction cross section, σ_a is absorbing extinction cross section, a and b is coefficient related with medium. ω_0 is center frequency. The numerical expression of $\sigma_e(\omega)$ is

$$\sigma_e(\omega) = \frac{10\alpha}{\lg e}\frac{\omega_0}{2\pi}m^{-1} \tag{3.19}$$

α is the attenuation coefficient. Based on the definition of extinction cross section, the pressure plane function could be expressed :

$$\frac{dP(z,\omega)}{dz} = -\sigma_e(\omega)/2P = -\sigma_{a0}((\frac{\omega}{\omega_0})^a + \sigma_{r0}(\frac{\omega}{\omega_0})^b)/2P \tag{3.20}$$

Based on (3.20), we developed software and calculate out the pressure on focus .The simulation result is in chapter 4 Figure 4.19.

3.5 Radiation force simulation

If we get the pressure P from (3.20) ,we get the intensity from equation (3.17)

$$I = \frac{P^2}{2Z_0}, \tag{3.21}$$

Z_0 is characteristic impedance of the material, which is defined as follows

$$Z_0 = \frac{1}{\kappa c} = \sqrt{\frac{\rho}{\kappa}} = \rho c \tag{3.22}$$

The intensity based on this formula is simulated in Figure 4.19.

Based on the intensity, we could calculate the radiation force [16]

$$\Delta F = \frac{\sigma_e(\omega)I}{c}\Delta V \tag{3.23}$$

$$\bar{f}(0,z,\omega_0)=\frac{\Delta F(z,\omega_0)}{\Delta V}=\frac{1}{2\pi cZ_0T_{on}}\int d\omega\sigma_e(\omega;\omega_0)\left|P(z,0,\omega;\omega_0)\right|^2,$$

(N/m^3) (3.24)

The simulation result is showed in chapter 4 Figure 4.20 and Figure 4.23.

3.6 Tissue Heating

Another important term is tissue heating. It is related with the acoustic energy. Tissue absorbs ultrasound wave energy and the energy increases the tissue temperature.The temperature increment depends on energy, heat capacity and volume. The energy on per unit of the beam direction is expressed as [16]:

$$\frac{\Delta Q_h(z,\omega_0)}{\Delta z}=\frac{1}{2\pi Z_0}\int d\omega\sigma_a(\omega)\int d^2r_\perp\left|P(z,\underline{r}_{\perp,}\omega;\omega_0)\right|^2, \text{ Joule/m,} \quad (3.25)$$

Insert equation (3.18) into (3.24), equation (3.24) becomes

$$\frac{\Delta Q_h(z,\omega_0)}{\Delta z}=\frac{\sigma_{a0}(\omega_0)}{2\pi Z_0}\int d\omega(\frac{\omega}{\omega_0})^b\int d^2r_\perp\left|P(z,\underline{r}_{\perp,}\omega;\omega_0)\right|^2, \text{ Joule/m,} \quad (3.26)$$

If the area of the beam is defined as

$$A_b(z,\omega;\omega_0)=\frac{\int d^2r_\perp\left|P(z,\underline{r}_\perp,\omega;\omega_0)\right|^2}{\left|P(z,0,\omega;\omega_0)\right|^2} \quad (3.27)$$

$A_b(z,\omega;\omega_0)$ is the same conception as in (3.6) and (3.9).They are related with the beamwidth . If insert $A_b(z,\omega;\omega_0)$ into (3.25), we get

$$\frac{\Delta Q_h(z,\omega_0)}{\Delta z}=\frac{1}{2\pi Z_0}\int d\omega\sigma_a(\omega;\omega_0)A_b(z,\omega;\omega_0)\left|P(z,0,\omega;\omega_0)\right|^2,$$

Joule /m (3.28)

Energy per m^3 delivered to the tissue, averaged across the beam is expressed as

$$\frac{\Delta Q_h(z,\omega_0)}{\Delta V}=\frac{1}{2\pi Z_0A_b(z,\omega_0)}\int d\omega\sigma_a(\omega;\omega_0)A_b(z,\omega;\omega_0)\left|P(z,0,\omega;\omega_0)\right|^2,$$

$Joule/m^3$ (3.29)

From (3.28), we can see the energy $\frac{\Delta Q_h(z,\omega_0)}{\Delta V}$ is inversely with $A_b(z,\omega_0)$,the smaller beam area is, the higher energy will be. So this is the reason why we design the

transducer to get smaller beamwidth. The energy on the beam direction is simulated and the result in Figure 4.22 and Figure 4.25.

Heat capacity is [16]:

$$C_p = 4.2\times10^6\ Joule/m^3\ ^oK, \tag{3.30}$$

The increase in temperature of the tissue

$$\begin{aligned}\Delta T(z,\omega_0) &= \frac{\Delta Q_h(z,\omega_0)}{\Delta V C_p}\\ &= \frac{1}{2\pi Z_0 A_b(z,\omega_0) C_p}\int d\omega \sigma_a(\omega;\omega_0) A_b(z,\omega;\omega_0)\left|P(z,0,\omega;\omega_0)\right|^2, {}^oK\end{aligned} \tag{3.31}$$

The approximate numerical expression for tissue increased temperature[16] :

$$\Delta T \approx \sigma_{a0}\frac{P^2}{2Z_0 C_p}T_{on}, {}^oK \tag{3.32}$$

The temperature in beam direction is simulated and showed in Figure 4.21 and Figure 4.24.

3.7 Impedance measurement

Linear array transducer is used in this study. Inside the transducer the piezoelectric element is divided into128 parallel elements along the azimuth length and these elements are connected by electronic switching so that only a certain area of the transducer works at a time instant.

In other way, the linear array was connected to 128 electronics driving system which has independent amplifiers and matching networks. If the maximum input electric is given, how lager the power could converte to acoustic energy? It is depends on the impedance match network. From the equation (3.32), It is obviously that impedance is the main factor of the efficiency. So we used impedance tester instrument to test each elements impedance amplitude and phase .The simulation and measurement result is shown in chapter 4 Figure 4.27 and Figure 4.28.

3.8 Transducer efficiency

From the above discussion, we know that intensity, radiation force and tissue heating are all proportional with pressure P^2, so if we want to obtain the maximum radiation force, intensity and tissue heating, we should maximize pressure P^2 on the transducer surface. We know the ultrasound pressure is converted from electronic power by piezoelectric material. Because the electronics input power is easy to measure and control, if the efficiency of the transducer is known, we can get the converted energy and the pressure on the transducer surface. The relation of the efficiency is below[16]:

$$\eta(\omega) = \frac{P(\omega)\left|Z_{el}(\omega)\right|}{\omega_s \theta_{el}(\omega) V_{tt}{}^2(\omega).Z_0} \tag{3.33}$$

In this relation , $Z_{el}(\omega)$ is the transducer input impedance, $\theta_{el}(\omega)$ is phase of the impedance ,we measured these two parameter as described in 3.7. Based on the impedance we measured ,we simulated the efficiency see results in chapter 4 figure 4.29 and energy transform relation. see chapter 4 Figure 4.30.

Chapter 4 Results and Discussion

Based on the software Forwardsim[1], and some measurement instruments: impedance tester, hydrophone, Oscilloscope, temperature meter and temperature cameral, we studied the transducer property and performance from different perspectives. Then we took into consideration for all factors and design out an animal experiment.

The transducer was modeled with Forwardsim [1]. The transducer size, material elastic and thermal property are configured inside Forwardsim[1] as showed in table 4.1:

Table 4.1: Transducer parameters in simulation

Terms	Value
Number of elements in elevation	1
Number of elements in azimuth	128
Elevation element size	0.5mm
Azimuth element size	0.3mm

4.1 Center frequency simulation results

In order to determine the transducer center frequency, we investigated the radiation force, energy and temperature variation in focus with the frequency scan from 1Mhz-14Mhz. The specific method is we set 1MHz,2MHz,3MHz……14Mhz as the transducer center frequency one by one, then pick out radiation force, energy, temperature value in focus respectively.

Simulation conditions:

Aperture: 14.4 mm, 48 elements

Focus: 25mm

Pressure U0: 0.15MPa

Pulse length: 10cycles

Medium: water

4.1.1 Radiation force in focus with frequency variation

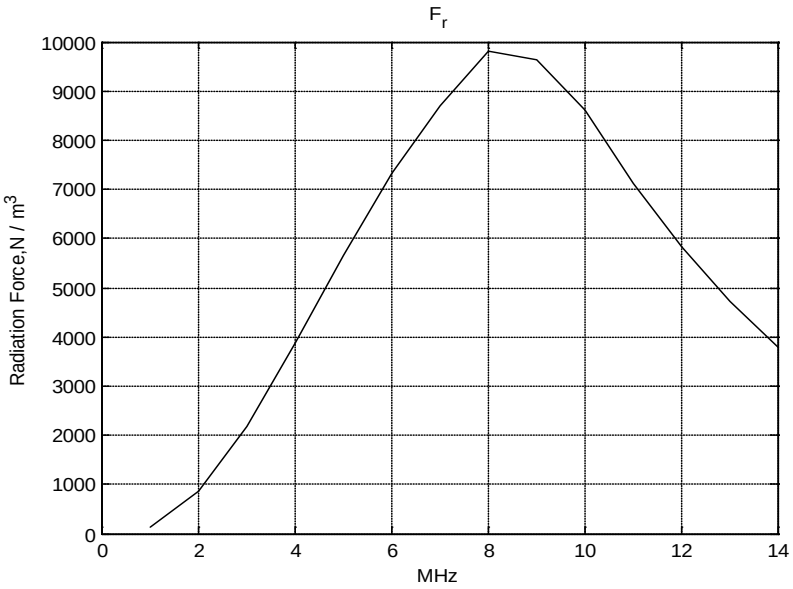


Figure 4.1 Radiation force in focus vs frequency scan

It can be seen that the highest radiation force response in focus will achieve when the center frequency is 8MHz. The maximum radiation force is $9800 N/m^3$. If we consider the -3dB attenuation, the frequency range is from 5MHz to 13MHz.

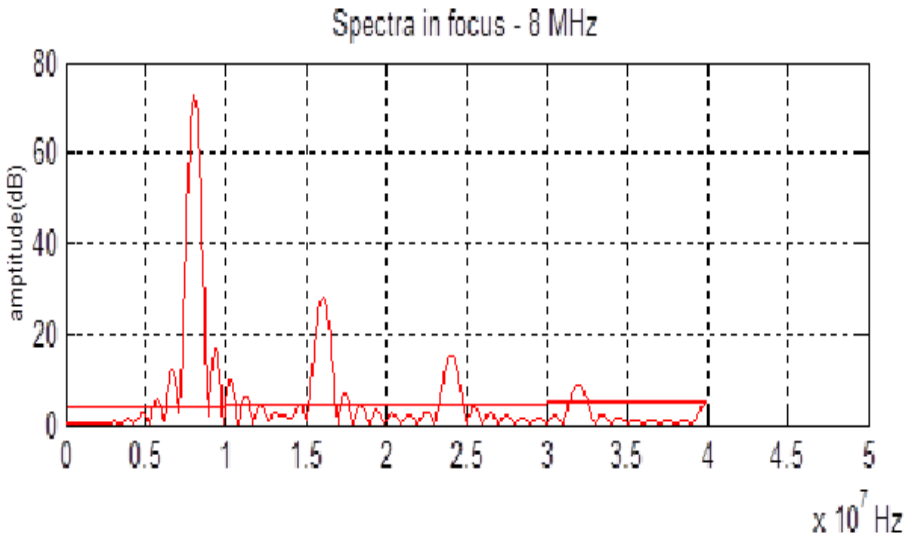


Figure 4.2 frequency spectrum in focus for the center frequency is 8MHz

In order to see the frequency spectrum width, we did Fourier Transformation (FT) for the 8MHz focus pulse. It is seen that the spectrum width is approximately 1MHz. With 8MHz as its central frequency, the maximum amplitude is 70dB at 8MHz. It also

could be seen that two times, three times harmonic occur in focus, but the amplitude is quite small.

