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HEATING AND DESTRUCTION OF BIOLOGICAL TISSUE BY HIGH-INENSITY FOCUSED ULTRASOUND

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Abstract. Processes of heating and destruction of the breast fat tissue under the action of focused high-intensity ultrasound generated by a 128-element transducer are considered. The simulation of a thermal problem is carried out by anumerical solution of the heat transfer equation. The acoustic pressure field in the tissue is calculated using the Rayleigh integral. A system of dimensionless scaling parameters is proposed to describe the non-stationary process of heat propagation. The influenceof the space localization of foci in a series of pulses on the lesion size is analyzed. The results demonstrate the advantages of a tissue processing program withspatially divergingfocal points of pulses, consisting in a more uniform heating of the tissue and the formation of a continuous ablation area. The impact of the perfusion process on the lesion size is considered.

Keywords: high-intensity focused ultrasound, tumor ablation, heat transfer equation, heat propagation in tissue

1. Introduction

High-intensity focused ultrasound (HIFU) is widely used for the treatment of tumors of various nature, competing with both traditional surgical methods and other non-invasive technologies of bio-tissue destruction [1-3]. The HIFU procedure provides the ablation of the tumor by the application of the series of intensity ultrasound pulses. The formation of necessary lesion area with minimal destruction of health tissue and minimal possibility of the tumor rupture requires a carefully planned therapy irradiation program. The efficiency of such program depends on the parameters of single pulses (the intensity and duration) within the series, locations of pulse focal points within a tumor, number and time sequence of pulses.A comprehensive study (obtaining the data on the spatial-temporal evolution of lesion areas and temperature fields in tissues) of the HIFU therapy is possible with the use of computer simulation technologies.

The paper presents the results of three-dimensional modeling of the non-stationary process of heating and ablation of bio-tissue (breast fat)by HIFU for the pulse intensities in focal point from 100 to 400 W/cm^2 and pulse durations from 0.5 s up to 2 s. For such moderate regimes the lesion formed preferably by thermal mechanism of HIFU action [2,3]. The paper focuses on the following three aspects: (i) estimation of the intensity field for the given 128-element transducer array, (ii) the study of the thermal impact on the tissue of single pulse parameters, (iii) the analysis of the influence of thesequence of HIFU pulses on lesion area and choice of optimal therapy irradiation program.

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2. Formulation of the problem

Non-stationary process of tissue heating by a single focused ultrasound pulse or a series of pulsesfrom a multi-element transducer is under consideration. A Cartesian coordinate system with the origin in the geometric focus of transducerwhere the *Z* axis coincides with the axis of the transduceris applied (Fig. 1).

The thermal process is described by the heat equation [4]:

$$c\rho \frac{\partial T}{\partial t} = div(\lambda \ grad \ T) + Q_H + Q_b, \tag{1}$$

where c, λ, $\rho$are the heat capacity, thermal conductivity coefficient and density of the tissue respectively. Q_H is the specific ultrasonic power absorbed by the tissue, Q_b characterizes the heat dissipated by perfusion. In the quasi-plane wave approximation, the source term in (1) is assumed to be $Q_H = 2\alpha I$ (I is the ultrasound intensity in the tissue, α is the absorption coefficient) [2]. The term responsible for the cooling of the tissue due to perfusion is represented as $Q_b = -c_b W_b \left(T - T_b\right)$ (c_b, W_b, T_b – heat capacity, volume flow rate and blood temperature, respectively) [5,6]. With a constant λ coefficient, this equation is known as the bio-heat thermal equation (BHTE) [5-7].

The propagation of ultrasound in the medium and the temperature field evolution are calculated independently [8-12]. According to the parameters of the intensity field I, the power of thermal source Q_H is determined, which is used later in solving the heat transfer equation. Thus, it is assumed that the intensity distribution of the focused ultrasound radiation in the tissue I is known, does not depend on the temperature of the medium and does not change during a pulse time duration τ. After the time τ has elapsed, the pulse terminates, and the corresponding intensity becomes zero. Details of the intensity field approximation are given in the next paragraph.

The thermophysical parameters used in the paper (c = 2348 J/(kg·K), λ = 0.21 W/(m·K), ρ = 911 kg/m^3) correspond to the parameters of the breast fat tissue [13]. Absorption coefficient value isα_{ref} = 7.25 m^{-1} for the ultrasound frequency f_{ref} = 1 MHz [14] (the dependence on the frequency f is assumed to be linear, i.e. for thefrequency of 2 MHz α = 14.5 m^{-1}). Blood flow parameters: c_b = 3617 J/(kg·K), W_b = 0.78·10^{-6} m^3/(kg·s) [13], T_b = 309.6 K.

