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RESEARCH PAPER

Numerical Study of the Use of High Intensity Focused Ultrasound in Termo-Ablation of Liver Tumors in a Multilayer Tissue Model

Mansour Rafeeyan [a,*], Seyed Mehdi Shafaatia [a], Reza Roohi[b]

[a] *Mechanical Engineering Department, Yazd University, Yazd, Iran.*
[b] *Mechanical Engineering Department, Fasa University, Fasa, Iran.*

Abstract

The high intensity focused ultrasound (HIFU) has been proved to be effective in local tumor ablation. Although HIFU utilization in ablation of liver cancer with single layer simulation is studied before, the procedure multi-layer numerical simulation, to the best of author knowledge, has not been conducted. In the present study, computational modeling of the HIFU with multi-layer simulation was carried out to determine the treatment effectiveness. The homogeneous Westervelt equation and bio-heat Pennes equation are solved by COMSOL software to determine the acoustic pressure and temperature distribution respectively. The results show that increasing the transducer frequency by keeping other parameters constant would increase the maximum acoustic pressure and the pressure increase depends on the square of the frequency increase. Also, the maximum tissue temperature increases intensely with respect to the frequency increase. The effect of changing the amplitude of the ultrasonic transducer, the duration of the wave radiation and considering multi-layer tissue were investigated. Amplitude change directly changes the maximum pressure and the maximum temperature increase depends on the square of the amplitude increase.

Keywords: HIFU; Tumor ablation; liver cancer; Multi-layer simulation; Westervelt equation

1. Main text

The high intensity focused ultrasound (HIFU) is a rapidly developing technology for the ablation of tumors. Liver tumor is one of the most common malignancies worldwide. When an ultrasound beam passes through a volume of tissue, some of the energy of the primary acoustic field is absorbed locally by the tissue and turned into heat. It results in a temperature rise whose magnitude is a function of the physical properties of the medium, ultrasound device and the frequency and intensity of the acoustic field. Since the tissue between the HIFU transducer and the liver consists of skin, fat and muscle and they have different properties, this article intends to provide a more accurate and complete simulation considering them.

Liver is a part of the digestive system that helps the body absorb, store and use the nutrients in food. Toxins, such as those found in alcohol or drugs, are also excreted from the blood by the liver, making them harmless or directing them to the waste stream to leave the body. Cancer develops when the cells that grow abnormally and out of control, spread to surrounding tissues and kill healthy cells.

Liver cancer is the sixth most common cancer in the world and one of the deadliest gastrointestinal cancers and it is the fourth deadliest cancer since it is detected in advanced stages. Liver cancer is a type of cancer that originates in the liver or spreads elsewhere in the body [1].

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[*] Corresponding author. Tel.: +983531232498, *E-mail address:* rafeeyan@yazd.ac.ir

Liver cancer is divided into two main categories:

Primary liver cancer: This type of cancer starts in the liver. Hepatocellular carcinoma (HCC) accounts for approximately 90% of primary liver cancer with steadily rising incidence globally [2, 3].

Secondary liver cancer (metastatic): This type of cancer spreads to another part of the body. Secondary liver cancers are named and treated based on where they started. Metastatic liver cancer (MLC) is more prevalent than primary liver cancer (PLC) but no less harmful. For example, pancreatic cancer that has spread (metastasized) to the liver is called "pancreatic cancer that has spread to the liver" and is treated like pancreatic cancer [4, 5].

Treatment of liver cancer depends on how much the liver is affected and whether the cancer is primary or secondary. Specialists are considering all available treatment options for a variety of liver cancers, the most common of which are surgery, chemotherapy and radiotherapy. Each of these methods has its own limitations and side effects [6-9].

Surgery can be used when the tumor is confined to an area of tissue. If the tumor spreads to different organs of the body, it becomes impossible to use surgery. Chemotherapy is a non-invasive procedure, but because the drugs do not reach the tumor well enough and affect healthy middle tissues, there are usually many side effects. Many such as hypersensitivity to infection, infertility, hair loss, anemia, fatigue, nausea and vomiting. Radiotherapy is also a non-invasive method, but this method, in addition to tumor tissue, also affects healthy middle tissues. Therefore, this method can't be used in the treatment of deep tumors [10].

One of the new non-invasive methods in the treatment of cancer is hyperthermia. Hyperthermia is a treatment condition in which the temperature of tumor tissues is controlled, from 37 ° C, which is the normal temperature of the body, to temperatures above from 40 ° C to 43 ° C. In these conditions, tumor tissue is destroyed by different mechanisms, depending on temperature and other tissue conditions. Hyperthermia can be caused in several ways, including microwaves, radiofrequencies, lasers and ultrasound [11].

One of the advantages of ultrasound waves over other waves is their focal nature. In high-intensity focused ultrasound (HIFU), concave transducers are used to concentrate the waves in a specific area to raise its temperature. The therapeutic function of HIFU is simply shown in Figure 1. In a concentrated ultrasound field, the acoustic intensity near the transducer is kept low enough so that the adjacent tissue is not damaged. In the focal region, the intensity is much higher and the absorption of the acoustic field is so high that it changes the structure of tissue proteins.

An ideal treatment method has the following characteristics [12, 13]:

- Recovery time is very short.
- The patient feels the least pain.
- It should specifically only damage the tumor and not damage healthy intermediate tissues.
- To be done in a short time.
- Have the least bleeding.

HIFU method has all the above features. This method, unlike other methods, is also suitable for deep tumors. The main goal of HIFU treatment is to use high intensity focal ultrasound to destroy the cancerous tumor without damaging the middle tissues.

One of the advantages of ultrasound waves over other waves is their focal nature. In high-intensity focused ultrasound, concave transducers are used to concentrate the waves in a specific area to raise its temperature. The therapeutic function of HIFU is simply shown in Figure 1. In a concentrated ultrasound field, the acoustic intensity near the transducer is kept low enough so that the adjacent tissue is not damaged. In the focal region, the intensity is much higher and the absorption of the acoustic field is so high that it changes the structure of tissue proteins.

High intensity focused ultrasound (HIFU) is an emerging, noninvasive ablation procedure that can ablate various solid tumors, including primary and secondary liver cancer. It can focus ultrasound energy on the lesions of interest and induce tumor coagulative necrosis by thermal effect [13].

Langevin was the first to observe that ultrasound has a lethal effect on living tissues. The ability of focused ultrasound to non-inversely damage the targeted tissue deep in the body was first explored by Lynn et al, who tested the ultrasound modality in the brain. After this exploration, many researchers analyzed ultrasound-induced bio effects, and they tested the technique for a large number of applications. The feasibility of HIFU ablations with an extracorporeal device under ultrasound guidance in the liver was demonstrated by Vallancien and coworkers. HIFU uses focused ultrasound at high intensities, allowing the deposition of sufficient energy to cause a well-demarcated volume of coagulation necrosis, independent of soft tissue type, first described in 1994 [14].