4.1.2 Energy in focus with frequency variation

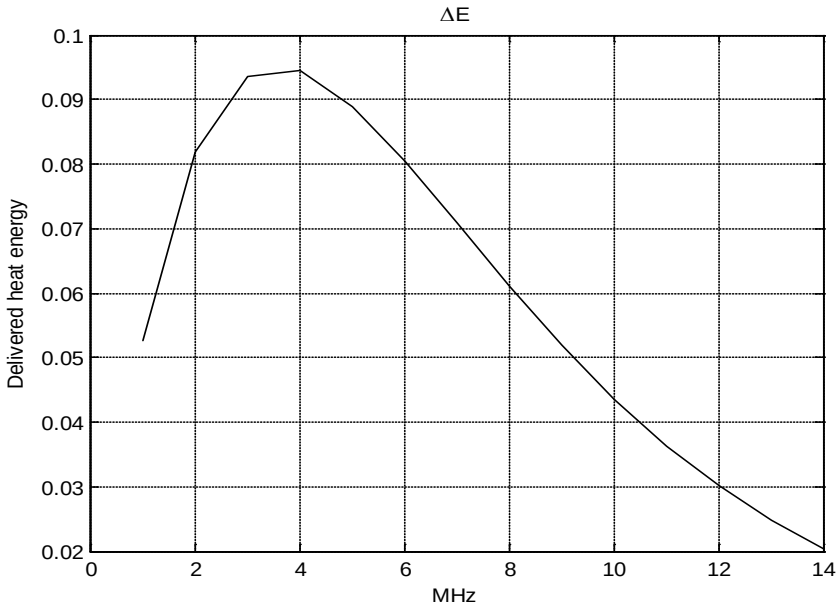


Figure 4.3 Energy in focus vs frequency scan simulation

From figure 4.3, we could see that the highest energy deviates due to diffraction, The biggest energy happens at frequency 4Mhz which is $0.95J/m^3$.

4.1.3 Temperature in focus with frequency variation

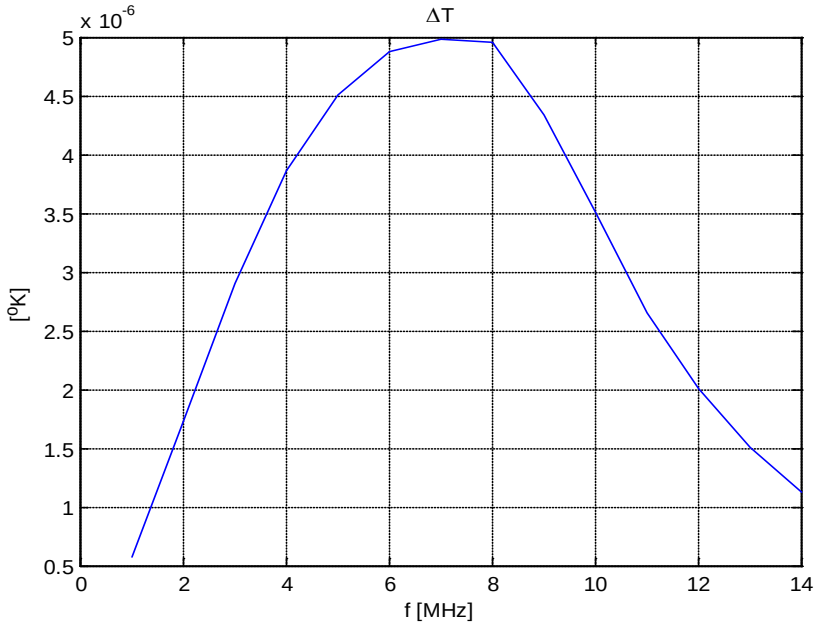


Figure 4.4 Temperature in focus vs frequency scan

Based on formula (3.30), it is found that the highest temperature in focus occurs when the transducer work at frequency 8 MHz. It is easy to understand, because the highest radiation force is in 8MHz, so the tissue or medium absorb more energy, therefore the temperature increases greatly.

From the frequency scan for radiation force, energy and temperature, we can easily see when the center frequency is 8MHz, the radiation force, temperature can reach to the maximum limit. Therefore, the best center frequency is 8MHz for this kind transducer.

4.2 Focus option

In order to see how the focus affects the radiation force, energy, temperature and pressure, we chose the focus in 20mm, 21mm, 22mm…30mm respectively to simulate, then picked out the focus value to draw the figure below.

Simulation conditions:

Aperture:	14.4 mm, 48 elements
Center frequency:	8MHz
Pressure U0:	0.15MPa
Pulse length:	10cycles
Medium:	water

The results shows below

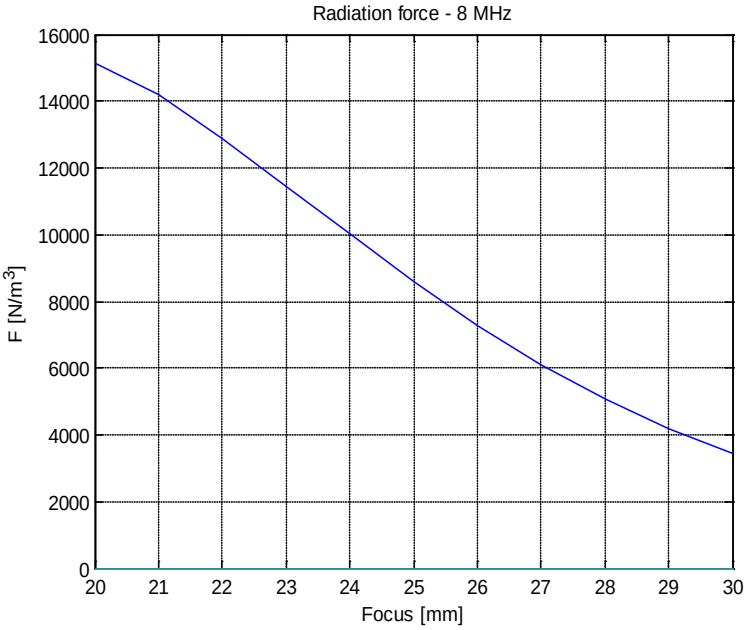


Figure 4.5 Radiation force in focus vs focus scan

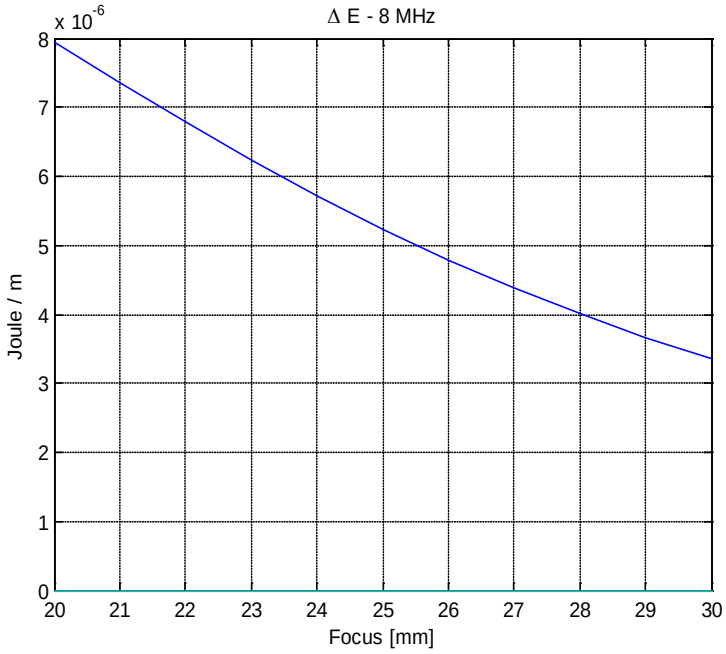


Figure 4.6 Energy in focus vs focus scan

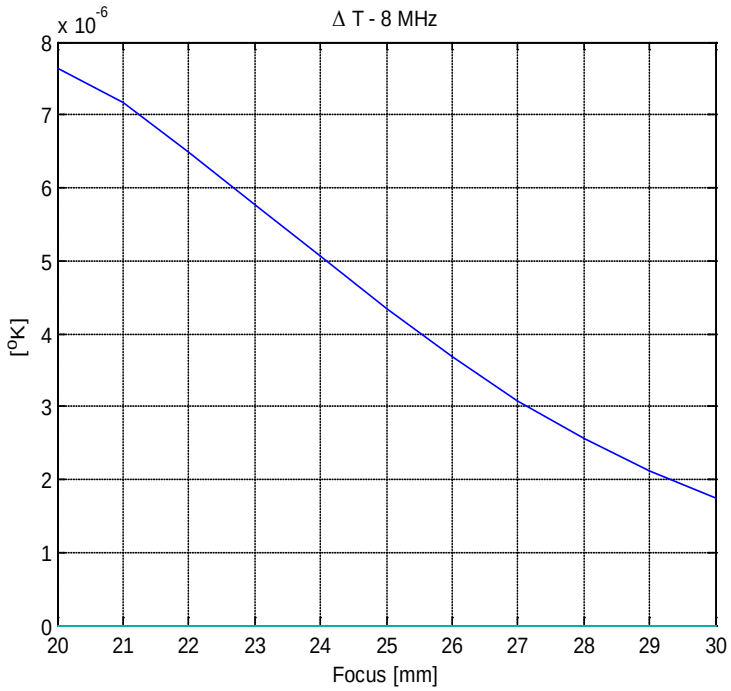


Figure 4.7 Temperature in focus vs focus scan

Figure 4.5-4.7 gives the scanned data of radiation, energy, temperature with different focus. The variation trends are with enlarging the focus, the radiation, energy, temperature in focus are decreased. Because the near focus will induce bigger beam form angle, so the energy is more concentrated at the focus, so get high amount for each parameter. Another reason is the long distance propagation will cause more energy to be absorbed by tissue or medium.

4.3 Aperture choice

For the high frequency transduce, the high radiation force in focus is expected. The aperture size is also very important parameter that affects the focus radiation force or intensity. The aperture size in elevation is 5mm is fixed. So aperture size optimization only can be done for azimuth size. We did the whole aperture performance simulation (from 0.3mm to 38.4mm, which means from 1elements to 128 elements) in azimuth size variation. The specific method is we set azimuth size in 0.3mm, 0.9mm, … 38.4mm one by one to simulate, then pick out radiation force, energy, temperature value in focus to draw a figure.

Simulation conditions:

Aperture:	14.4 mm, 48 elements
Center frequency:	8MHz
Focus:	25mm
Pressure U0:	0.15MPa
Pulse length:	10cycles
Medium:	water