The numerical solution of equation (1) is performed by the finite-difference method [4]. A predictor-corrector scheme is applied. The scheme provides the second order of approximation in time and space $O\left(\tau_{step}^2 + h_{step}^2\right)$ (τ_{step}, h_{step}– steps in time and spatial coordinates). The testing of the simulation code was performed by comparing the results with analytical solution to the problem of unsteady heat propagation from the cylinder as described in [15]. The number of nodes in the computational grid was in the range of 5 – 100 million.

At the initial time moment, the temperature of the entire region was set equal to T_0 = 309.6 K. The temperature at the boundaries of the region was assumed constant and equal to T_0.

To determine the area of thermal ablation of tissue, the approach [16] was used, according to which the thermal dose is defined as

$$t_D = \sum_{t=0}^{t=t_{fin}} R^{T_{ref} - T_m} \Delta t, \tag{2}$$

where t_D is the time equivalent of the thermal dose determined in this work relative to the temperature 56°C [3, 17], T_m is the average temperature value over a small time interval Δt (in calculations $\Delta t = \tau_{step}$), T_{ref} = 56°C (329 K) is the reference temperature value, t_{fin} is the final moment of time, R = 0.5 for T > 43°C (316 K) and R = 0.25 for T < 43°C (316 K). The heat dose required to reach the tissue destruction threshold using the HIFU method

t_{56} = 1.76 s [3,17] corresponds to the dose determined relative to 43°C, t_{43} = 240 min, in hyperthermia [16].

3. Ultrasound intensity field

The numerical calculation of the intensity field is fulfilled for a multi-element array transducer (Fig. 1), consisting of 128 radiating elements arranged in an Archimedean spiral on a concave spherical surface [18]. The operating frequency of the transducer is 2 MHz, the maximum possible intensity of the sound field in the focus of the device is up to 80 kW/cm^2. The advantage of a multi-element transducer is the possibility of moving the focus electronically without the need for physical movement of the device itself.

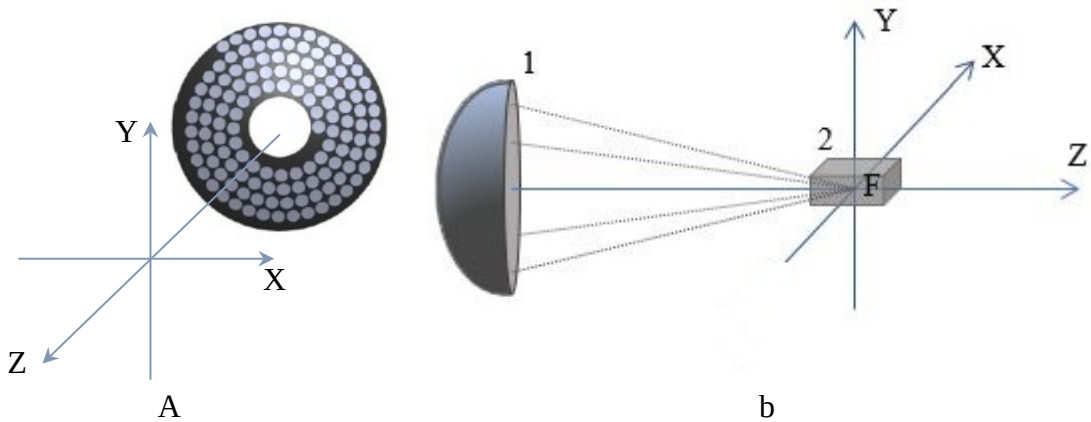


Fig. 1. Multi-element transducer (a) and calculation scheme (b). 1 – transducer, 2 – heated tissue volume, F – geometric focus of the transducer