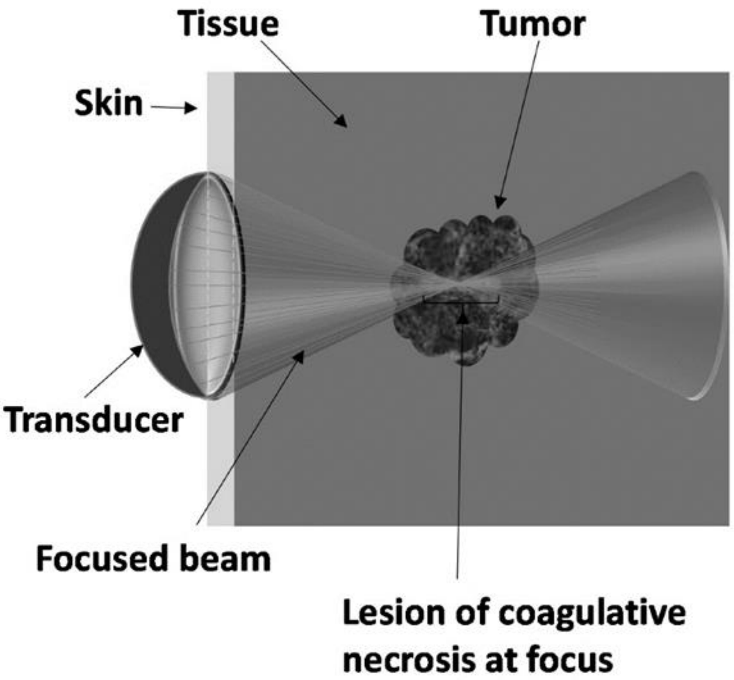


Figure 1- Application of HIFU in tumor necrosis without damaging the tissues in the wave path [12]

The first larger clinical studies were conducted by Wu and colleagues using ultrasound imaging with a JC ablation device between 1999 and 2004 [15].

Wu et al. used an analytical solution based on a linear theory to model the focused Gaussian beam and to calculate the temperature distribution that is generated in a two-layered medium [16]

Curra et al. investigated the effect of blood flow on heat generation in the use of HIFU in the treatment of liver tissue cancer [17]. Based on the results, it was shown that the heat transfer of blood vessel convection causes the highest temperature in the direction of blood flow.

Hariharan et al. studied the effect of a large blood vessel on the effect of HIFU treatment using a three-dimensional computational model and showed when a blood vessel is affected by a beam of ultrasound wave the lesion is significantly treated [18].

Sheu et al. studied a three-dimensional acoustic fluid model for estimating tumor temperature in liver tissue exposed to HIFU using the linear form of Westervelt equation. The results showed that HIFU changes the characteristics of blood flow in the arterial branches of the liver [19].

Solovchuk et al. studied HIFU liver tumor treatment using nonlinear Westervelt equation. The results showed that the sound current has a significant effect on the temperature of the venous wall with a diameter of 3 mm. Solovchuk et al. conducted another study to predict the temperature distribution in near-vascular liver tumors. Based on the results, it was shown that the speed of ultrasound waves is greater than blood flow velocity in vessels with a diameter of 7 mm and as a result, HIFU can be effective in destroying liver tumors [20].

Mohammadpour et al. studied the cooling effect of the vascular bed from simple geometry includes the terminal arterial branches. Also, the effect of vascular density on temperature distribution was included [21].

In previous studies, the tissue under the influence of HIFU has been performed on a single layer or two-layered tissue phantom (tissue + water). This study presents a multiple layered tissue model including muscle skin, fat and liver and studies the effect of HIFU on it.

2- Investigating the governing equations of ultrasound waves

To obtain the temperature distribution of the tissue under HIFU radiation, first the wave equation must be solved in the tissue environment to get the acoustic pressure distribution. Then the thermal equation is solved using the results of the solution of the first equation to obtain the temperature distribution. In mathematical modeling of linear wave propagation of this research, the Westervelt equation is used [22]. The Westervelt wave propagation equation is used after removing expressions with greater accuracy than the second order in the momentum equation:

$$\nabla^2 \mathrm{P} - \frac{1}{c_0^2}\frac{\partial^2 \mathrm{P}}{\partial t^2} + \frac{\delta}{c_0^4}\frac{\partial^3 \mathrm{P}}{\partial t^3} + \frac{\beta}{\rho_0 c_0^4}\frac{\partial^2 \mathrm{P}^2}{\partial t^2} = 0 \tag{1}$$

where □ is the dimensionless nonlinear coefficient, P is the acoustic pressure, t is time, c0 is the initial sound velocity, ρ0 is the initial tissue density and δ is the acoustic influence. In Equation (1), the first two terms on the left represent the linear propagation of the wave without loss and the third term indicates the losses due to thermal conductivity and viscosity. The last term indicates the nonlinear acoustics that cause mechanical and thermal changes in the tissue.

For linear modeling, the nonlinear expression in the Westervelt equation is omitted and the linear diffusion equation is obtained as follows:

$$\nabla^2 \mathrm{P} - \frac{1}{\mathrm{C}_0^2}\frac{\partial^2 \mathrm{P}}{\partial \mathrm{t}^2} + \frac{\delta}{\mathrm{C}_0^4}\frac{\partial^3 \mathrm{P}}{\partial \mathrm{t}^3} = 0 \tag{2}$$

The wave intensity is also obtained from the following equation:

$$I = \frac{\mathrm{P}^2}{2\rho \mathrm{c}} \tag{3}$$

In the next step, in order to find the temperature distribution in the tissue and for this purpose the Pennes equation is used [23]:

$$\rho_t C_t \frac{\partial T}{\partial t} = (k_t \nabla^2 T) - \rho_b c_b \omega_b (T - T_a) + Q_m + q \tag{4}$$

In this equation, k_t is the thermal conductivity of the tissue, ω_b is the rate of blood volume passing through the target tissue, c_b is the specific heat capacity of the blood, T is the temperature, T_a is the temperature of the blood inside the tissue, q is the amount of energy transferred into the cancerous tissue, C_t is the specific heat capacity of tissue and ρ_t is the density of cancerous tissue. Q_m is the amount of metabolic heat production or heat generated by the body's metabolism which is obtained from the following equation:

$$Q_m = Q_0 \left(1 + \frac{\mathrm{T} - T_0}{\mathrm{b}}\right) \tag{5}$$

where Q_0 is the metabolic heat production at temperature T_0 and b is the rate of change of heat with temperature [24]. The heat produced in the tissue due to HIFU q is affected by two important parameters; the absorption coefficient of acoustic waves and the wave intensity, which the first is of the intrinsic properties of the tissue and the second is obtained by solving the wave equation. Therefore:

$$q = 2\alpha_{abs} I \tag{6}$$

where α_abs is the wave absorption coefficient by the tissue which is a function of the wave frequency as follows:

$$\alpha = \alpha_0 \left(\frac{f}{f_0}\right)^{\eta} \tag{7}$$

α _0 is the wave absorption coefficient at the frequency f_0 = 1 MHz. η also is a constant coefficient that for soft tissue η = 1.

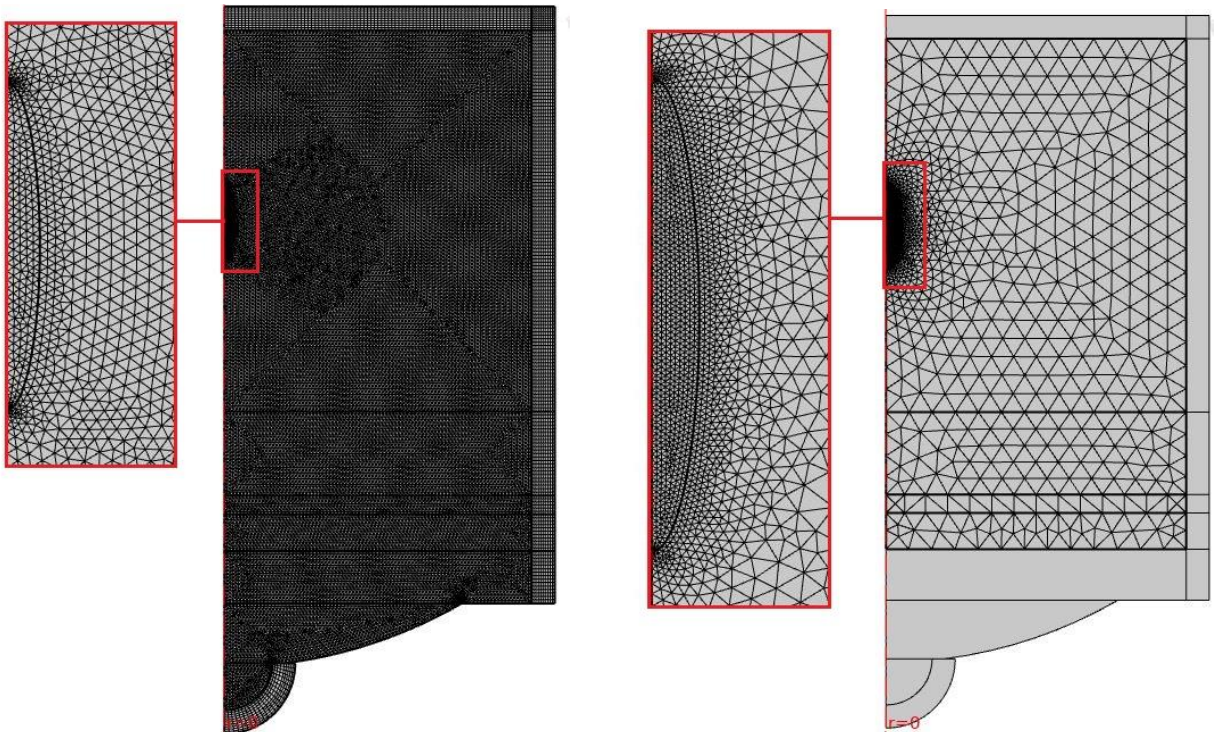
The wave equation is solved in the frequency domain and the heat equation in time domain.