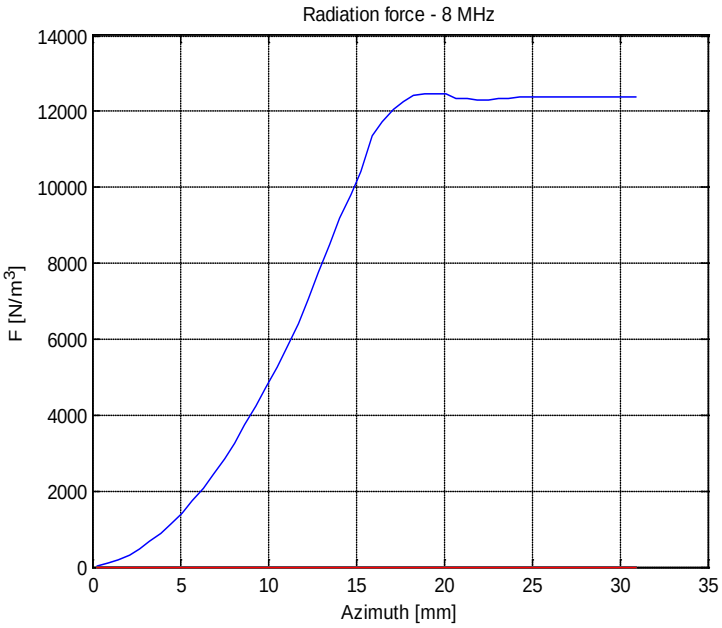


Figure 4.8Radiation force in focus vs aperture scan

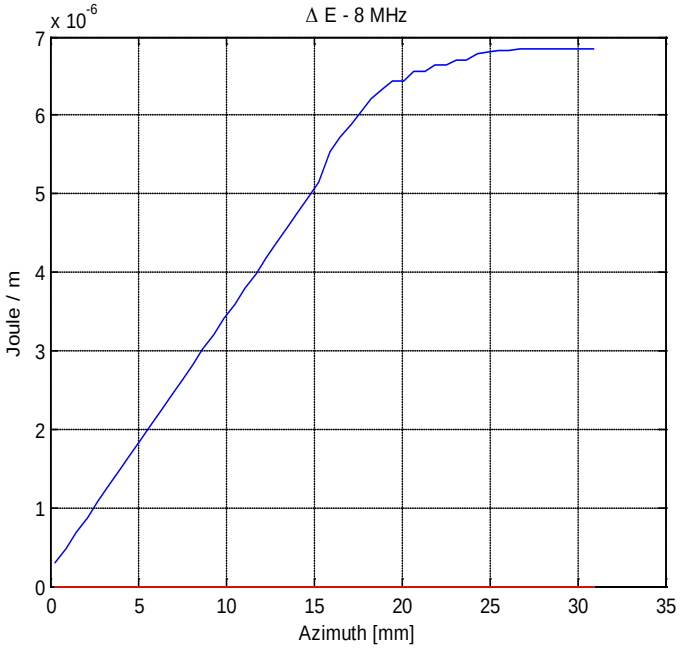


Figure 4.9 Energy in focus vs aperture scan

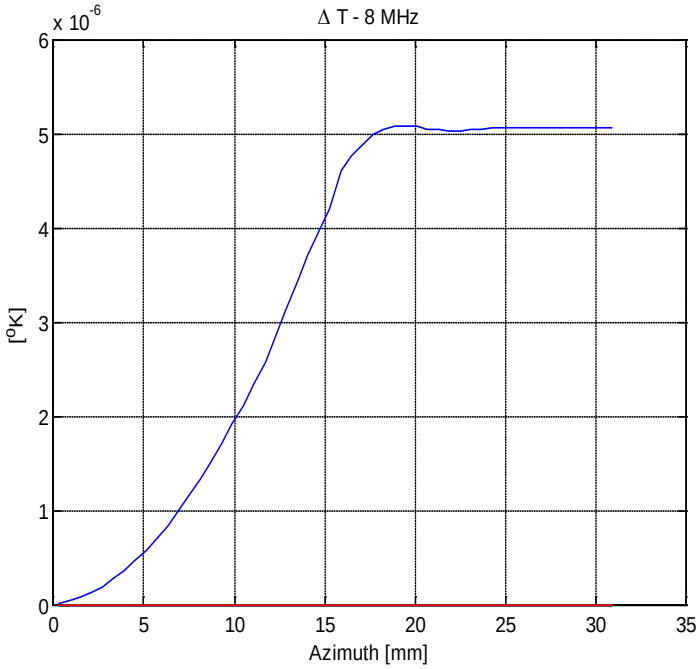


Figure 4.10 Temperature in focus vs aperture scan

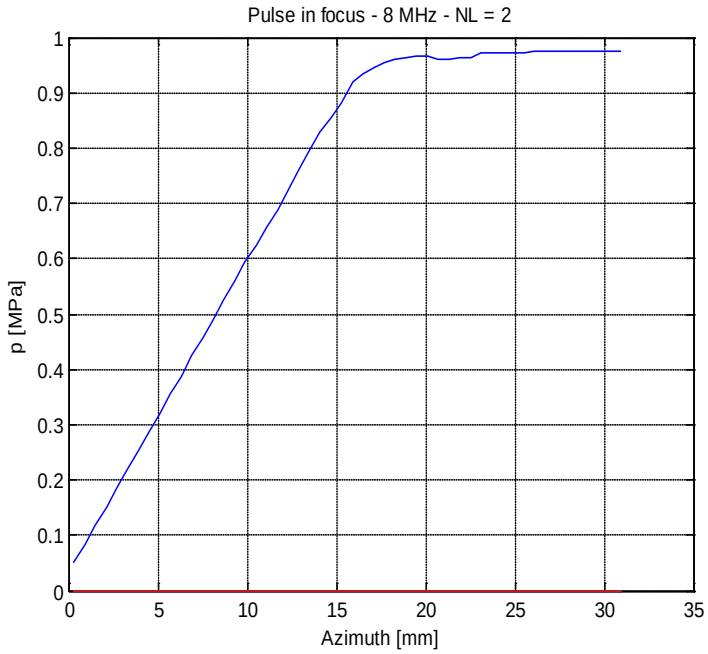


Figure 4.11 pressure in focus vs aperture scan

The ultrasound radiation force, temperature, energy, pressure in focus were simulated with different aperture size. As we can see from Figure4.8-4.11, if the azimuth size is below 15 mm(50 elements), ultrasound radiation force, temperature, energy, pressure in focus increased linearly. When the aperture is bigger than 15mm,

the variation becomes nonlinear. And we also notice that when the aperture exceed 20mm (64 elements), radiation force, temperature, energy, pressure keep constant this size. It means if transducer aperture elements are more than 64 elements, enlarging aperture is no contribution to improve the radiation force, temperature, energy, pressure in focus.

In this experiment, both thermal limitation and high intensity should be considered together. So based on compromising, we choose the aperture size 14.4 mm*5mm(48 elements) for active area.

4.4 Beamwidth in focus

In ultrasound transducer, beamwidth includes half power beamwidth(-3dB) and quarter power beamwidth (-6dB). beamwidth is the size between the two pionts of -3dB or -6dB in the main lobe.

Beamwidth determines the radiation force, intensity and temperature in focus.If the beamwidth is narrow, high radiation force, intensity and temperature are available.

We studied how aperture size ,center frequency and focus distance influence the beamwidth .

It was studied from three methods: empirical formula, software simulation, hydrophone measurement.

4.4.1 Aperture size affects beamwidth

4.4.1.1 Empirical formula calculation results

Using the empirical formulas in chapter 3, could illustrating how the beamwidth is related with aperture size

$$FN = F / D \tag{4.1}$$

FN is F number, F is focus , D is aperture size ,here we give the focus F is 25mm, D is aperture size ,we choose aperture size D 14.4mm(48elements).

$$FN = F / D = \frac{25mm}{14.4mm} = 1.7 \tag{4.2}$$

So the azimuth beamwidth D_{Fa} in 3dB can be expressed

$$D_{Fa} = \lambda FN = \frac{\lambda F}{D_a} = \frac{0.192 * 25}{14.4} = 0.33mm \tag{4.3}$$

The elevation beamwidth D_{Fe} in 3dB can be expressed

$$D_{Fe} = \lambda FN = \frac{\lambda F}{D_e} = \frac{0.192*25}{5} = 0.96mm \quad (4.4)$$

So the focus area is

$$A_F = D_{Fa}.D_{Fe} = \frac{\lambda^2 F^2}{D_e D_a} = 0.316mm^2 \quad (4.5)$$

If in 12 dB

So the azimuth beamwidth D_{Fa} in 12dB can be expressed

$$D_{Fa}(12dB) = \lambda FN = \frac{2\lambda F}{D_a} = \frac{2*0.192*25}{14.4} = 0.68mm \quad (4.6)$$

The elevation beamwidth D_{Fe} in 12dB can be expressed

$$D_{Fe}(12dB) = \lambda FN = \frac{2\lambda F}{D_e} = \frac{2*0.192*25}{5} = 1.92mm \quad (4.7)$$

So the focus area in 12 dB is

$$A_F(12dB) = D_{Fa}.D_{Fe} = \frac{2^2\lambda^2 F^2}{D_e D_a} = 1.305mm^2 \quad (4.8)$$

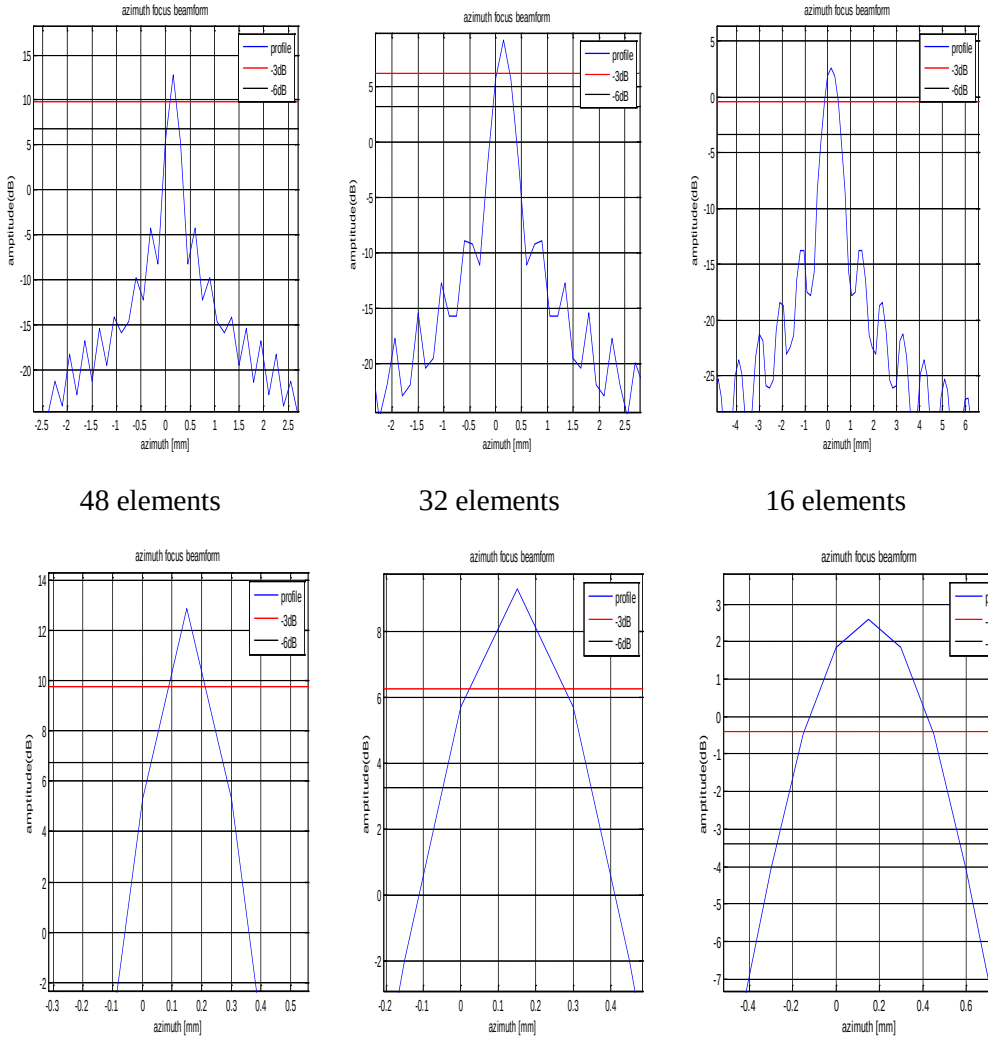
4.4.1.2 Forwardsim beamwidth simulation results

In order to investigate the relation between aperture size (number of elements) and beamwidth performance, we did the beamwidth simulation in 48 elements(14.4mm), 32 elements(9.6mm) and 16 elements(4.8mm) aperture.

Simulation conditions:

Center frequency:	8MHz
Focus:	25mm
Pressure U0:	0.15MPa
Pulse length:	10 cycles
Medium:	water

Azimuth beamwidth simulation results:



48 elements　　32 elements　　16 elements

48 elements(zoom in)　　32 elements(zoom in)　　16 elements(zoom in)

Figure4.12 azimuth beamwidth variation with the aperture size

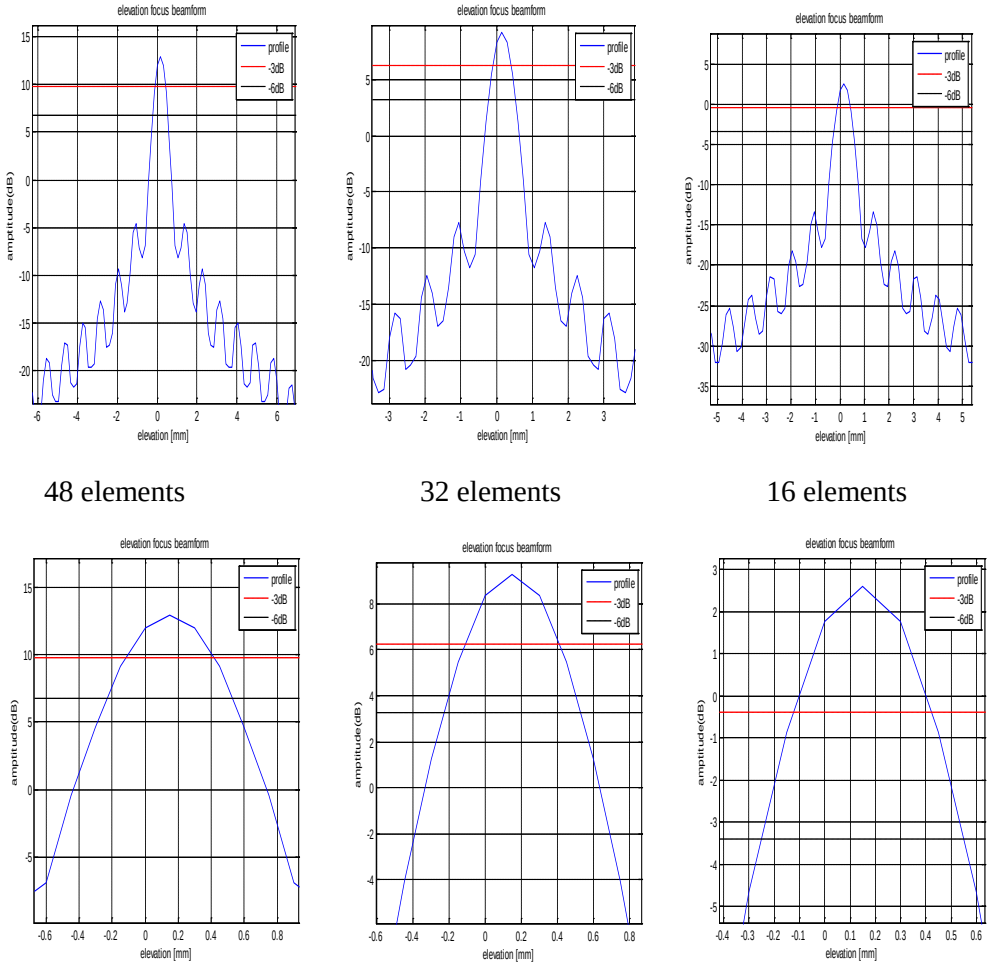
The first row charts show the whole beam profile in focus. The second row are amplified -3dB and -6dB beam profiles. Then the beamwidth is read and written in table 4.2.

table 4.2 azimuth beamwidth in different aperture

	48 elements	**32 elements**	**16 elements**
-3dB beamwidth	0.15mm	0.26mm	0.60mm
-6dB beamwidth	0.26mm	0.42mm	0.90mm

From table 4.2, we know the azimuth beamwidth is increased with the increasing of aperture size.