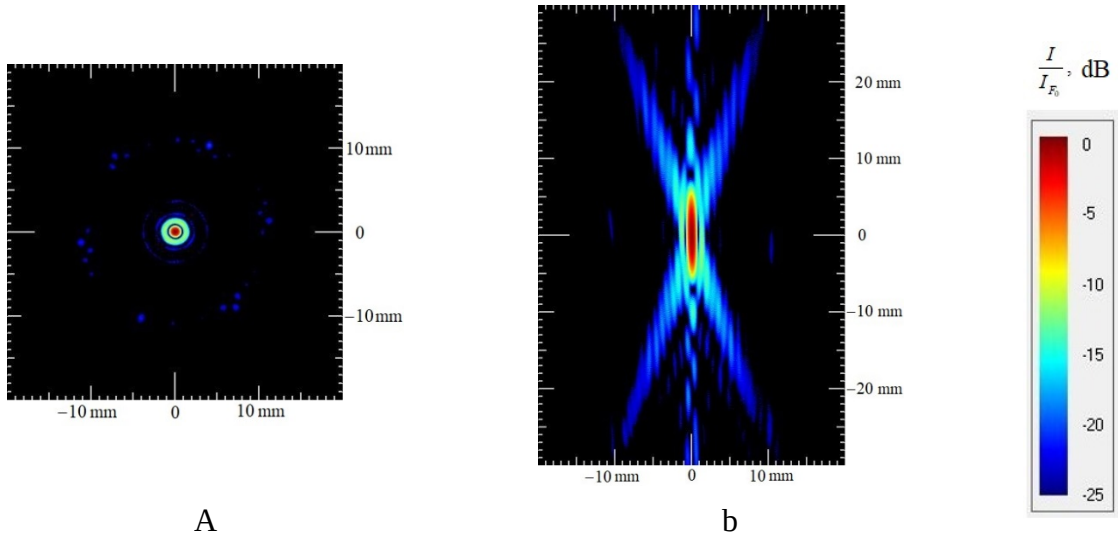
High values of the intensity and pressure may result in cavitation [1-3], the use of which for therapeutic purposes is not considered in this paper. For moderate ultrasound intensities at the focal point from 100 to 400 W/cm^2, the maximum pressure in the focus does not exceed 3.5 MPa. In the specified range of parameters, nonlinear effects can be neglected [17,19] and the simulation of the acoustic field of an ultrasonic multi-element transducer can be carried out in a linear approximation using the Rayleigh integral [2,20].

The complex acoustic pressure p from a single surface element is defined

$$p = -i\frac{kc_m\rho_m u}{2\pi}\int_S \frac{e^{-(\alpha_m+ik)r}}{r}dS\ . \tag{3}$$

Here u is the normal component of the velocity of a small element of the transducer's surface dS, k is the wavenumber, c_m is the speed of sound, ρ_m is the density of the medium, α_m is the absorption coefficient of the medium, r is the distance from the element of the surface dS to the pressure calculation point. The integration is performed over the entire surface of the transducer element S. The total ultrasound field of the transducer array was calculated as a superposition of the fields of the individual elements, taking into account their location. The intensity of the ultrasound wave is defined as $I = p_a^2/(2c_m\rho_m)$ (p_a – pressure amplitude) [2,3].

The results of calculations of the intensity field in the water medium (c_m = 1480 m/s, ρ_m = 1000 kg/m^3, α_m = 0.092 m^{-1})are shown in the Fig. 2 below. In the vicinity of focal point, the contours of ultrasound intensity for the XY plane perpendicular to the axis of symmetry of the transducer (Fig. 2a) are circles and for the XZ plane passing through its axis of symmetry (Fig. 2b) have ellipsoidal shape.



A b

Fig. 2. The intensity of the sound field of the transducer

For the use in the heat problem solution, an approximation of the ultrasound intensity in the focal spot was constructed on the basis of the calculations performed. The intensity in points with coordinates X, Y, Z at different positions of the focus X_F, Y_F, Z_F can be approximated by formulas (all coordinates are in millimeters, measured from the center of curvature (geometric focus) of transducer; an increase in Z corresponds to a distance from the transducer)

$$\begin{aligned} &I = I_F e^{10^{-3} p(z)} e^{q(r)}, \\ &p(z) = -0.1z^4 + 0.2z^3 - 4.5z^2 - 3z, \\ &q(r) = -0.5r^4 - 0.35r^2, \\ &z = Z - Z_F \qquad r^2 = (X - X_F)^2 + (Y - Y_F)^2. \end{aligned} \tag{4}$$

The maximum value of the intensity I_F depends on the position of the focus in the working area

$$\begin{aligned} &I_F = I_{F,0} e^{10^{-6} P(Z_F)} e^{10^{-4} Q(R_F)}, \\ &P(Z_F) = -0.01 Z_F{}^4 + 1.1 Z_F{}^3 - 65 Z_F{}^2 - 1300 Z_F, \\ &Q(R_F) = -0.0035 R_F{}^4 - 4.7 R_F{}^2, \\ &R_F^2 = X_F^2 + Y_F^2. \end{aligned} \tag{5}$$

$I_{F,0}$ is intensity in the center of the spot, located in the geometric focus of the transducer.