2. Discretization

In this study, the COMSOL Multiphysics is utilized for simulation of HIFU treatment. The tissue is modeled in 2D and acoustic pressure and heat fields are solved to determine the treated region. Two different mesh sizing have been used because two equation are decoupled. The first mesh was created to simulate and solve the wave equation and obtain the acoustic pressure distribution, which consists of finer lattices, and the second lattice was used to solve the Pennes heat equation and determine the temperature distribution. Figure 2 shows an overview of these networks. As it can be seen in the figure, smaller networks have been used in the focal area and larger networks in the side areas.

3. Simulation and solving equations

To simulate and solve the problem of liver tumor ablation, in order to investigate the effect of transducer frequency, transducer amplitude and time, the problem with different values of these parameters are solved and the results will be investigated.



(a) (b)

Figure 2. Computational grids in order to solve a) Wave equation, b) Pennes equation. (In the first case the focus is on the whole geometry, but in the second one grids are more focused on the focal area.)

For this purpose, to investigate the effect of frequency change, by keeping the value of the converter amplitude and time constant, the problem for the frequency value of 1 and 2 MHz was solved. To evaluate the effect of amplitude, values of 3.8 and 7.9 nm and constant values of frequency and time were considered. To investigate the effect of time, the problem was solved for times of 1 second, 30 seconds, 300 seconds and 600 seconds.

It should be noted that in this analysis, a two-dimensional symmetric model is used and according to Figure 3, the body tissue was multilayered and included skin with a thickness of 7.81 mm, fat with a thickness of 4 mm, muscle with a thickness of 17.88 mm and liver to be 85.98 mm thick [23].

By rotating the model around the vertical axis, the geometry becomes a cylinder. Also, the specifications related to different organs of the body are considered according to Table 1.

Table 1- Properties of different layers of tissue [24]

Properties	Skin	fat	Muscle	Liver
Density (kg / m3)	1100	910	1050	1055
Speed of Sound (m / s)	1540	1430	1560	1570
Thermal conductivity (W / m ° C)	0.28	0.24	0.51	0.51
Specific heat capacity (J / kg ° C)	3500	3800	3700	3600

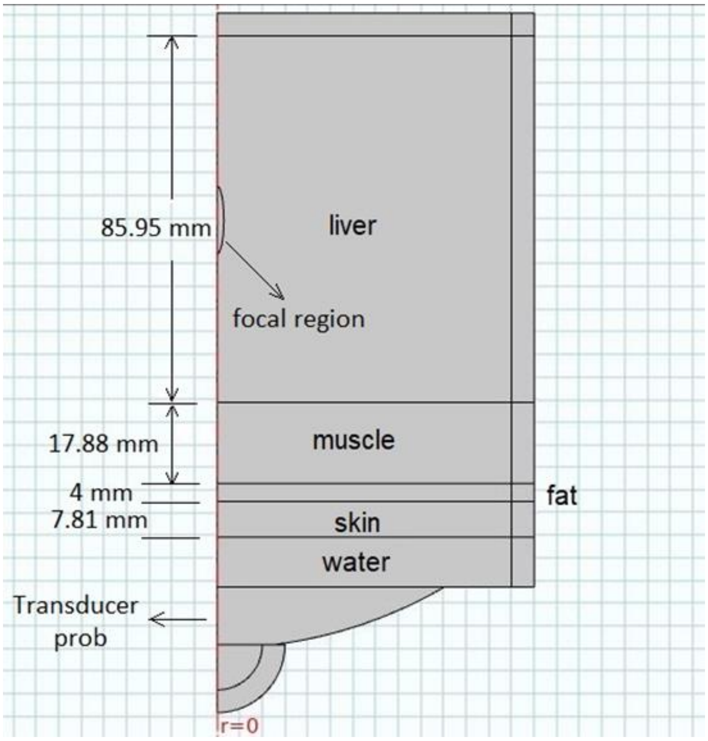


Figure 3 - Physical model with different layers of tissue

4. Results and Discussions

In this section, the results of comparative analysis are presented and using it, the effect of the desired parameters in the problem can be achieved. The results are presented in three sections: The effect of transducer frequency change, transducer amplitude and radiation time. In all these sections, the studied texture is considered as multi-layered and in the last part, the research results are compared with each other by considering single-layer and multi-layer tissue.

5-1- Effect of transducer frequency

In this section, in order to study the effect of the transducer frequency changes, the two results are compared. The frequency range used for tumor ablation is usually between 1 and 4 MHz, and in the research, we have considered the values of 1 and 2 MHz for the frequency of HIFU transducer. In both cases, the heat source is disconnected after one second and the results are recorded up to the fifth second.

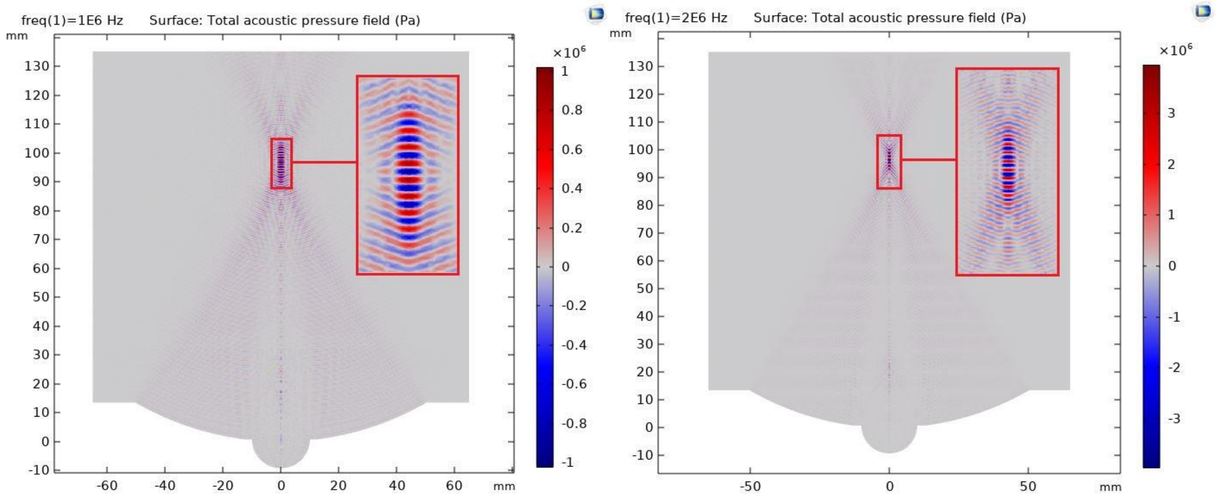
a. Changes in the acoustic pressure distribution

As can be seen in Figures 4, 5 and 6, by doubling the transducer frequency, the maximum acoustic pressure value has quadrupled and the pressure distribution in the focal area has become more concentrated.

