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Numerical Study of Microbubble Dynamics Subjected to Ultrasound and Its Effect on Thermal Ablation of Biological Tissue

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ABSTRACT: High-intensity focused ultrasound is a non-invasive method and provides many therapeutic applications for physicians. One of the ways to increase the efficiency of High-intensity focused ultrasound is using a Levovist contrast agent, which consists of microbubbles. In the present study, we calculate the pressure field due to the High-intensity focused ultrasound using the Helmholtz equation for linear ultrasonic wave propagation. Using the Keller-Miksis equation, we calculate the thermal effects caused by microbubble injection after determining the acoustic pressure. The Pennes bioheat transfer equation is used for studying the tissue temperature distribution. The simulation results show that in the presence of a microbubble under the influence of a High-intensity focused ultrasound pressure field, increasing the applied frequency and power increases the value of heat sources caused by the microbubble oscillation. An increase in the temperature of biological tissue can be observed after the injection of microbubbles. Within the pressure range of 2.54 MPa, the tissue temperature at the focal point, for the case where the microbubble with the initial radius of 50 μm is injected, increases by 8.28 $^{\circ}C$. Meanwhile, if a microbubble with an initial radius of 50 micrometers is injected, there is a further increase in the tissue temperature by 57.72%. In the absence of microbubbles, the corresponding temperature rise is only 5.42 $^{\circ}C$ for the same operating conditions. Finally, the Arrhenius model shows that the microbubbles with different initial radii increase the ablated tissue volume by about 38%.

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1- Introduction

High-Intensity Focused Ultrasound (HIFU) plays a very important role in the development of engineering processes and medical treatment methods. Today, these waves are widely used in urinary and biliary tract stone breaking, medical imaging, oxidation reaction intensification, enzyme activity control, industrial cleaning, etc. [1].

In medicine, the concept of the ideal treatment of tumor cancers means the complete removal of the tumor without damaging the normal and healthy tissue structure around the tumor. HIFU treatment is a non-invasive surgical method with the privilege of reducing the recovery period after treatment and the patients can return to their normal life sooner.

One of the possible strategies to optimize the HIFU treatment is the use of ultrasound contrast agents for the thermal ablation of tumors. These materials increase the conversion rate of acoustic energy into heat during the HIFU treatment. The microbubbles have gained increasing popularity as potential agents for the treatment of solid tumors with the help of HIFU due to the special feature of changing their shape and radius size caused by the induced acoustic pressure [2].

In a study by Stewart et al. [3], 55 women who had uterine fibroid tumors were treated with HIFU with an acoustic intensity of 500 to 700 $W \cdot cm^{-2}$ and the thermal effect of HIFU on the tumor was investigated. The results of this study showed that tissue necrosis occurs beyond the tumor area. This study determined the importance of HIFU simulation in its prediction and controllability.

Aswin et al. [4] in 2019, using a 3D numerical model, investigated the effects of injecting microbubbles in the vicinity of the tumor by considering the interaction between the microbubble cloud and the non-linear HIFU field using Navier-Stokes compressible equations on a fixed grid. In this research, it was found that among the thermal mechanisms for microbubbles, the viscous dissipation caused by microbubble fluctuations has the main role in the temperature increase.

In the present study, the HIFU radiation to the tissue and the interaction of this field with the microbubble caused by the Levovist injection on the volume of tissue necrosis have been investigated. using the common range of power and frequency of the transducer in clinical and therapeutic applications, the effect of the injected microbubble size and the change of its radius on the generated heat have been studied. Finally, the

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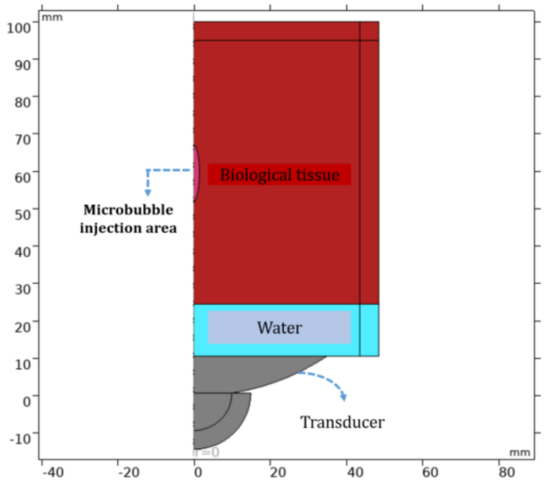

Fig. 1. The computational domain including the biological tissue, the ultrasound transducer, and the area of the microbubbles' injection.

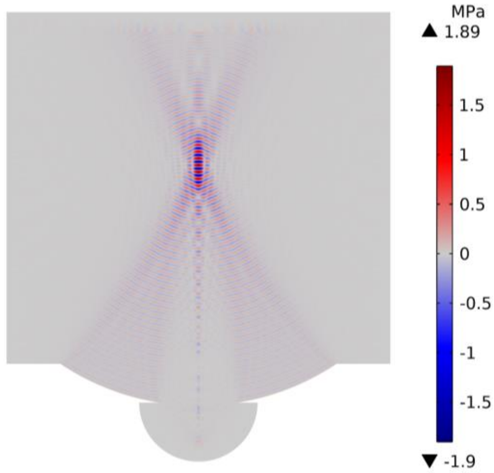

Fig. 2. The HIFU pressure distribution in the biological tissue where the transducer is set at 1 MHz and 5 W operating conditions.

effect of microbubble contrast agent injection on the increase in temperature and the volume of ablated tissue caused by HIFU has been analyzed.