The approximations (4) - (5) slightly depends on the medium nature. The approximation error in the vicinity of focal point in the range of 0 - (-10) dB does not exceed 0.5 dB both in water and in a mixed medium (70% water, 30% layer of fat tissue, the focus is in the fat tissue).

4. Single pulse

In the case of a single pulse, the pattern of tissue heating is symmetrical about the longitudinal axis Z and is characterized by one coordinate in cross sections $R = \sqrt{X^2 + Y^2}$. The pulse

parameters considered in this paper are presented in the Table 1. The simulation was performed for a time interval of 10 s. The perfusion process, according to the data of [12], does not have a significant impact on the heat distribution process at such small-time scales and was not considered in the calculations.

Table 1.Simulation parameters for the impact of a single pulse

N	I_F,W/cm^2	t_H ,ms	λ, W/(mK)	*Os*	τ_H	*By*	E_a,J
1	100	2000	0.21	0.4	0.224	0.0896	2.79
2	200	250	0.21	0.8	0.028	0.0224	0.7
3	200	500	0.21	0.8	0.056	0.0448	1.39
4	200	1000	0.21	0.8	0.112	0.0896	2.79
5	300	500	0.21	1.2	0.056	0.0672	2.09
6	350	500	0.21	1.4	0.056	0.0784	2.44
7	400	500	0.21	1.6	0.056	0.0896	2.79
8	200	1000	0.42	0.4	0.224	0.0896	2.79

I_F – the intensity in the focal point, t_H – pulse duration, λ – coefficient of thermal conductivity, E_a – energy absorbed by the tissue during a pulse, *Os*, τ_H, *By* – dimensionless parameters

The heat process during a single pulse can be divided into two successive stages: heating the tissue during the pulse and the subsequent cooling of the tissue due to thermal conductivity (Fig. 2a).

For the constant thermal conductivity coefficient, the contribution of the absorbed ultrasound energy to the thermal process is characterized by a dimensionless parameter (Ostrogradsky number):

$$Os = \frac{\ell^2 Q_F}{\lambda T_0}, \tag{6}$$

Where ℓ is the characteristic size, $Q_F = 2\alpha I_F$ is the specific power of the heat source in focus. The characteristic size is assumed to be 0.94 mm and is equal to the radius of the circle in the plane $Z = 0$, for the points of which the relation $I/I_F = 0.5$ is satisfied.

The characteristic time scale can be defined as $t_0 = \frac{c\rho\ell^2}{\lambda}$. Fat tissue value corresponds $t_0 \approx 9$ s. For the pulse process, you can enter a dimensionless parameter characterizing the exposure time:

$$\tau_H = \frac{t_H}{t_0}. \tag{7}$$

Here t_H is the pulse duration.

The parameter determines the size of the heat propagation area during the pulse. Large values of the thermal conductivity coefficient correspond to large values τ_H.

An important characteristic of the process is the value of total energy absorbed by the tissue, which depends on both the intensity of the ultrasound and the duration of the pulse. To describe the process of heat distribution, instead of the parameter *Os*, it is convenient to use the dimensionless parameter *By*:

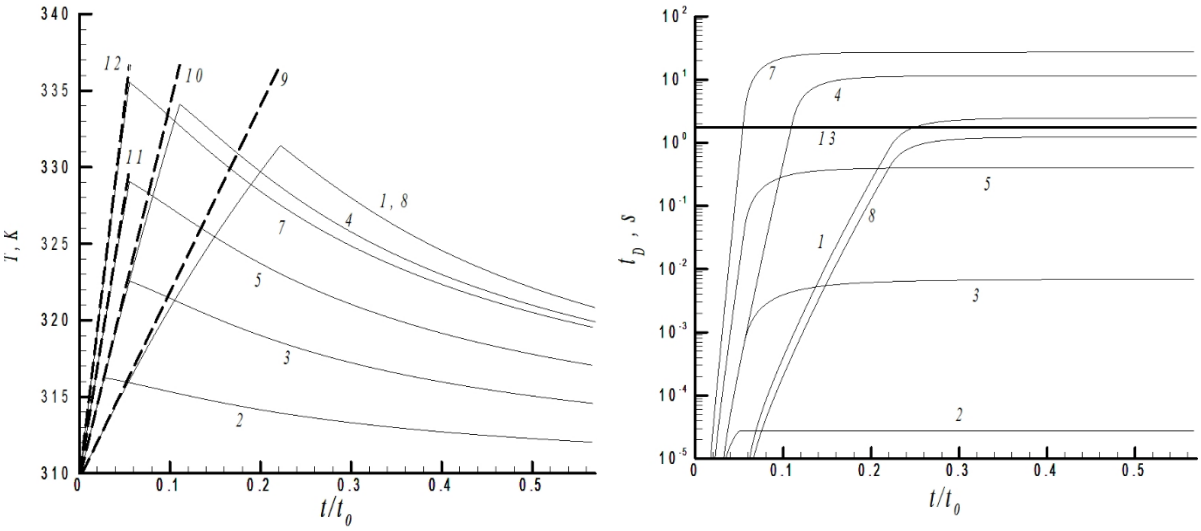
$$By = Os \cdot \tau_H = \frac{Q_F t_H}{c\rho T_0}. \tag{8}$$