As shown in Figure 5, the maximum value of acoustic pressure occurs in the focal region, and with a doubling of the frequency, the maximum value of acoustic pressure quadruples. Figures 7 and 8 also show the distribution of sound waves and the intensity of the acoustic field.

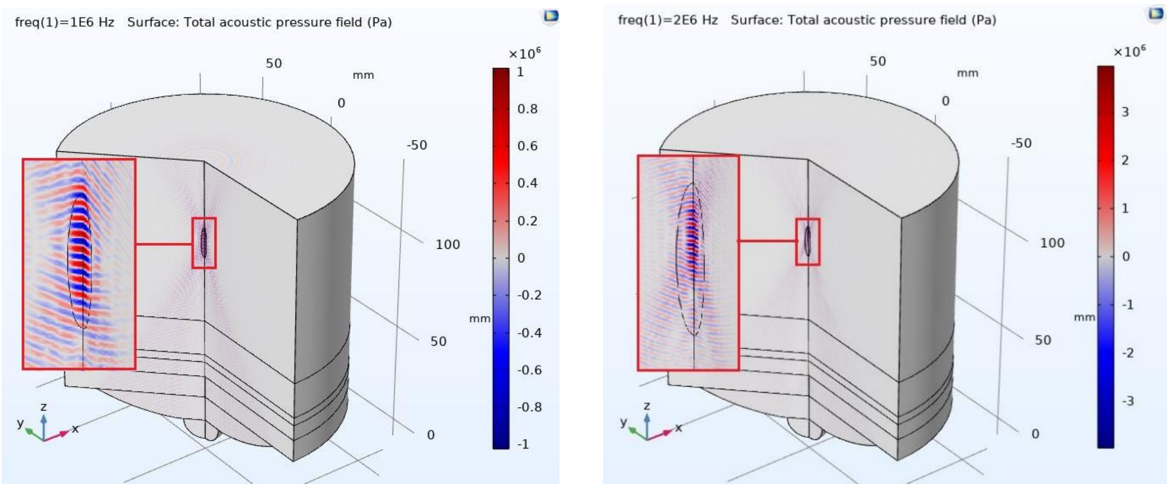
b. Changes in temperature distribution

Temperature rise in two different transducer frequencies are shown in Figures 9 and 10. It can be seen that doubling the transducer frequency has a great effect on increasing the temperature difference and the amount of temperature increase from about one degree to about 9 degrees Celsius. Due to the rise, it is necessary to determine the frequency more carefully to prevent unexpected damage to organs. It can also be found that to determine the extent of tissue damage and control the treatment process, the frequency of the transducer is an effective and determining parameter to distinguish the extent of tissue damage and control of the treatment process. In addition, the desired treatment process can be undertaken by changing it. Also, it can be seen in Figure 10 that by moving away from the focal area by 0.5 mm, the temperature rise is significantly reduced and the side organs of the tumor will not be damaged.



(a) (b)

Figure 4 - Acoustic pressure for (a) 1 MHz frequency (b) 2 MHz frequency



(a) (b)

Figure 5 - Three-dimensional view of acoustic pressure for (a) 1 MHz frequency (b) 2 MHz frequency

5-2- Effect of transducer amplitude

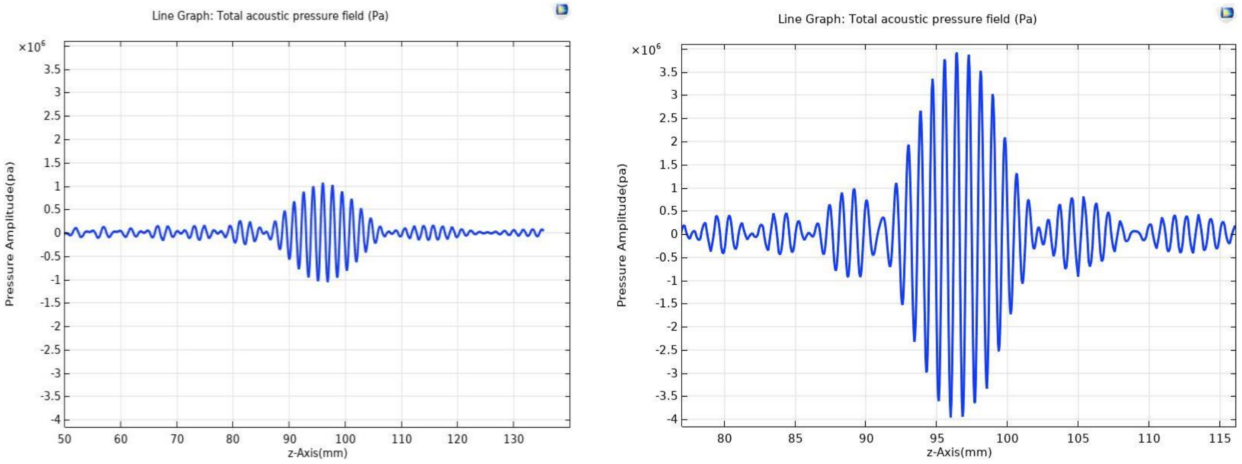
In this section, in order to investigate the effect of the transducer amplitude change on the acoustic pressure distribution as well as the tissue temperature distribution under HIFU radiation, the two results are compared by keeping the value of all parameters constant and changing only the amplitude of the ultrasonic transducer used. In both cases, the heat source was disconnected after one second and the results were recorded up to the fifth second for (a) 1 MHz and (b) 2 MHz frequencies.

a. Changes in acoustic pressure distribution

As shown in Figures 11 and 12, by doubling the amplitude of the transducer oscillation, the maximum acoustic pressure value is almost doubled and also the pressure distribution has not changed significantly.

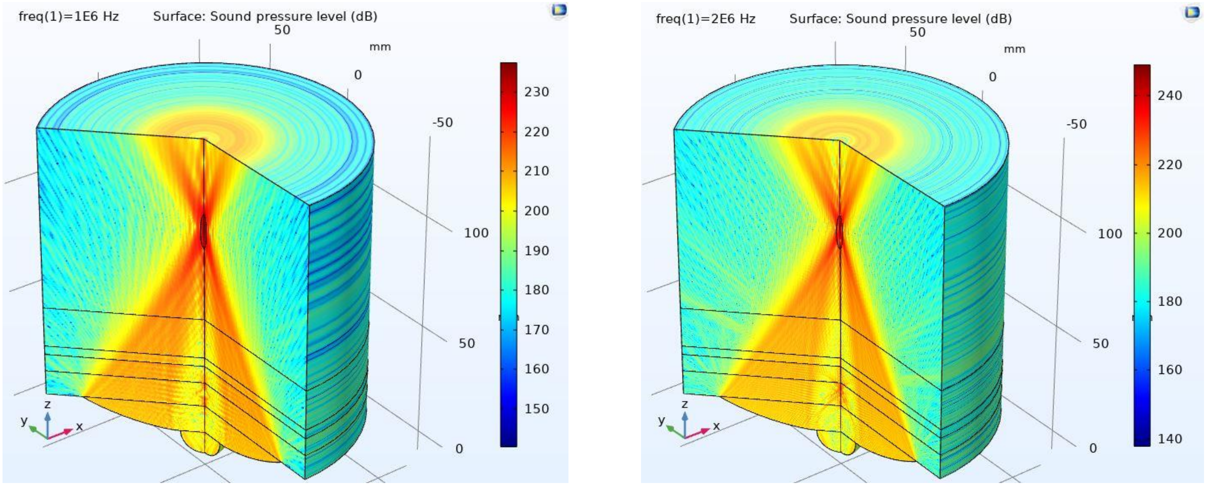
b. Changes in temperature distribution

Examining the results of thermal analysis in Figures 13 and 14, it can be seen that doubling the transducer amplitude has increased the temperature rise from about one degree to about 4 degrees Celsius.