Elevation beamwidth simulation results:



48 elements 32 elements 16 elements

48 elements(zoom in) 32 elements(zoom in) 16 elements(zoom in)

Figure4.12 Elevation beamwidth variation with the aperture size

table 4.3 elevation beamwidth in different aperture

	48 elements	**32 elements**	**16 elements**
-3dB beamwidth	0.52mm	0.54mm	0.56mm
-6dB beamwidth	0.76mm	0.78mm	0.80mm

From table 4.3, we found the variation of the elevation beamwidth is increased by a very small amount when the aperture size is decreased. This is because the elevation aperture is fixed in 5mm.

4.4.2 Frequency affects beamwidth

Simulation conditions:

Aperture: 16 elements

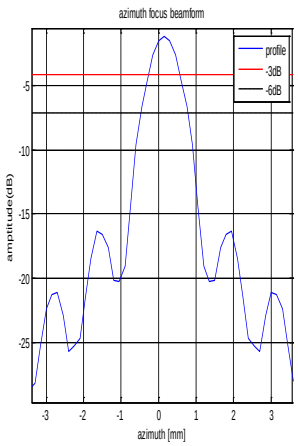
Focus: 25mm

Pressure U0: 0.15MPa

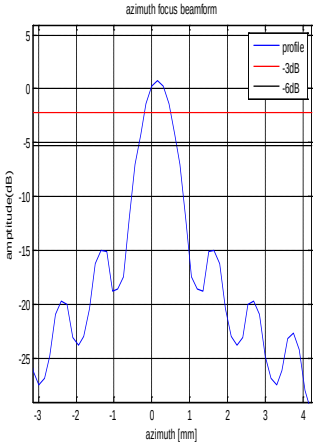
Pulse cycle : 10

Medium: water

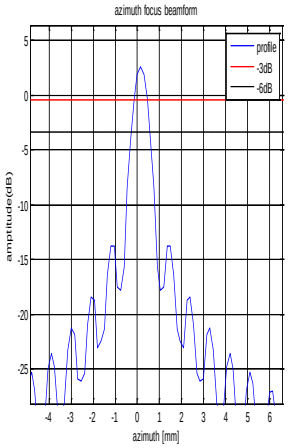
Azimuth beamwidth simulation results:



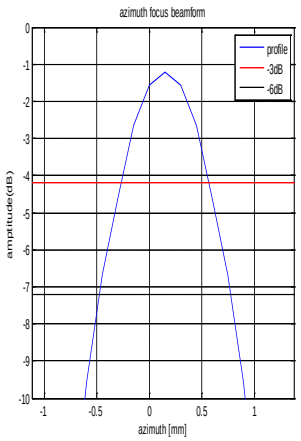
6MHz



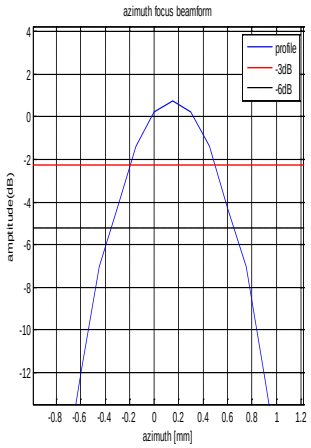
7Mhz



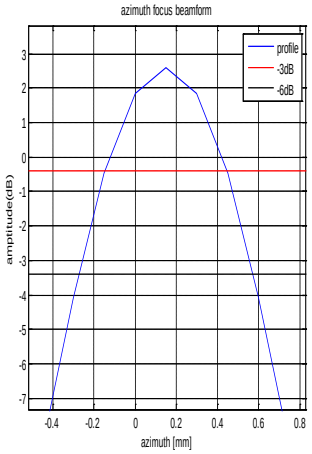
8Mhz



6MHz (zoom in)



7Mhz(zom in)



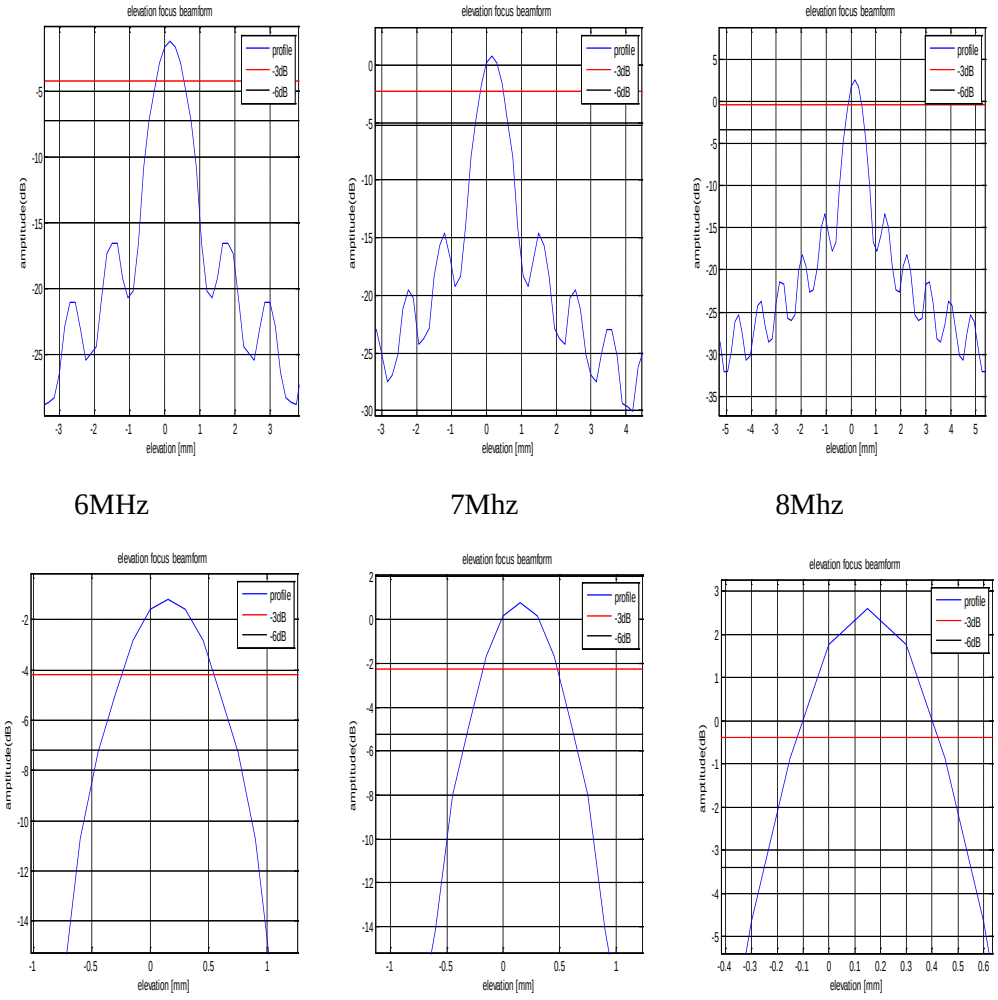
8Mhz(zoom in)

Figure4. 13 azimuth beamwidth variation with the frequency

Table 4.4 azimuth beamwidth in different center frequency

	6MHz	**7MHz**	**8MHz**
-3dB beamwidth	0.90mm	0.70 mm	0.60mm
-6dB beamwidth	1.20mm	1.00mm	0.90mm

Elevation beamwidth simulation results:



6MHz 7Mhz 8Mhz

6MHz (zoom in) 7Mhz(zom in) 8Mhz(zoom in)

Figure 4.14 elevation beamwidth variation with the frequency

Table 4.5 azimuth beamwidth in different center frequency

	6MHz	**7MHz**	**8MHz**
-3dB beamwidth	0.85mm	0.70 mm	0.56mm
-6dB beamwidth	1.20mm	1.05mm	0.80mm

From table 4.4, 4.5, we found that with the increasing of transducer center frequency, the azimuth beamwidth becomes smaller. So here shows obviously why the high frequency transducer is used for high intensity application.

4.4.2 Focus affects beamwidth

Simulation conditions:

Aperture: 48 elements

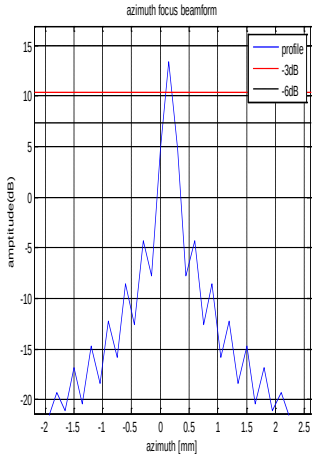
Center frequency: 8MHz

Pressure U0: 0.15MPa

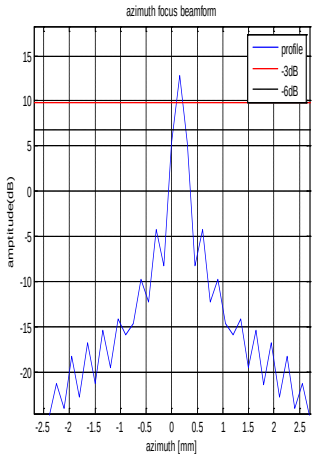
Pulse cycle : 10

Medium: water

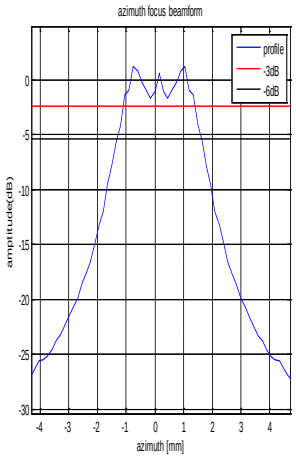
Azimuth beamwidth simulation results:



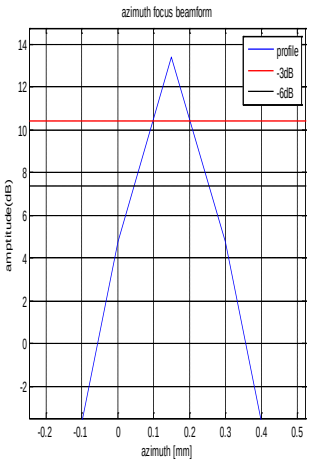
Focus 22 mm



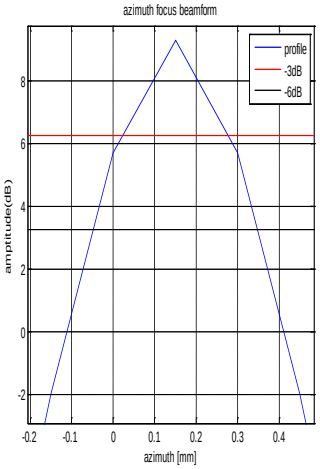
focus 25mm



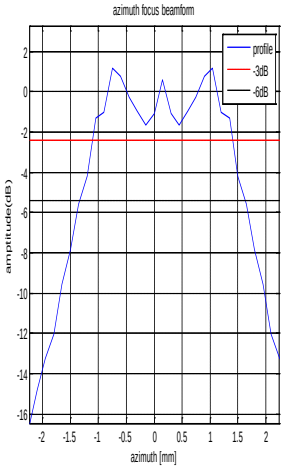
focus 28mm



Focus 22 mm(zoom in)



focus 25mm(zoom in)