For the same values of τ_H and *By*, the temperature changes in the dimensionless time t/t_0 will be similar. As an illustration of the similarity, Fig. 3a shows the dependence of

temperature on dimensionless time t/t_0 at the focal point for calculationcases 1 and 8. The cases differ in thermal conductivity coefficient, pulse time and maximum intensity at the focus (Table 1), but are characterized by the same dimensionless parameters τ_H and *By*. The corresponding curves (1) and (8) coincide. But the values of the heat dose, determined according to (4), are different (Fig. 3b) for these cases.

Cases 3,5,7 are characterized by the same value of the parameter τ_H and different values of the parameter *By*. The greater absorbed energy (i.e. parameter *By*) leads to the higher temperature maximum at the focal point. For these cases τ_H=0.056<<1 and thermal conductivity has a weak effect on the temperature of the tissue at the heating stage. Fig. 3a for cases 3,5,7 (and 1,4,8) shows both the calculated temperature curves at the focal point and straight dashed lines corresponding to the analytical temperature estimation assuming no heat conduction. The analytical values for cases 3,5,7 are close to the calculated ones.

Increasingτ_H with the constant value of *By* (cases 1,4,7 and corresponding curves) leads to a more intensive cooling of the region at the stage of tissue heating by ultrasounddue to thermal conductivity. The heat conduction process is especially noticeable and important for the calculation case 1, for which τ_H is comparable to the unit ($\tau_H \approx 0.224$) and there is a maximum difference between the simulated temperature distribution and the analytical estimation (line). With the same value of energy absorbed by the tissue E_a for case 7, the maximum temperature at the end of the pulse is higher than in cases 4 and 1.



A b

Fig. 3. The evolution of the temperature (a) and thermal dose (b) in the focal point. The curve number corresponds to the case number according to the Table 1. The dashed straight lines 9 - 12 are the data of the analytical solution without thermal conductivity, corresponding to the conditions of cases 1,4,5,7, respectively, 13 is the thermal ablation threshold of the tissue

For the cooling stage, the process of heat conduction is important, both for estimating the temperature and the efficiency of the process of thermal ablation of the tissue. The evolution of the thermal dose in the center of the focal area is shown in figure 3b. After some time at the cooling stage, the heat dose curves are "frozen". This time depends on the parameters and for all the considered cases corresponds to the interval $t/t_0 < 0.3$. For cases 2, 3, 5 and 8, thermal ablation of the tissue does not occur. For cases 4 and 7, the destruction of the tissue in the center of the spot is observed at the completion of the pulse; for case 1, ablation of the tissue occurs after the completion of the pulse. Despite the same energy E_a (the

same values of *By*) absorbed by the tissue in cases 1, 4 and 7, the valuesof the thermal dose at the focal point differ significantly.