(a) (b)

Figure 6 - Acoustic pressure changes along the vertical axis for (a) 1 MHz frequency (b) 2 MHz frequency



(a) (b)

Figure 7- Distribution of sound pressure level for (a) 1 MHz frequency (b) 2 MHz frequency

5-3- Effect of the treatment time

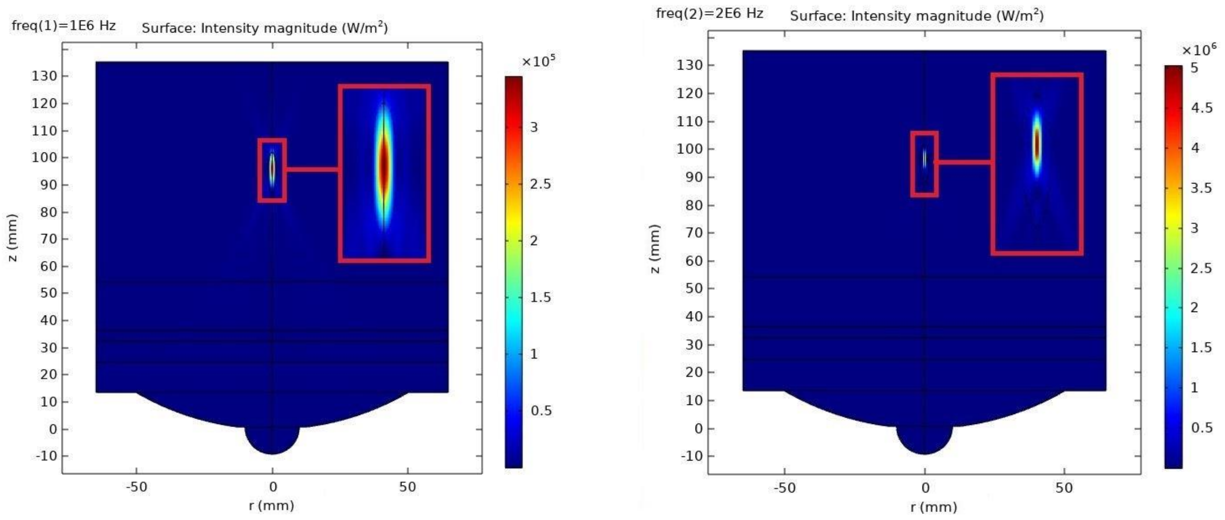
As the radiation time of HIFU waves increases, there is no change in the distribution of acoustic pressure but the temperature increases over time. To investigate the effect of time and find the optimal radiation time, the problem is solved in four radiation times of 1 second, 30 seconds, 300 seconds and 600 seconds and the results are presented in Figures 15 and 16. The frequency in all cases is constant and equal to one megahertz and the oscillation amplitude of the converter is also constant and equal to 3.8 nanometers.

As can be seen, after 5 minutes the temperature increase decreases exponentially and the temperature becomes almost constant, so to reach higher temperatures the frequency or amplitude of the converter should be increased.

5-4- Comparison of results by considering texture as single and multilayer

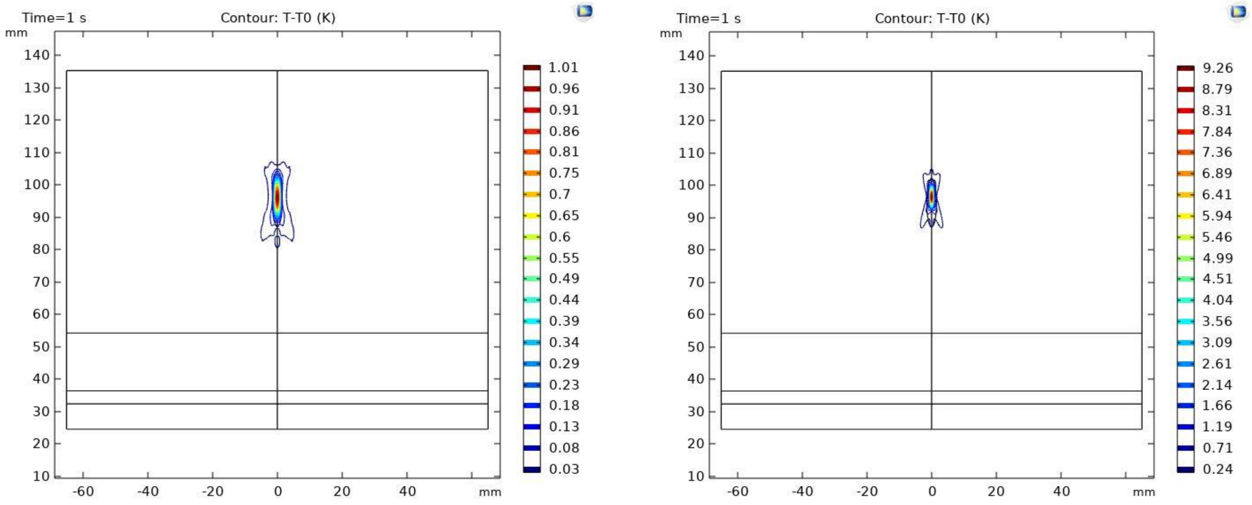
In this section, by comparing the results in two cases, the effect of considering different body layers in the destruction of liver tumor is examined. Figure 17 shows that not considering different tissue layers changes both the size and location of the maximum acoustic pressure. The maximum acoustic pressure varies up to 5% by using single layer model.

Also, by comparing the temperature contour in the focal area, after 30 seconds, it can be seen that the maximum temperature is different in single-layer and multi-layer models (Figures 18 and 19).



(a) (b)

Figure 8- Acoustic intensity field for (a) 1 MHz frequency (b) 2 MHz frequency



(a) (b)

Figure 9 - Temperature rise for (a) 1 MHz frequency (b) 2 MHz frequency

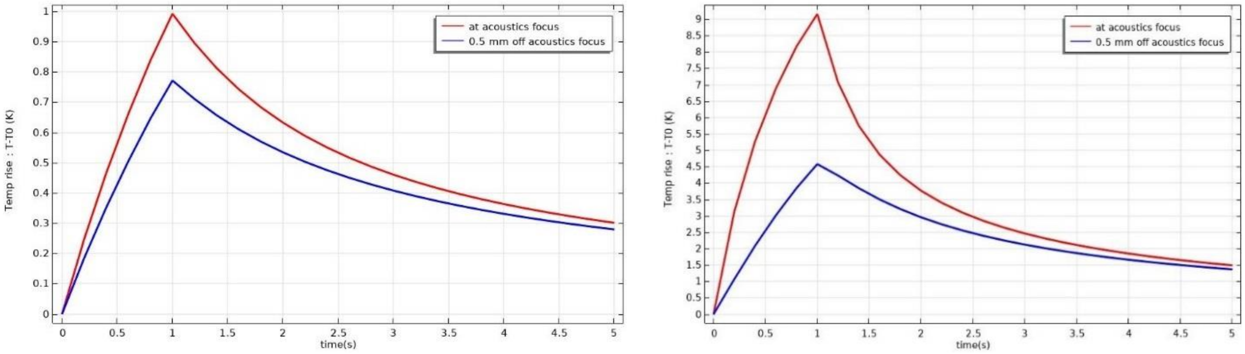
5. Conclusion

In the present study, a HIFU transducer was numerically examined to ablate liver tumor with a multi-layer tissue model. In addition, the Westervelt equation and the Pennes heat transfer equation were solved to obtain the acoustic pressure and the temperature fields. Based on the obtained diagrams and information, the following results can be extracted:

- Increasing the transducer frequency leads to increasing the acoustic pressure in the tissue and this rise is directly related to the second power of the frequency increase. Also, in the increase of acoustic pressure, the maximum amount of temperature in the focal area increases and causes more destruction of tumor tissue.