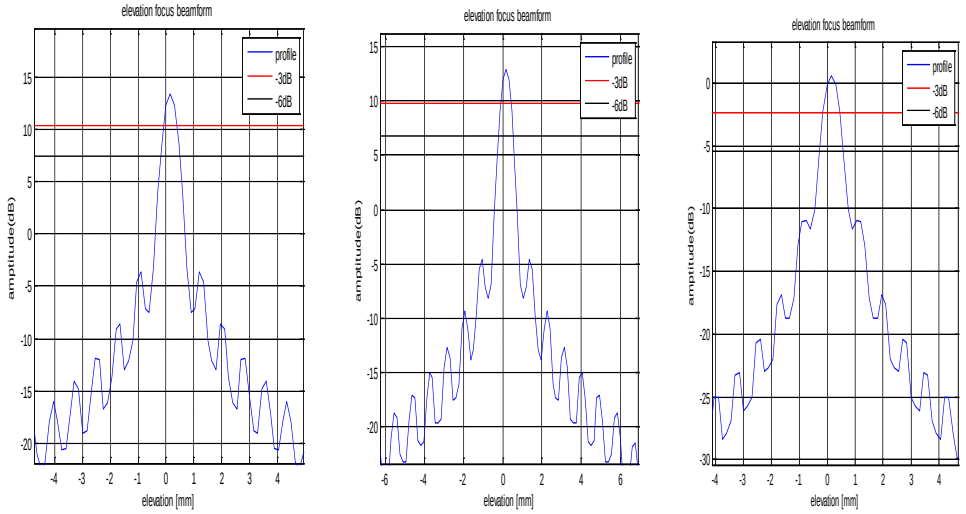
focus 28mm(zoom in)

Figure 4.15 azimuth beamwidth variation with the focus

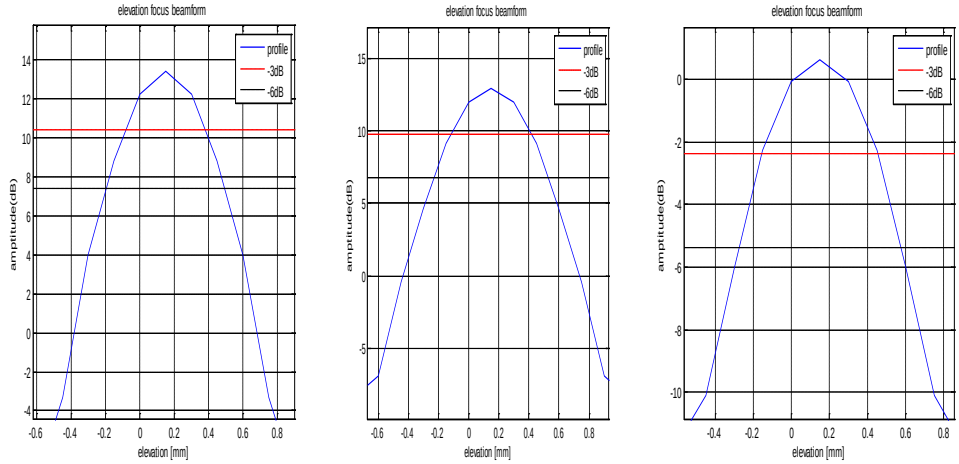
Table 4.6 azimuth beamwidth in different focus

	Focus 22mm	**Focus 25mm**	**Focus 28mm**
-3dB beamwidth	0.10mm	0.15 mm	2.5mm
-6dB beamwidth	0.20mm	0.26mm	3.1mm

Elevation beamwidth simulation results:



Focus 22 mm　　Focus 25mm　　Focus 28mm



Focus 22 mm(zoom in)　　Focus 25mm(zoom in)　　Focus 28mm(zoom in)

Figure 4.16 elevation beamwidth variation with the focus

Table 4.7 elevation beamwidth in different focus

	Focus 22mm	**Focus 25mm**	**Focus 28mm**
-3dB beamwidth	0.49mm	0.52 mm	0.61mm
-6dB beamwidth	0.70mm	0.76mm	0.88mm

From table 4.6,4.7, we found when focus is increased, the azimuth beamwidth become wider . The elevation beamwidth varies in the same trend.

4.5 Depth of focus

Depth of focus is a concept that measures the tolerance of displacement of focus.

Empirical formula calculation results:

The depth of focus in azimuth aperture:

$$L_F(1dB) = 2D_{Fa}(12dB)FN = 2*0.6*1.7 = 2.04mm$$
$$L_F(3dB) = 6D_{Fa}(12dB)FN = 2*0.6*1.7 = 6.12mm \quad (4.9)$$

Depth of focus simulation results:

Simulation conditions:

Aperture:	48 elements
Center frequency:	8MHz
Focus:	25 mm
Pressure U0:	0.15MPa
Pulse length :	10cycles
Medium:	water

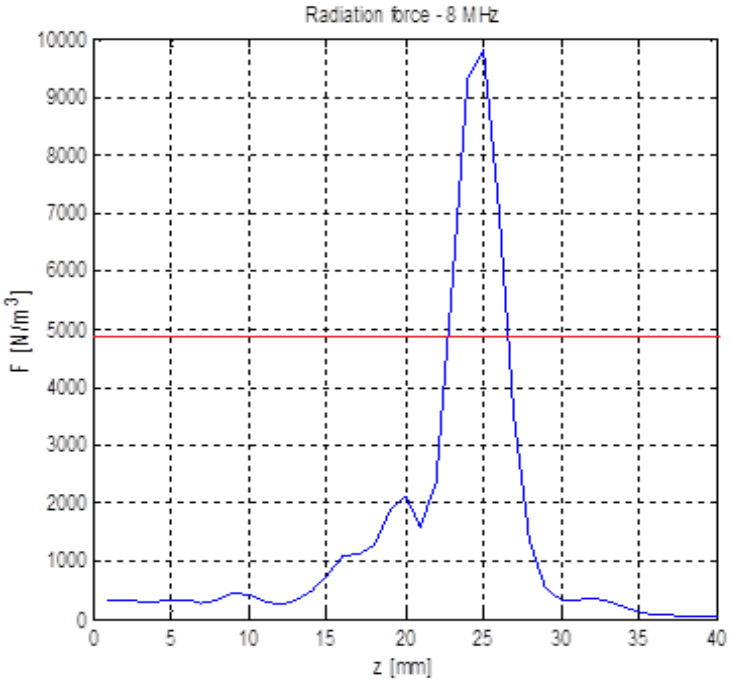


Figure 4.17 depth of focus simulation

The simulation result in figure 4.17 shows the depth of focus in -3dB is 5.5mm. Comparing with the empirical formula calculation results 6.12 mm, it is little smaller than the calculation result in (4.9). It because the medium is water in the simulation setting. But the medium calculated by the formula is air.

4.6 Ultrasound field simulation

The simulation results below are based on the formulas in chapter3.4, (3.20), (3.21), (3.24),(3.26),(3.29),(3.31). They show how the pressure, intensity, radiation force, temperature , heating energy vary with the space and frequency change .

Simulation conditions:

Aperture:	48 elements
Center frequency:	8MHz
Focus:	25 mm
Pressure U0:	0.15MPa
Pulse length :	10cycles
Medium:	Tissue