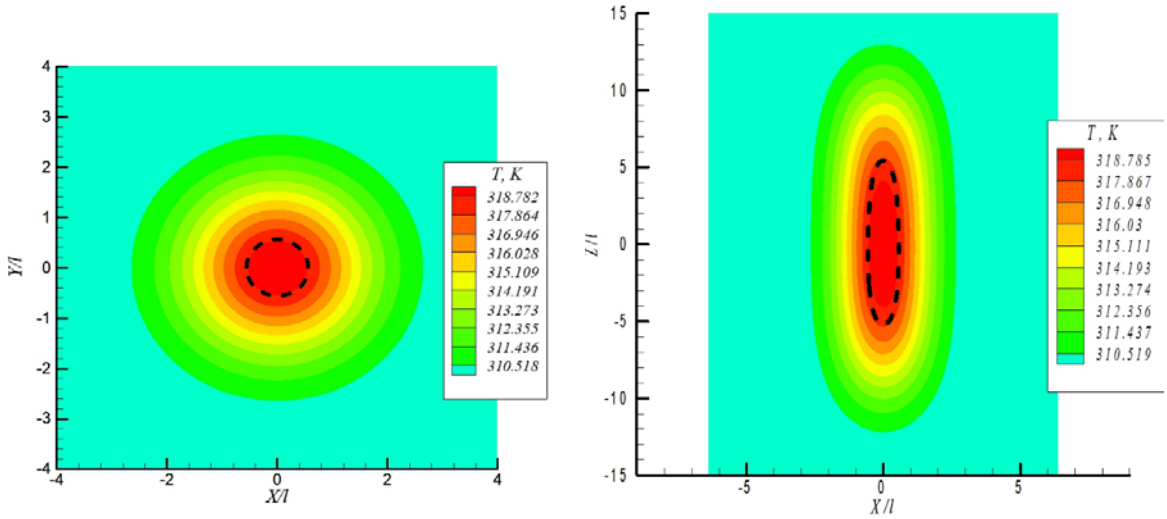


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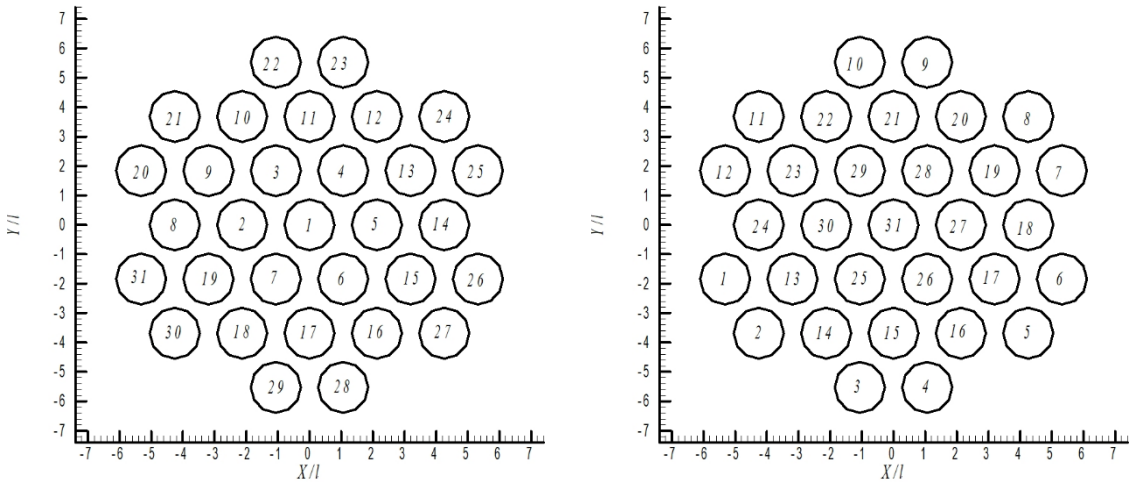
Fig. 4. The temperature fields (a, b) for the case 7, corresponding to the time t = 5 s = $10t_H \sim 0.56t_0$. The dashed line is the boundary of the tissue ablation area

The typical temperature distributions in a homogeneous medium with parameters corresponding to the breast fat tissue in the *XY* (*Z* = 0) and *XZ* (*Y* = 0) planes for the case 7 are shown in Fig. 4a and b. Temperature contours in the *XY* plane have the shape of a circle, and in the *XZ* plane the shape is close to ellipsoidal, with a maximum value in the center of coordinates. The boundary of the area of thermal ablation, determined according to (2), is highlighted in the figure by a bold dashed line. The shape of the ablation area corresponds to the shape of the temperature isolines.



A b

Fig. 5. Spatial distribution of focal points of a series of pulses. The number corresponds to the order of the pulse in the series. a - the program "from the center"(cases 1 and 3), b - the program "toward the center" (case 2)

5. Pulse series

For treatment of a tumor with a moderate or large size, it is necessary to use a series of HIFU pulses (therapy program). The foci of impulses must be localized at certain points within the

tumor. The number of pulses N_P, the location of the focal areas inside the tumor, the order of pulses and the time delay t_D between pulses will be additional parameters that together with the parameters of each pulse, determine the lesion area for the biological tissue.