- The temperature rise will be maximum only in the focal area and with only 0.5 mm away from the focal area, it will be seen a noticeable drop in tissue temperature. Although, it can be assured that HIFU waves will cause a significant increase in temperature in the expected area, only the cancerous tissue will be damaged.

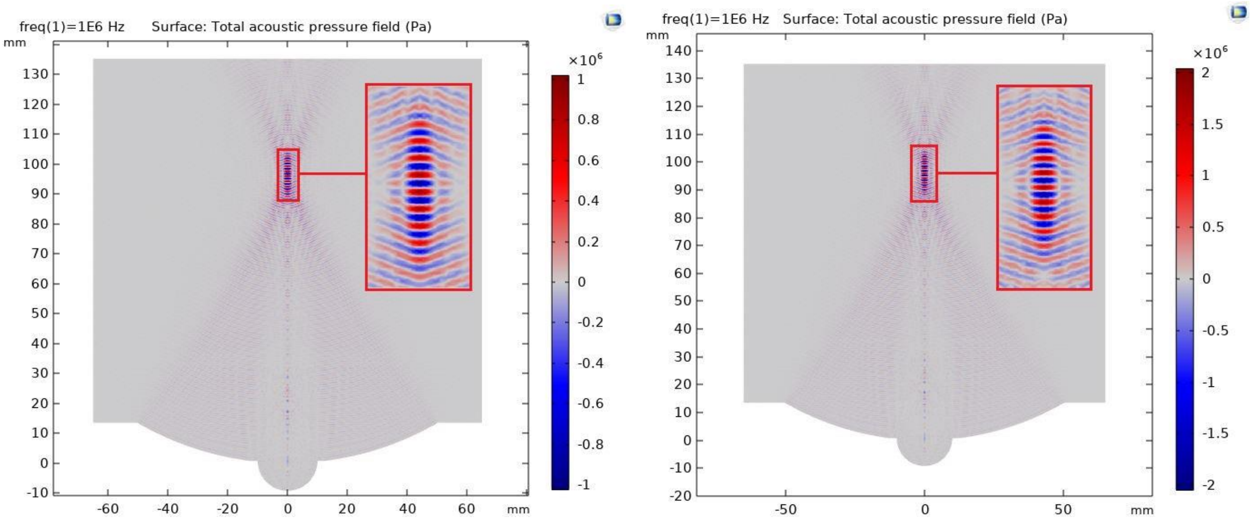
- Increasing the amplitude of the transducer, increases the acoustic pressure in the tissue and this rise is directly related to the increase in frequency. Due to the increase in acoustic pressure, the maximum amount of temperature in the focal area also increases.



(a) (b)

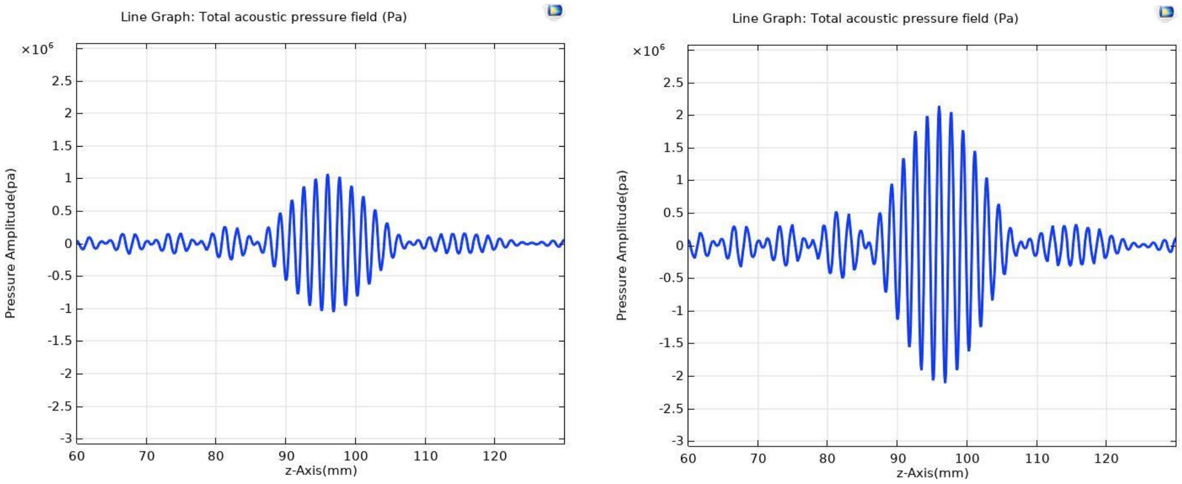
Figure 10 - Temperature rise (T-T$_0$) at two focal points and a point 0.5 mm from the focal point for

(a) 1 MHz frequency (b) 2 MHz frequency



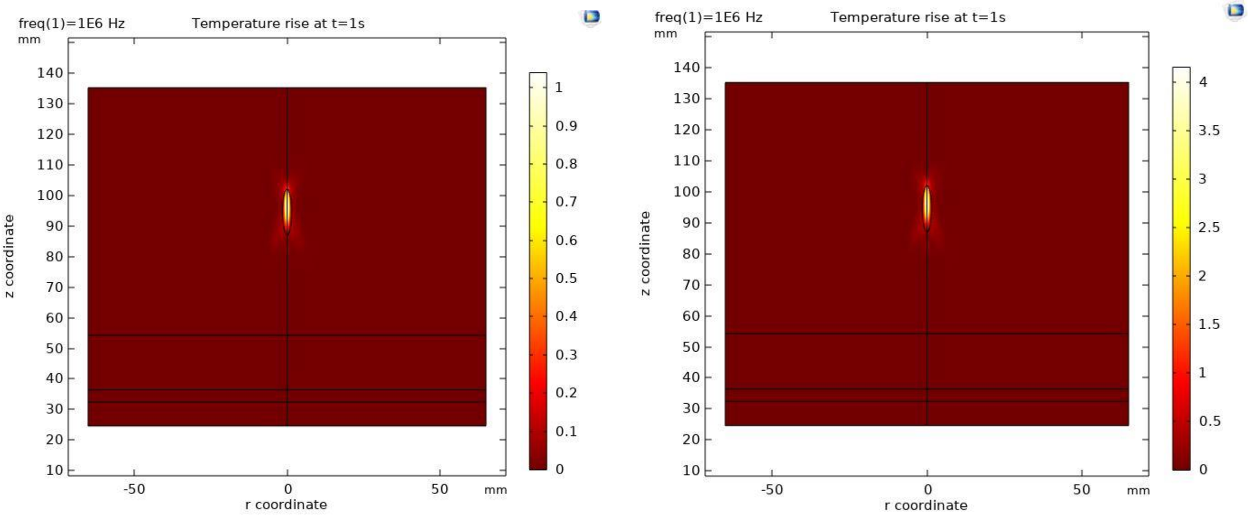
(a) (b)

Figure 11 - Acoustic pressure distribution for (a) 3.8 nm amplitude (b) 7.6 nm amplitude