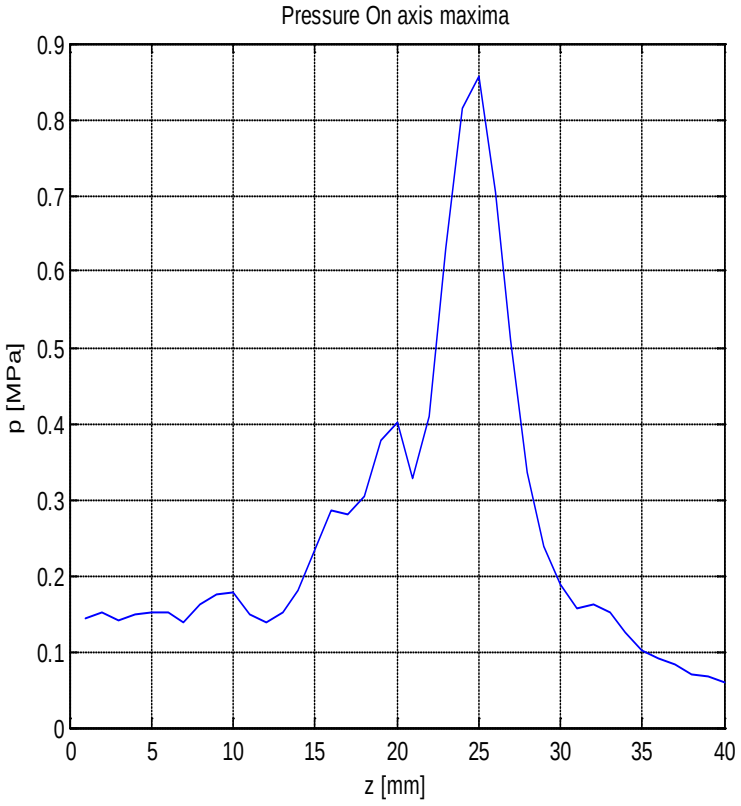


Figure 4.18 pressure on the center axis

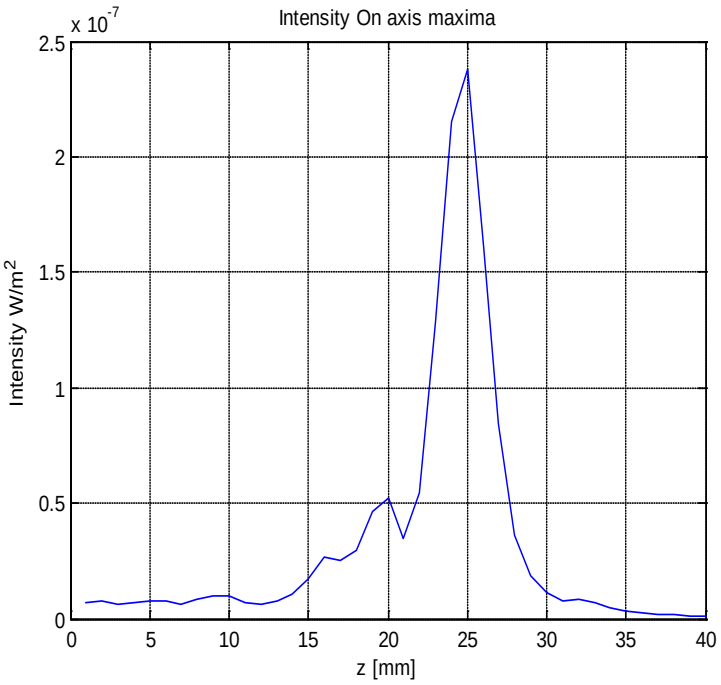


Figure 4.19 intemsity on the center axis

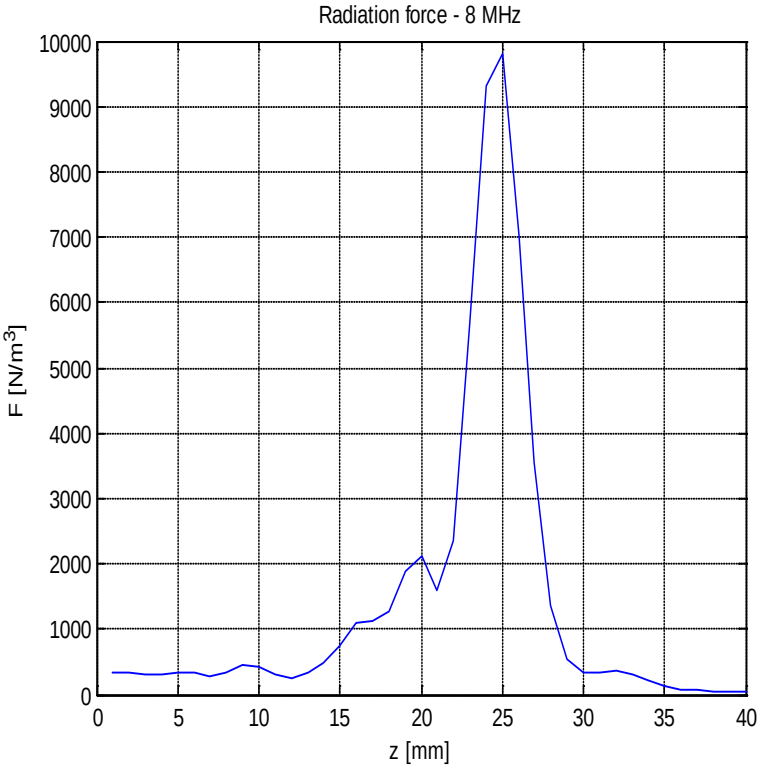


Figure 4.20 radiation force density on the center axis

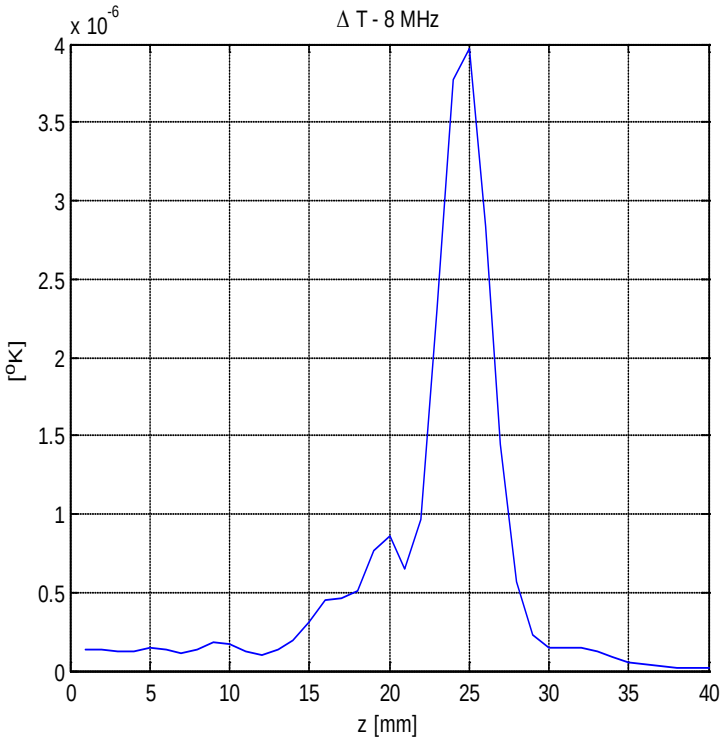


Figure 4.21 Temperature on the center axis

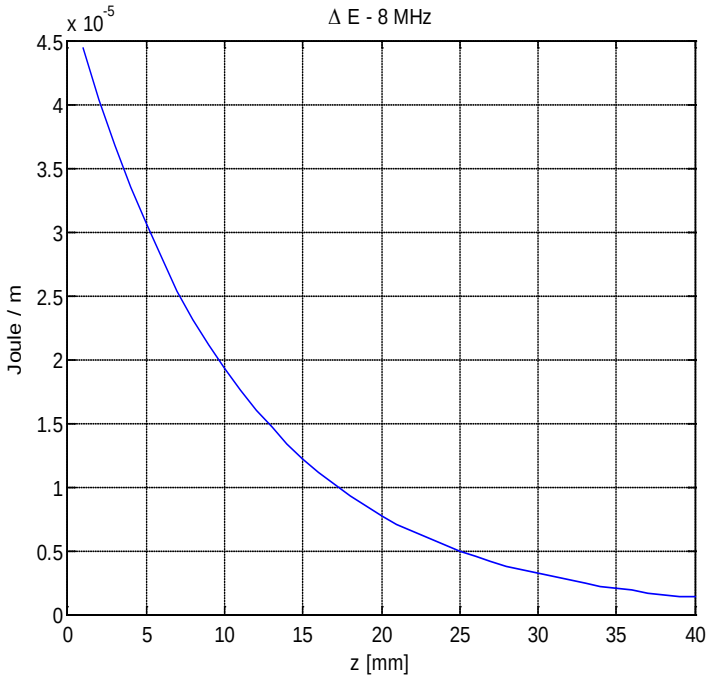


Figure 4.22 Energy variation on the center axis

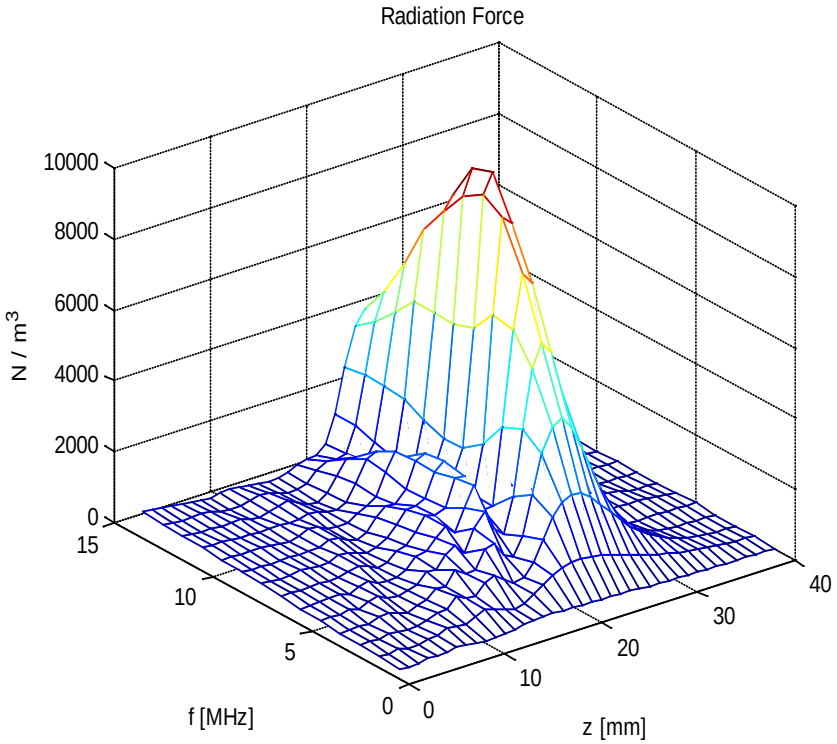


Figure 4.23 3Dimension field simulation for radiation force

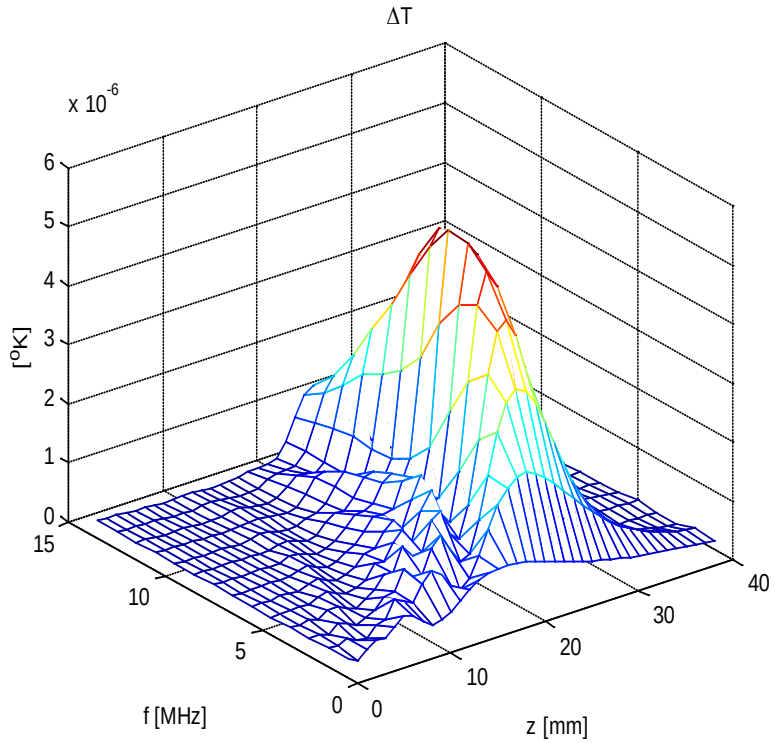


Figure 4.24 3Dimension field simulation for temperature

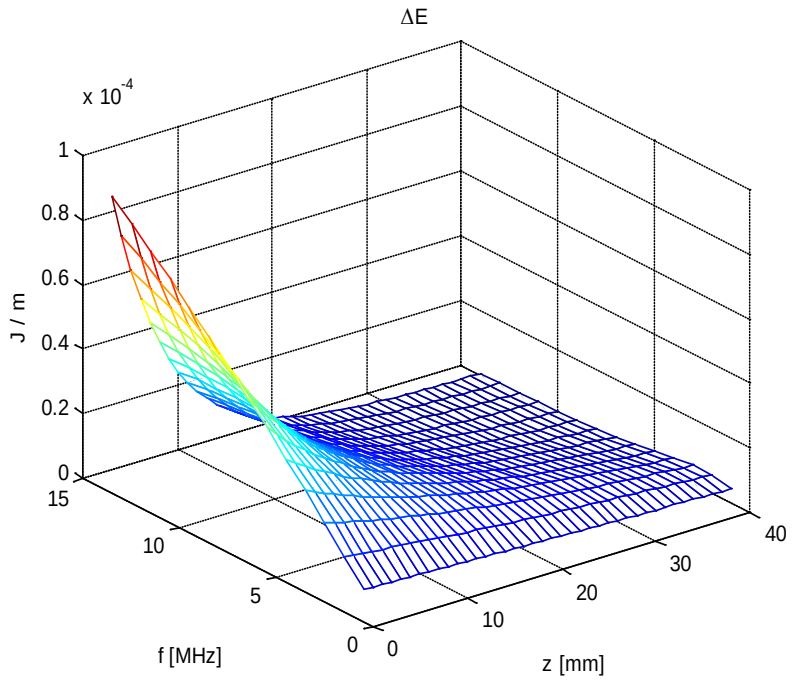


Figure 4.25 3Dimension field simulation for energy

4.7 Two mediums ultrasound radiation force simulation

Two medium, one is water and another is tissue .

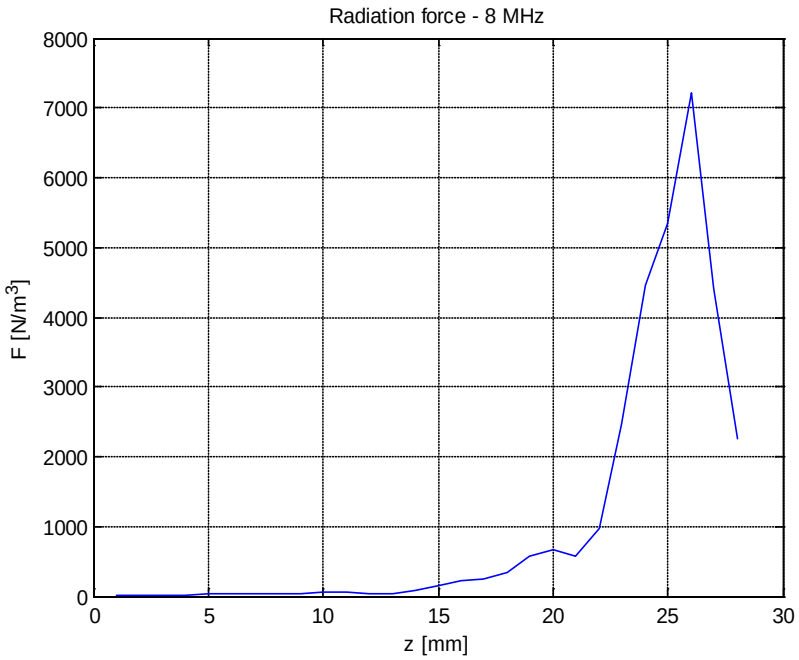


Figure 4.26 Two medium simulation

In experiment, radiation force propagates first in a water filled glove, afterwards comes into tumor. From 0mm to 25mm is water, from 25mm to 28 mm is tumor. Here gives the simulation of radiation force distribution in these two mediums. From Figure 4.26, we found there is a spike in the tumor surface due to massively increased scattering properties. And the radiation force is attenuated quickly after 25mm in tumor . This result is matched well with the actual situation.

4.8 Duration of pulse simulation

Simulation conditions:

Aperture:	48 elements
Center frequency:	8MHz
Focus:	25 mm
Pressure U0:	1 MPa
Medium:	Tissue

Table 4.8 Pulse duration effects radiation force ,energy and temperature in focus

	10cycles	**12 cycles**	**14cycles**	**16cycles**
Radiation force	6.06e5	6.05e5	6.1e5	6.16e5
Energy	2.73e-4	3.25e-4	3.8e-4	4.4e-4
Temperature	2.22e-4	2.66e-4	3.13e-4	3.6e-4

From table 4.8, we found with the increment of pulse duration, comparing with the increment of radiation force ,the energy and temperature is increased much.