In this paper, we consider a series of 31 pulses. Each pulse has an intensity field approximated by (4), (5). The maximal intensity of pulse is $I_{F,0}$ = 100 W/cm^2, the single pulse exposure time is 2 s. It was assumed that the ultrasonic pulses are activated in series, without a time delay (t_D = 0), the end of one pulse corresponds to the beginning of the next. Total processing time t_P = 62 s. The location of the focal points of the pulses in the *XY* plane is shown in figure 5for processing programs "from the center" (a) (simulation cases 1 and 3) and "towards the center" (b) (simulation case 2). The characteristic distance along the *X* axis between the focal points is h_x = 2 mm. The cases 1 and 2 were simulated without taking into account the perfusion, the case 3 – with the perfusion process.

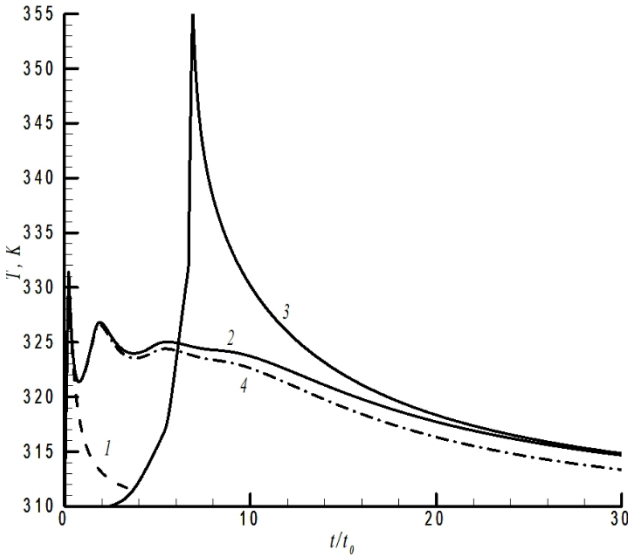


Fig. 6. The evolution of the temperature in the center of the region (0,0,0). 1 - single pulse, 2 - program "from the center" (case 1), 3 - program "toward the center" (case 2), 4 - program "from the center" with perfusion (case 3)

Figure 6 shows the temperature distribution in the center of the area under consideration. The maximum temperature of the central part for the processing program "from the center" (case 1) coincides with the case of a single pulse. Then, heat waves from neighboring areas (points), processed at later time, come to the center point, which corresponds to the appearance of additionalmaxima on the temperature curve. For the "toward the center" processing program, the situation is different (case 2). The processing of the central point takes place last in the series and corresponds to the already formed temperature field. The temperature maximum is shifted in time and significantly exceeds the temperature maximum for a single pulse. In fact, such a heating of the central point is redundant in terms of the "thermal dose" concept necessary for tissue destruction. Both treatment cases consist of a series of pulses, the total energy absorbed by the tissue is about 86 J and the center of the area cools much slower than the case of a single pulse. Despite the difference of the considered processing programs for the same value of the energy input over time, the change in temperature of the center point becomes the same.

Figure 7a shows the temperature field at the time $t = 5t_P$ for case 1. For large times $t >> t_P$, heat propagation does not depend on the processing program and the number of

pulses and will acquire a spherical character (looks like heat propagation from a point source). The result of the impact of a series of pulses on a tissue is the appearance of a lesion. The distribution of heat dose in the plane $Z = 0$ is shown in fig. 7b. The heat dose is not uniformly distributed. In a part of the region, the heat dose significantly exceeds the values required for tissue ablation.