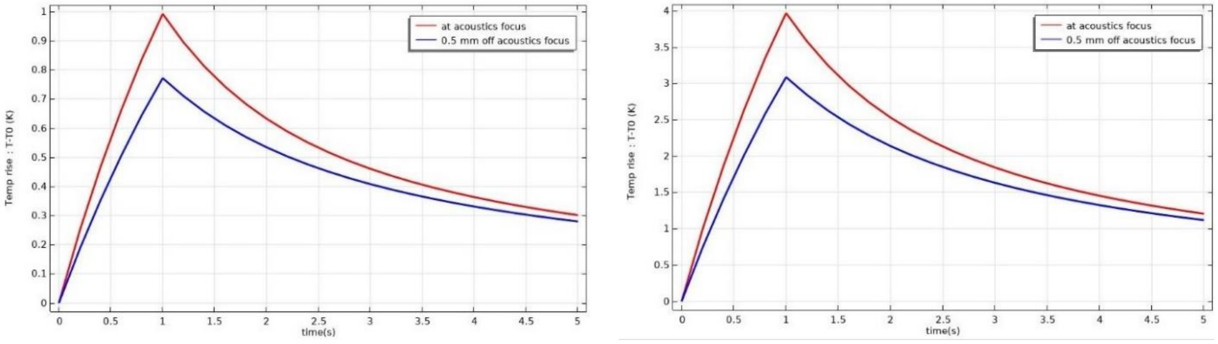
(a) (b)

Figure 12 - Acoustic pressure along the vertical axis for (a) 3.8 nm amplitude (b) 7.6 nm amplitude



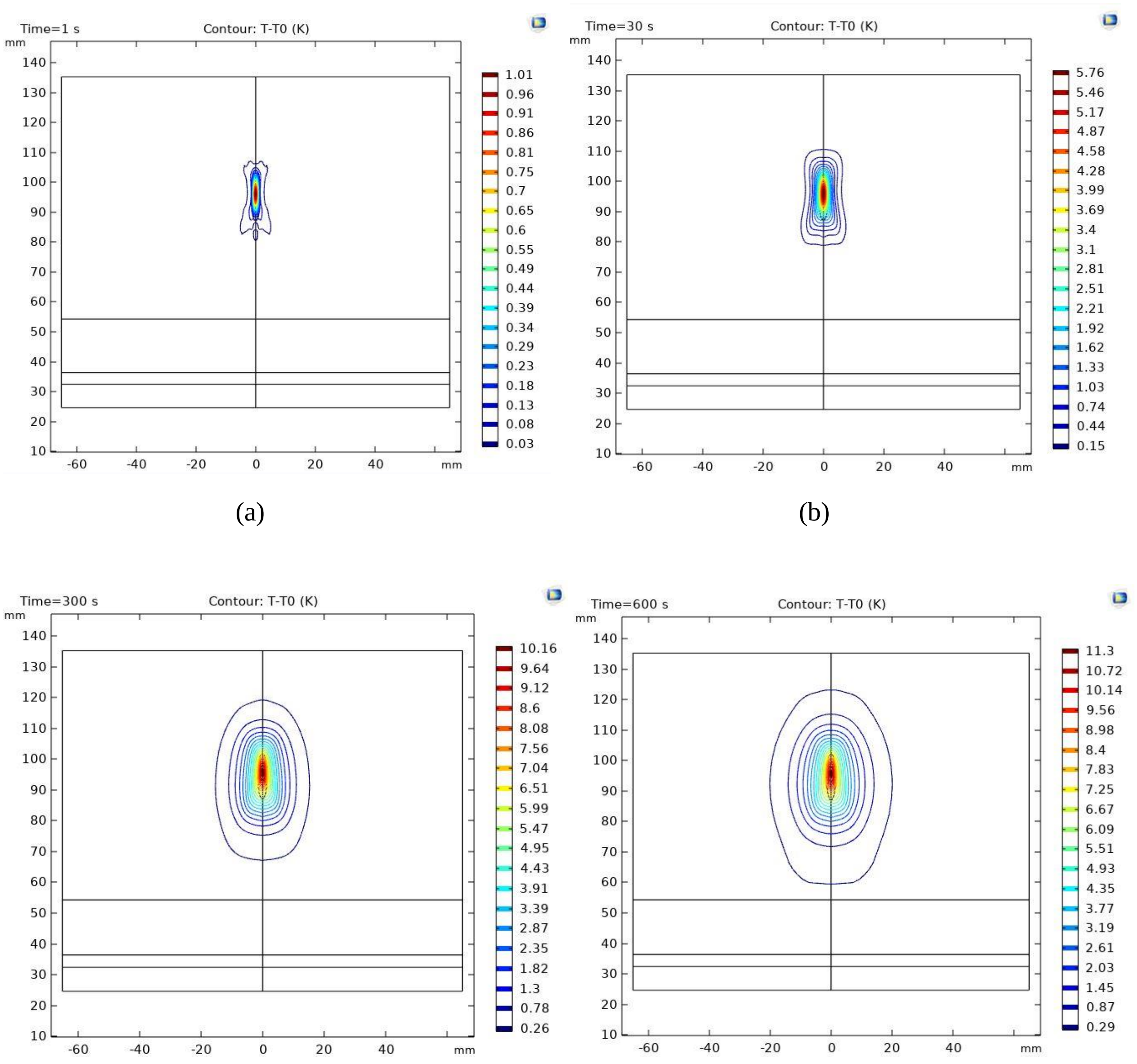
(a) (b)

Figure 13 - Temperature rise for (a) 3.8 nm amplitude (b) 7.6 nm amplitude



(a) (b)

Figure 14 - Temperature rise (T-T$_0$) over time at two focal points and a point 0.5 mm from the focal point for (a) 3.8 nm amplitude (b) 7.6 nm amplitude



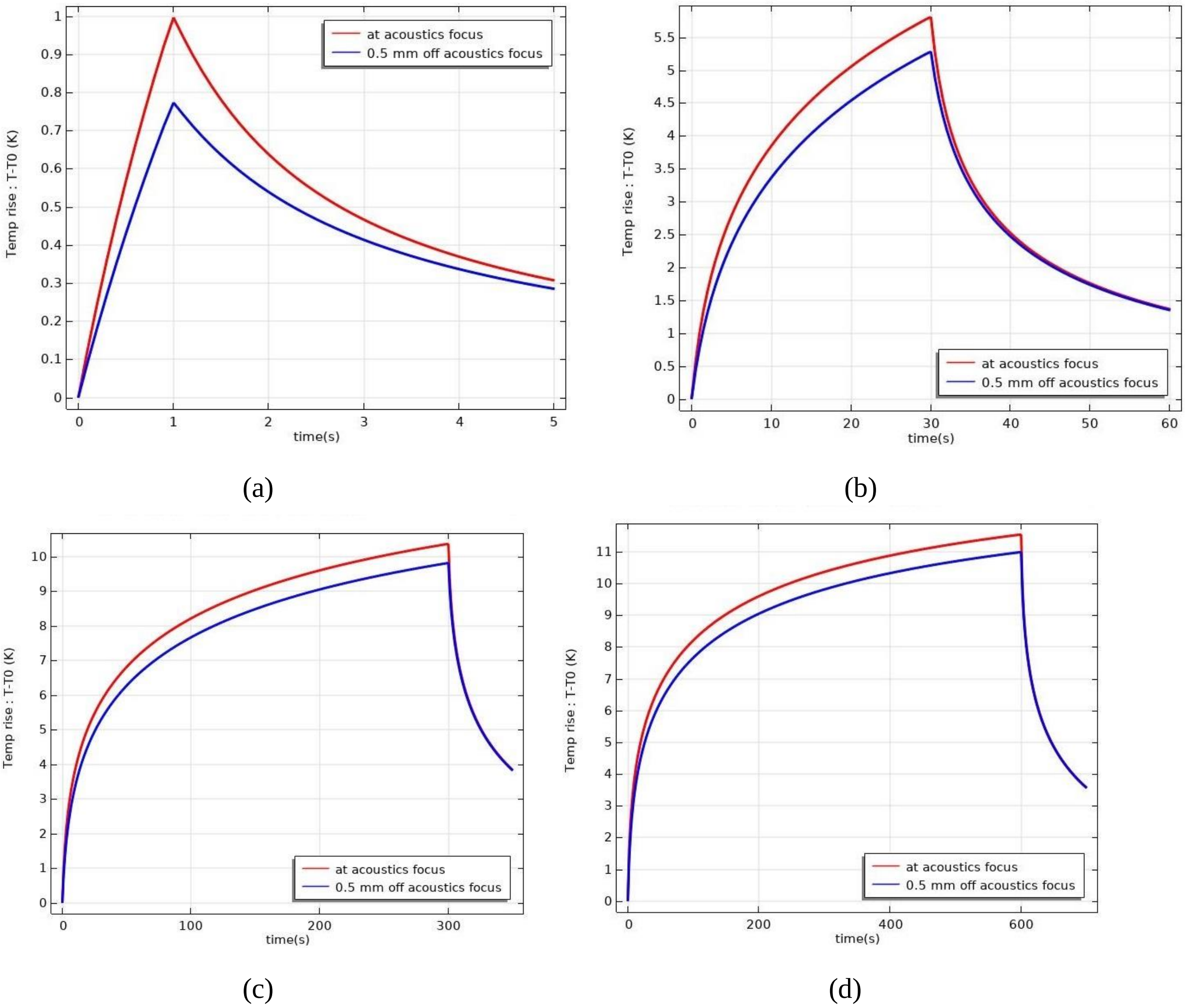
(a) (b)