4.9 Element impedance measurement results

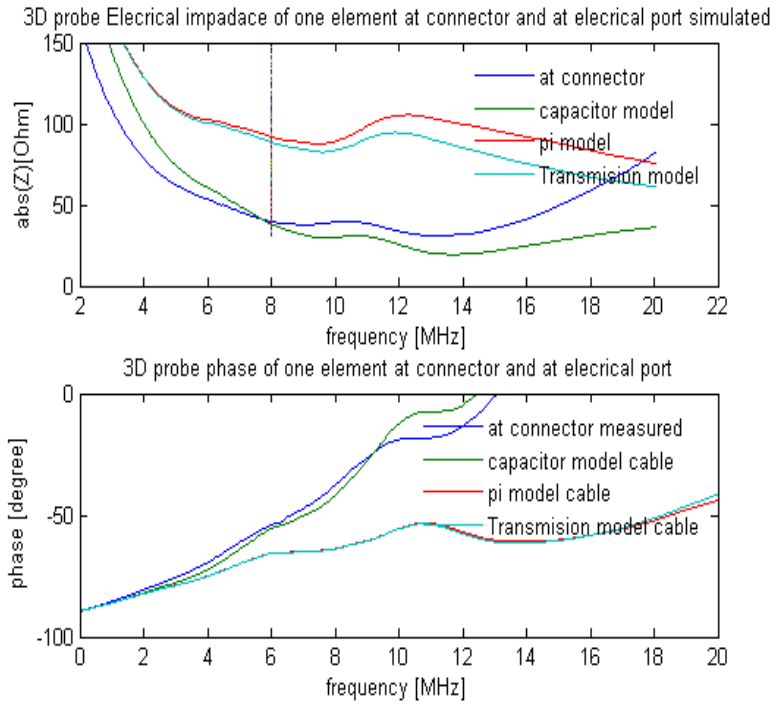


Figure 4.27 Transducer element impedance simulation results

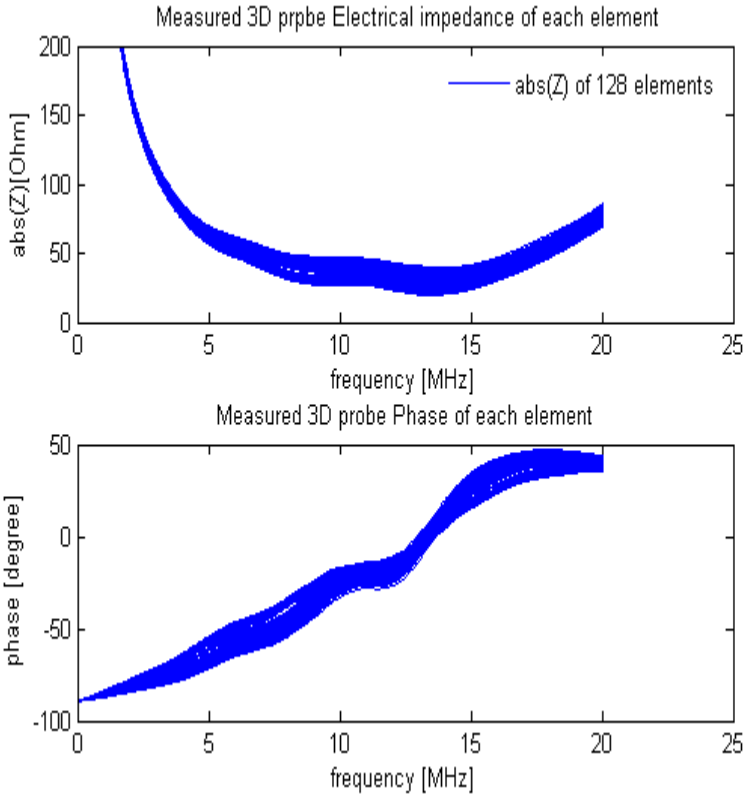


Figure 4.28 Transducer element impedance measurement results

Simulation and measurement for the transducer impedance were done with connector model, capacitor model, pi model and transmission model. The impedance of connector and capacitor model are similar, at 8MHz is $50\,\Omega\ \angle -30°$. The impedance of pi model and transmission model are similar, at 8MHz is $95\Omega\angle -60°$. The difference between these two groups is due to the large reflection coefficient induced by the pi model and transmission model.

Figure 4.28 is measurement for transducer each element. All the elements impedance at 8MHz are fitting in $50\Omega\angle -30°$. It shows that the connector and capacitor model are similar, The impedance result of connector and capacitor model is used for calculation efficiency.

4.10 Transducer efficiency measurement

Based on the impedance measurement results in 4.9, and use the formula (3.32), $\eta(\omega)=\dfrac{P(\omega)\left|Z_{el}(\omega)\right|}{\omega_s\theta_{el}(\omega)V_{tt}{}^2(\omega).Z_0}$, we calculated out the efficiency of transducer as shown in Figure 4.29 .

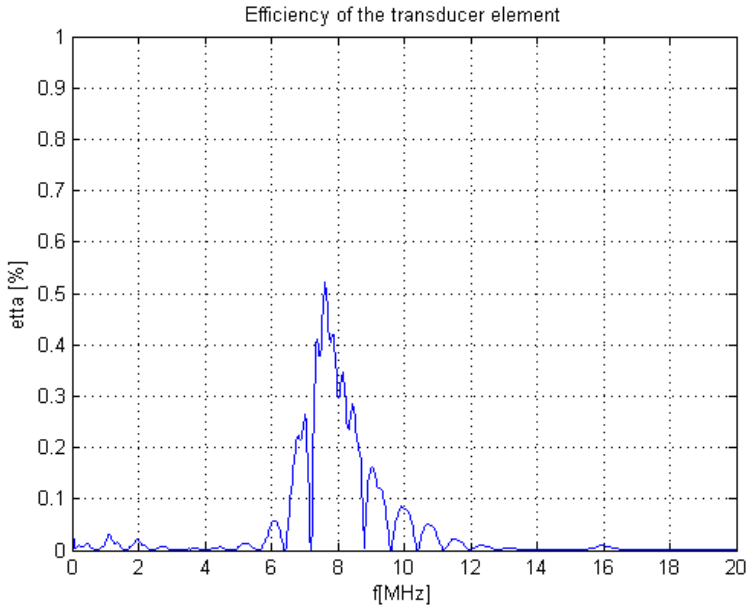


Figure4. 29 transducer elements efficiency measurement

We could see the efficiency is really low. The maximum efficiency appears at 7.75MHz. At 8MHz the efficiency is 0.31%.It is too low efficiency due to the transducer is a low intensity imaging transducer.

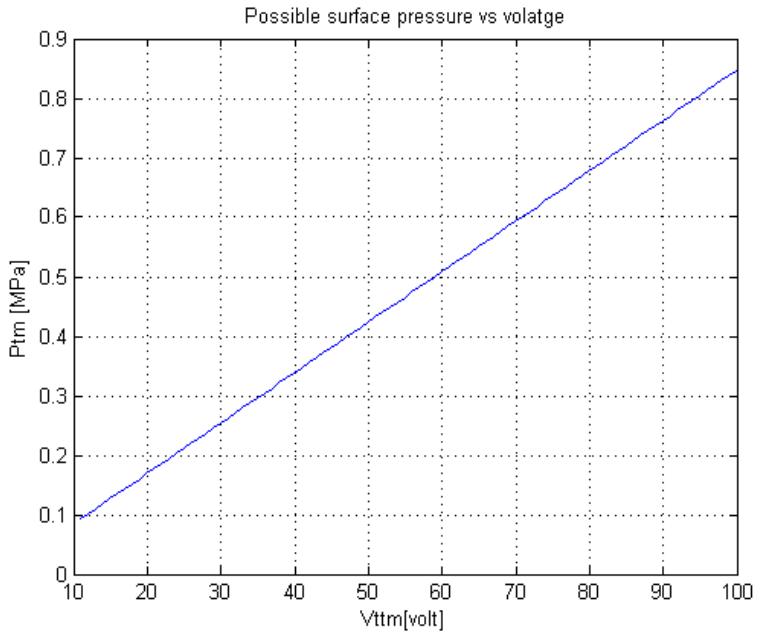


Figure 4.30 Transducer surface pressure vs different input voltage

The ultrasound pressure on transducer with different input power (represented by voltage in figure) were measured. As we see in figure 4.30, the pressure increased almost linearly with input power.

4.11 Transducer thermal properties measurement

Measurement conditions:

Aperture:	48 elements
Center frequency:	8MHz
Focus:	25 mm
Pressure U0:	1 MPa
Medium:	Tissue

Thermal property is very important for the transducer that is used in drug delivery. In this experiment, we need to gain the 25 $^{\circ}C$ increase in 10 minutes. The measurement is to investigate how to predict the temperature increment. The three main factors that affect temperature is pulse length, duty cycle and input voltage. But on the other hand, too high temperature will damage the matching layer (see figure 2.2) or even to the piezoelectric element and also lead to the destruction of the transducer. So in the measurement we control the temperature below 60 $^{\circ}C$.

The temperature measurements were carried on 8MHz pulse sequence, full aperture 38.4mm*5mm(128 elements) .The probe Ultrasonix 4DL14-5/38 was controlled by Ultrasonix SonixMDP ultrasound scanner. Input voltages were monitored by an oscilloscope.

Temperature sensor were contacted on the transducer surface and transducer body.The temperature from the two sensor could read and record through a temperature meter.

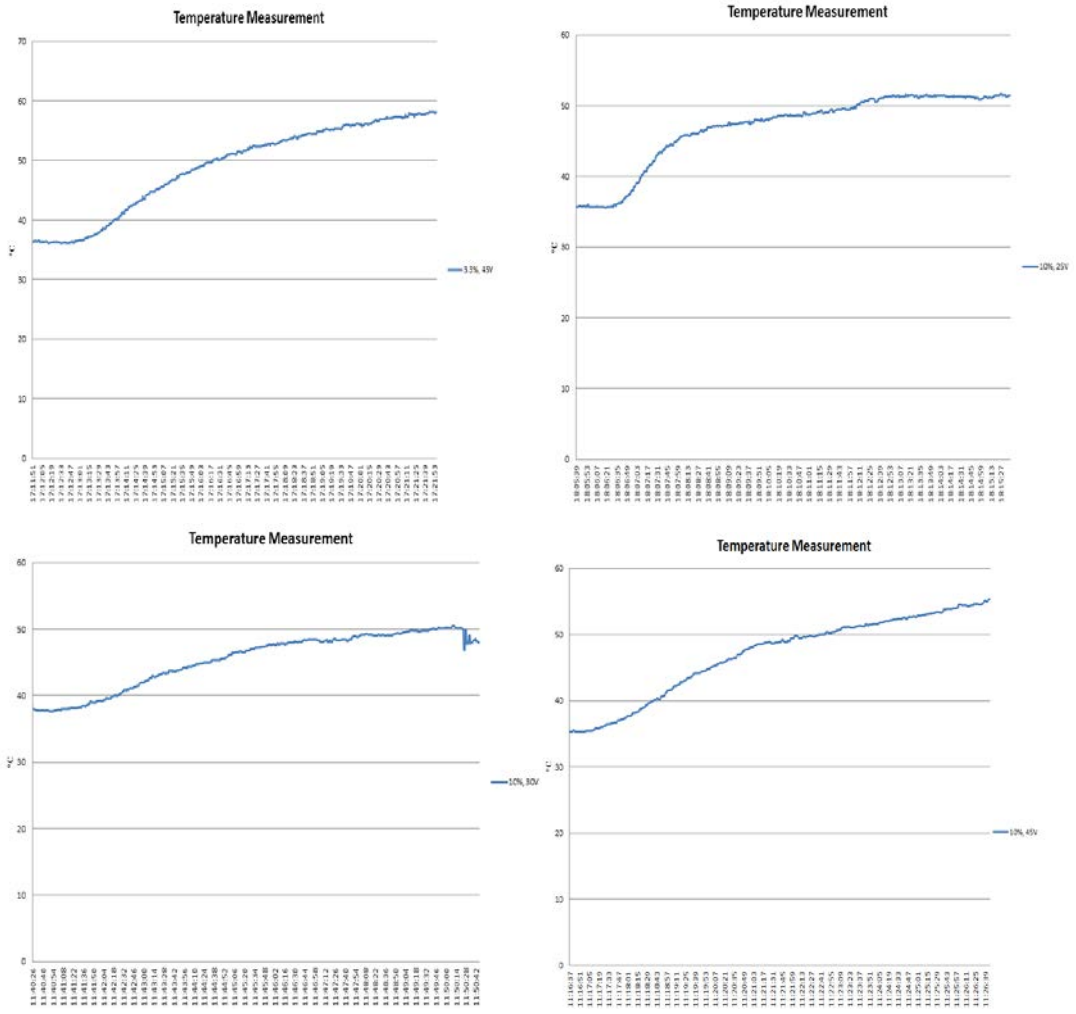


Figure 4.31 Transducer temperature measurement in ten minutes

Figure 4.31 is the transducer heating measurement results. $T_r = 1/PRF = 60us$ was used in four measurements, duty cycle are 3.5%,10%,10%,10% individually and the input voltage are 45V,25V,30V,45V respectively. After about 5 minutes the transducer will be in the steady state. If the voltage is 45V, even the duty cycle is only 3.3%, the temperature is easily to increase $25\,°C$ .So we could say that the main factor to effect the temperature increasing is input voltage.