2- Governing Equations

In order to simulate the microbubble-enhanced HIFU, the Helmholtz Eq. (1), Keller-Miksis Eq. (2), Pennes bioheat (3), and Arrhenius model (4) have been used. The equations are as follows: [5-7]

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

$$\left(1-\frac{\dot{R}}{c}\right)R\ddot{R}+\frac{3}{2}\dot{R}^2\left(1-\frac{\dot{R}}{3c}\right)=\left(1+\frac{\dot{R}}{c}\right)\frac{P\left(\dot{R},R,t\right)}{\rho}+\frac{R}{\rho c}\frac{\partial P\left(\dot{R},R,t\right)}{\partial t} \tag{2}$$

$$\rho_t C_t\frac{\partial T}{\partial t}=\nabla\cdot\left(k_t\nabla T\right)+\rho_b C_b\omega_b\left(T_b-T\right)+Q_{met}+Q_{ext} \tag{3}$$

$$\frac{\partial\alpha_n}{\partial t}=\int_0^t A_f e^{\frac{-E_a}{R_u T(t)}}dt \tag{4}$$

Where ρ is the density of the tissue, p is the acoustic driving pressure, ω is the angular frequency of the acoustic source, c_s is the speed of sound in the tissue R is the microbubble wall radius, $\dot{R}$ is the microbubble wall velocity, $\ddot{R}$ is the microbubble wall acceleration, C is the heat capacity, k is the thermal conductivity, ω_b is the blood perfusion rate, T is the tissue temperature, Q_{met} is the metabolic heat generation, and Q_{ext} is the volumetric heat generation. Also, α_n is the damage index, A_f is the pre-exponential factor, E_a is the activation energy, R_u is the molar gas constant.

3- Problem Definition and Numerical Solution Method

In the present study, in order to solve the governing equations of the microbubble-enhanced HIFU ablation, a numerical approach based on the simulation using COMSOL Multiphysics and FORTRAN software packages have been used. In order to accurately solve the governing equations of HIFU propagation in the biological tissue, the acoustic wavelength criterion has been applied. Accordingly, after checking the mesh independence, 142593 triangular elements of the second order have been used. To simulate the problem, the computational field schematic is shown in Fig. 1.

4- Result and Discussion

Through the governing equations, the HIFU pressure field within the computational domain for an applied frequency of 1 MHz and a power of 5 W has been calculated, which is shown in Fig. 2. As expected, the HIFU waves are focused in the target area and the maximum acoustic pressure occurs at the focal area. In order to study the effect of microbubble injection on the increase in the temperature of the focal region, according to Fig. 8, the temperature increase of the biological tissue is shown for three conditions without microbubble and in the presence of microbubble with 2 and 50 µm initial radii. The results at the focal point are reported at 3 MHz and 5 W for 20 seconds of irradiation and 30 seconds of the cooling process.

As mentioned, the aim of the present study is to investigate the volume of tissue ablation through the interaction of HIFU

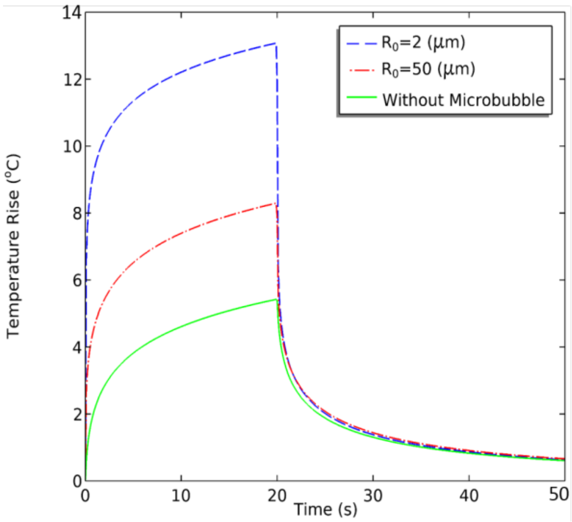

Fig. 3. A temperature increase of biological tissue with respect to time for 20 seconds of irradiation and 30 seconds of the cooling process at the focal point in working conditions of 3 MHz and 1 W.

waves with microbubbles. Table 1 is related to the thermal ablation with microbubble injection with an initial radius of 2 μm. According to this table, in the applied conditions of 1, 2, and 3 MHz and 10 W, the thermal sources caused by viscosity and secondary acoustic radiation due to microbubble oscillations increase the volume of tissue necrosis in the tumor area by 96.17, 38.53 and 38.55%, respectively, compared to the absence of microbubble.

Table 1. The volume of ablated tissue resulting from HIFU thermal source by microbubble injection with an initial radius of 2 μm

$V_{ab}\,(\mathrm{mm}^3)$	$t^*\,(\mathrm{s})$	$\theta_d\,(\%)$	$P_t\,(\mathrm{W})$	$f\,(\mathrm{MHz})$
-	-	<100	1	
0.008	9.88	100	5	1
4.61	0.36	100	10	
-	-	<100	1	
0.25	1.29	100	5	2
11.00	0.05	100	10	
-	-	<100	1	
0.61	0.36	100	5	3
13.62	0.15	100	10	

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