(c) (d)

Figure 15 - Contour of temperature rise for (a) t =1 s, (b) t = 30 s, (c) t = 300 s, (t) t = 600 s

- There is no change in the distribution of acoustic pressure over time, but the temperature of the tissue irradiated with HIFU waves continues to increase. Simultaneously the temperature distribution becomes smoother.

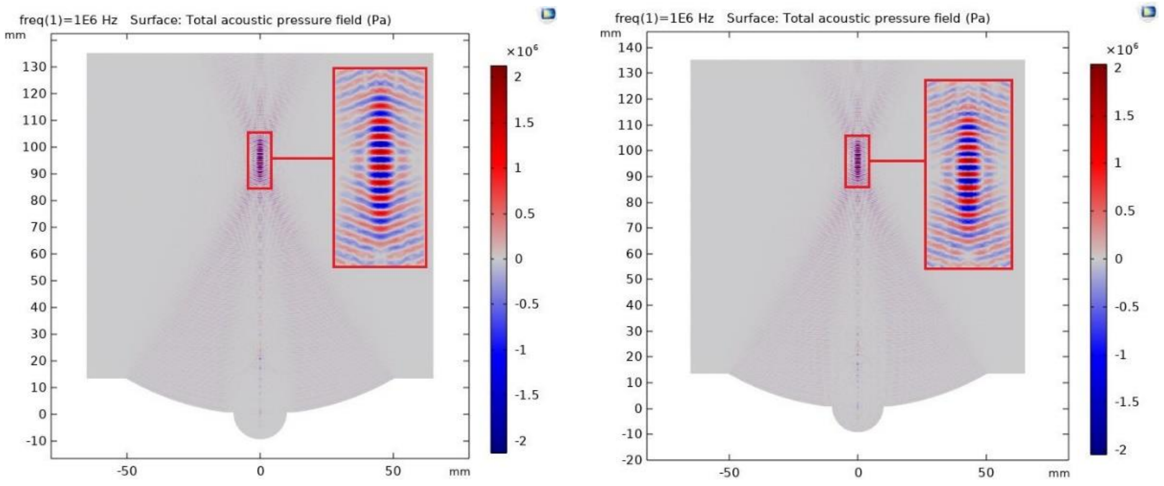
- By considering the exact characteristics of the different layers of the body that are in the path of HIFU waves, the results can be obtained more accurately and realistically. As well as the change in the maximum amount of acoustic pressure, the location of the maximum pressure also shifts slightly. Furthermore, the maximum temperature also changes.



(a) (b)

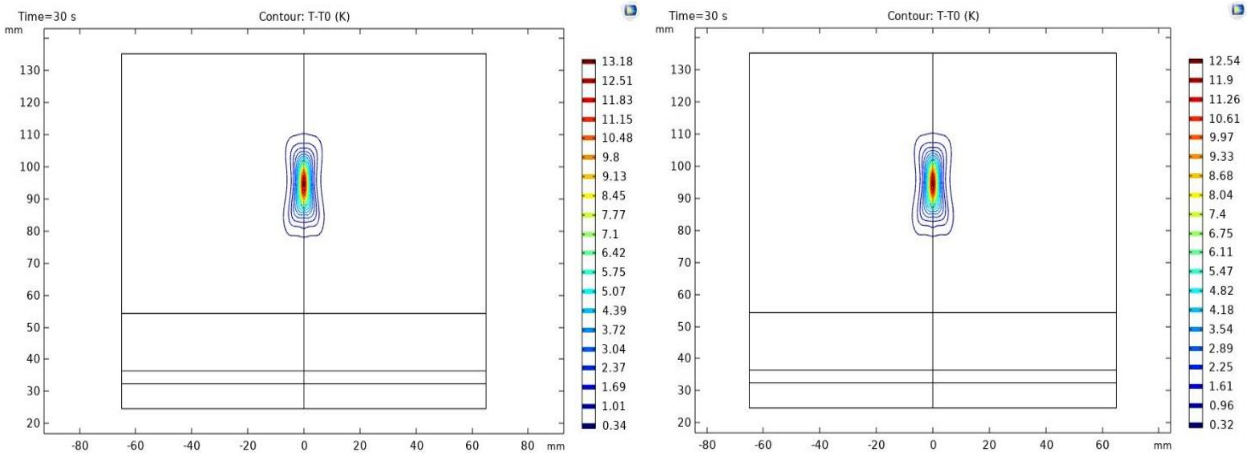
(c) (d)

Figure 16 - Temperature rise (T-T$_0$) over time at two focal points and a point 0.5 mm from the focal point for (a) t = 1 s, (b) t = 30 s, (c) t = 300 s, (t) t = 600s



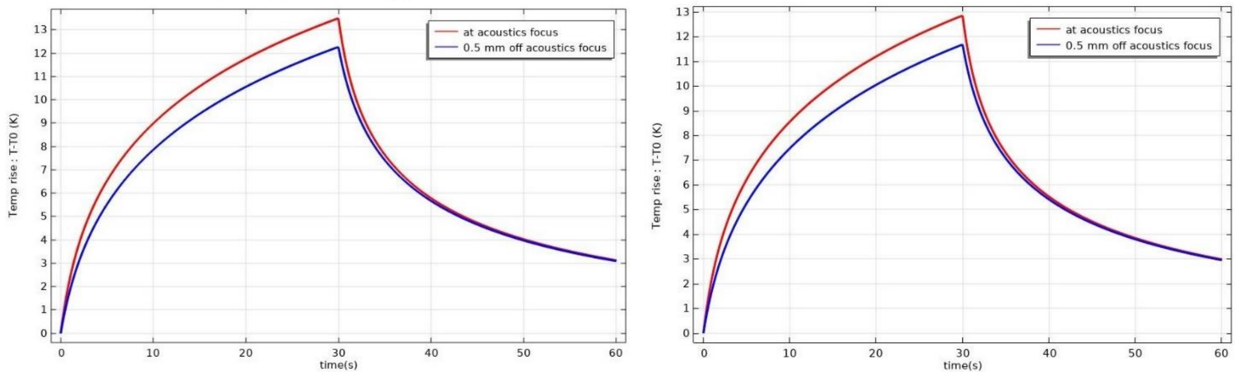
(a) (b)

Figure 17- Acoustic pressure distribution for (a) single-layer model (b) multi-layer model



(a) (b)

Figure 18- Contour of temperature rise for (a) single-layer model (b) multi-layer model



(a) (b)

Figure 19 - Temperature rise (T-T$_0$) over time at two focal points and a point 0.5 mm from the focal point (a) single-layer model (b) multi-layer model

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