We also did temperature camera measurement for the transducer in these conditions:

Measurement conditions:

Aperture:	48 elements
Center frequency:	8MHz
Focus:	25 mm
Pressure U0:	0.15 MPa
Pulse length:	10
Input voltage:	18V
PRF:	10KHz

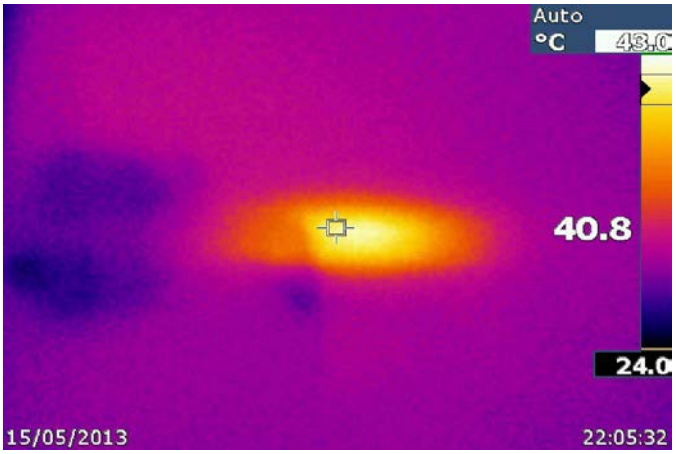


Figure4.32 Transducer thermal image [17]

From the figure 4.32, we see the 48 element active area is in the highest temperature. Simultaneously, the heating spread quickly to the peripheral area due to the elements have good thermal conductivity. This imaging is taken 1 minute after the power excitation. The temperature is increased to $43\,°C$ in the middle of active area and $40.8\,°C$ in the peripheral area. The left cool area is caused by a thermocouple sensor attached on the transducer. After 10 minutes, the active temperature reached to $52\,°C$ [17].

From the measurement of the transducer thermal property, we know the transducer has a thermal limitation due to the structure and material of the elements. The thermal limitation is temperature threshold. Simultaneously, the temperature of the transducer will be in stable after few minutes electronic excitation. The input voltage is

the main factor that can accelerate the temperature increasing. Duty cycle has no obviously contribution to temperature increasing.

4.12 The final experiment set

Based on the measurement and simulation results, we consider overall the factors, such as center frequency ,transducer thermal limitation, beamwidth, radiation force and so on, then the final experiment conditions are decided .see table 4.9

Table 4.9 Animal experiment conditions decision

Center frequency	8MHz
Aperture	14.4mm*5mm(48 elements)
Pulse length	10cycle
PRF	10KHz
Input Voltage	18V
Pressure	0.15MPa
Duration of exposure	10minutes
Focus	25mm…30mm

Chapter 5 Mice Experiments

5.1 Experiment set and process

In order to implement the experiment, prostate tumors were implanted prostate tumor on mice which were 6 days old. After 45 days, the tumors grew in size approximately 10mm*5mm*3mm.

Based on the simulation, calculation and measurement results described in chapter 4, we paid more attention on transducer thermal limitation and did some tradeoffs. A final experiment conditions were decided as it was shown in table4.3.

In order to ensure the chemotherapy quality on tumor, we control transducer 4DL14-5/38 worked in five focuses sequentially. It guaranteed that the tumor was scanned sufficiently.

The transducer Ultrasonix 4DL14-5/38 probe was driven by the Ultrasonix SonixMDP ultrasound scanner. An oscilloscope was used to monitor the input voltage .The transducer is mounted on a table and the transducer head facing towards a glover filled with water. The tumor is set in the focus of the transducer. Transducer is slightly adjustable with moving the clips.

The experiment setup is shown below.

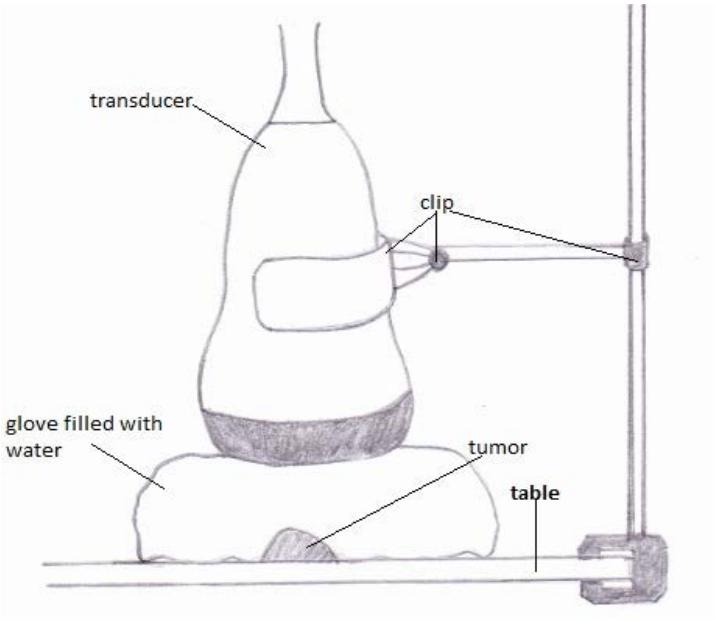


Figure 5.1 experiment setup

The mice tumor is set in focus. The interfaces between transducer and plastic glove, glove and tumor are filled with ultrasound gel. The gel is coupling medium that allows ultrasonic energy waves to travel freely among transducer head, glove and tumor skin. We adjust the clip to control the transducer position and make sure the tumor is in transducer focus.

The mouse was anesthetized after ten minutes and then the tumor is placed in the transducer focus. Transducer is slightly adjustable. At the same time, we get the imaging of the tumor from Ultrasonix SonixMDP. Through imaging we detected tumor and made sure that the tumor is in the focus, see the figure below. Then we locked the clip.

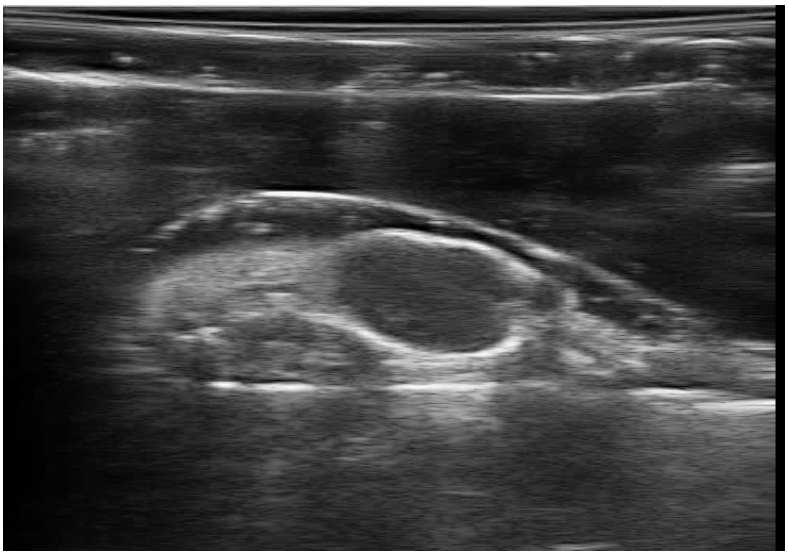


Figure 5.2 Tumor imaging from Ultrasonix SonixMDP

Afterwards, we input table 4.3 parameters in radiation force driving software USRF[2] and started 10 minutes therapy exposure on the tumor.

Table 5.1 Overview of experimental animals:

Mouse No	Administration	FITC
192	200ulDox+UF	100ul
193	200ulDox+UF	100ul
194	200ulDox+UF	100ul
197	200ul np+UF	100ul
198	200ul np+UF	100ul
201	200ul np+UF	100ul
202	Temperature	100ul

where

Dox: doxorubicin, a cytotoxic drug that is also fluorescent.

UR: Ultrasound radiation force

np : nanoparticles developed by Sintef

FITC: Fluorescin Isothiocyanate

Mouse 202 is used for measuring tumor temperature increasing caused by US exposure. The start temperature is measured before US exposure and the end temperature is measured immediately after the US exposure. In this experiment, the start temperature and the end temperature are in the same. Our analysis assume that the blood circulation make the temperature into balance with body.

After US exposure, mouse was killed. The prostate tumor was excised from mouse and embedded in OTC and froze in liquid N2 (-194.C). The frozen sections with a thickness of 5 um will be mounted on glass slide for microscopy observation.

5.2 Experiment results

The tumor sections were observed in microscope. The section imagings we got currently are shown below.

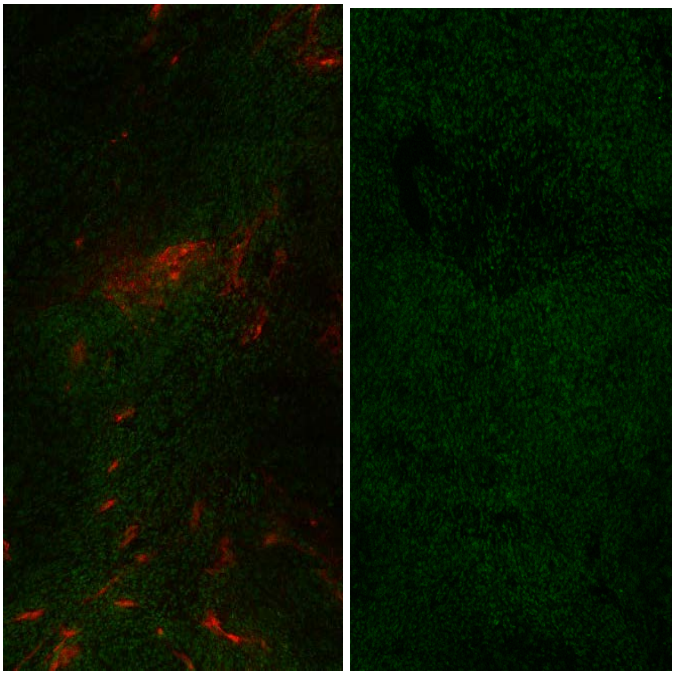


Figure5.3 Dox without US and Dox with UR

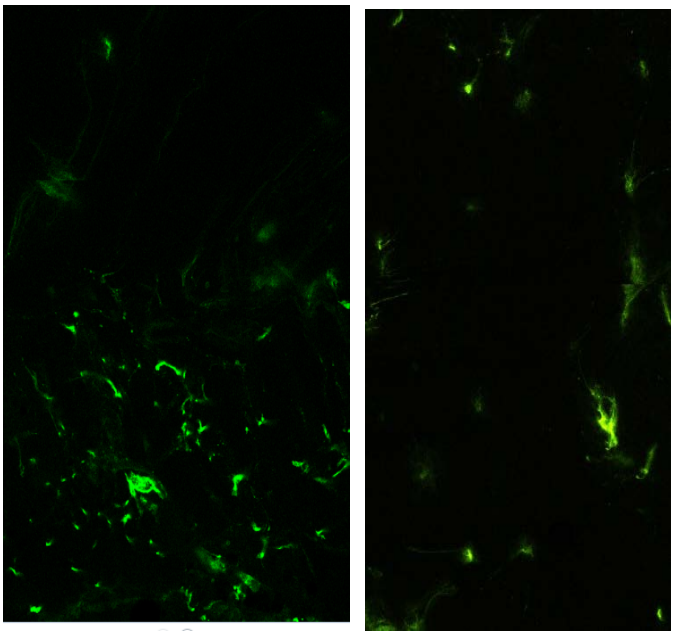


Figure5.4 NP without US and NP with UR

Where

Dox: Doxorubicin

NP: Nanoparticles

US: Ultrasound

Figure 5.3 are two doxorubicin images without ultrasound radiation force and with ultrasound radiation force. The doxorubicin are green spots distributed in the tissue. It means the drug is taken up by the tumor cells. The red lines are blood vessels.

Figure 5.4 are two nanoparticles images without ultrasound radiation force and with ultrasound radiation force. The particles contain fluorescent, so the green glitter material are nanoparticles.

Because of the time limitation, we cannot measure the concentration of drug in tumor, so difficult to see the ultrasound radiation force effect on the tumor.

Chapter 6 Conclusion

Ultrasound transducer is the important component in ultrasound radiation force transport drug in tumor. In order to get high radiation force or intensity in focus, center frequency, beamwidth, aperture size need to be optimized. Especially the beamwidth is a rather important parameter. The radiation force and intensity are inversely proportional to beamwidth, so in order to get narrow beamwidth, we can increase aperture size, center frequency and shorten focus. The pulse length, PRF are also key parameters related with focus energy and temperature, So they also were optimized and chosen before application. Transducer energy conversion efficiency determines the input power. Input power option is related with the transducer thermal limitation. So thermal limitation measurement has done before inputting power.

From experiment application, we found the simulation and measurement results match very well with the actual transducer situation.

Chapter 7 Future Work

Of course, the research of ultrasound radiation force for drug delivery in tumor has started many years, and have gotten much progress, and we hope this work will continue.

Up to now, the amount of radiation force or intensity amount effecting on tumor which “push” the drug into the tumor cells without burning off the cells is not precisely in our study. We need a way to estimate how large the ultrasound radiation force or intensity should be applied to different tumors. From this point, an accurate model of tumor might be necessary. This requires more experiments to understand the physics relation between ultrasound and tumor membrane mechanical properties. On the other hand, a high radiation force or intensity and high efficiency transducer is needed in future study.

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