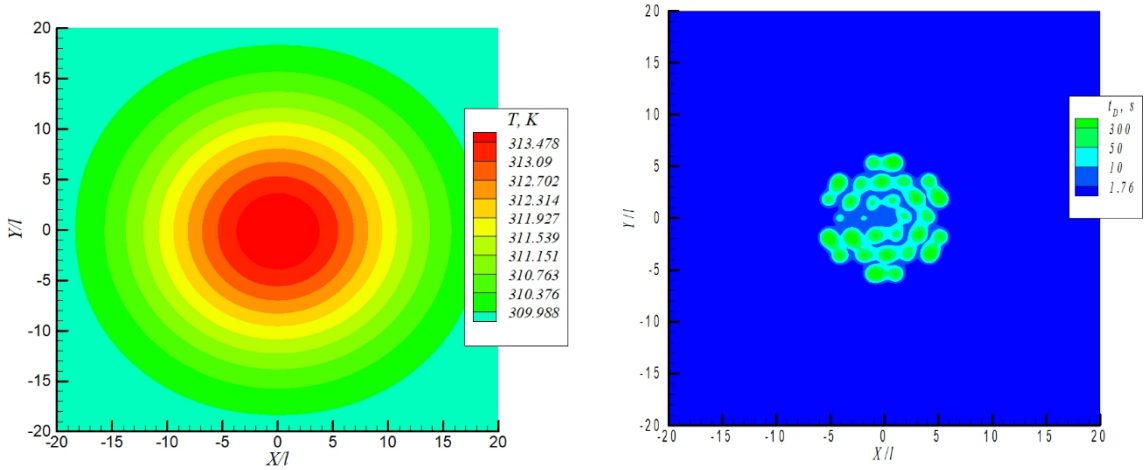


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Fig. 7. Temperature (a) and thermal dose (b) in the $Z = 0$ plane for case 1, $t = 5t_P = 310$ s

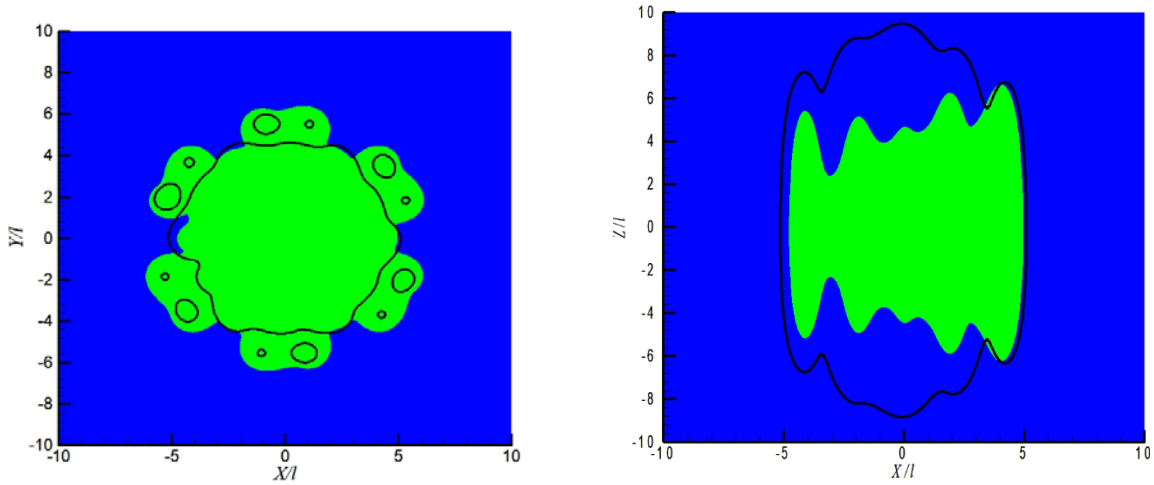

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Fig. 8. The boundary of the lesion area in the transverse plane $Z = 0$ (a) and in the longitudinal plane $Y = 0$ (b). The color field is case 1 ("from the center"), the line is case 2 ("towards the center")

The process of tissue ablation continues after the end of the program (a series of pulses) and stops in the time interval $t_P < t < 2t_P$. The lesion region for the time $t = 2t_P$ is shown in Fig. 8. Attention should be paid to the significant difference between the lesion boundaries for the programs "from the center" and "toward the center". For the treatment program "toward the center" in the *XY* plane, there are zones of intact tissue, which is not permissible during tumor treatment. On the other hand, this treatment program allows you to get a large area of thermal ablation in the longitudinal direction. Considering the presence of intact zones and excessive for ablation overheating of the center of the region, for the considered range of parameters, the program "from the center" should be recognized as more effective.

The total observation time of the temperature in the tissue during its processing by a series of pulses with a total duration of 62 s was $t = 5t_p$ = 310 s. At such long-time intervals, the process of heat transfer can be affected by the perfusion [12]. To analyze the effect of perfusion, an additional calculation 3 was carried out (case 3), corresponding to the "from the center" program. Accounting for perfusion for breast fat (characterized by a low coefficient of volumetric blood rate) leads to a decrease in the temperature of the central point of the area (corresponding to the geometric focus), starting from the time point $t/t_0 > 3$ (Fig. 6). By the time $t/t_0 = 30$, the difference in the temperature of the center of the region for cases 1 and 3 is 1.5 K. In spite of so small impact of the perfusion process on the tissue, temperature the lesion shape is sufficiently different for cases with and without perfusion (see Fig. 9).The lesion for the case with taking into account perfusion contains intact zones.

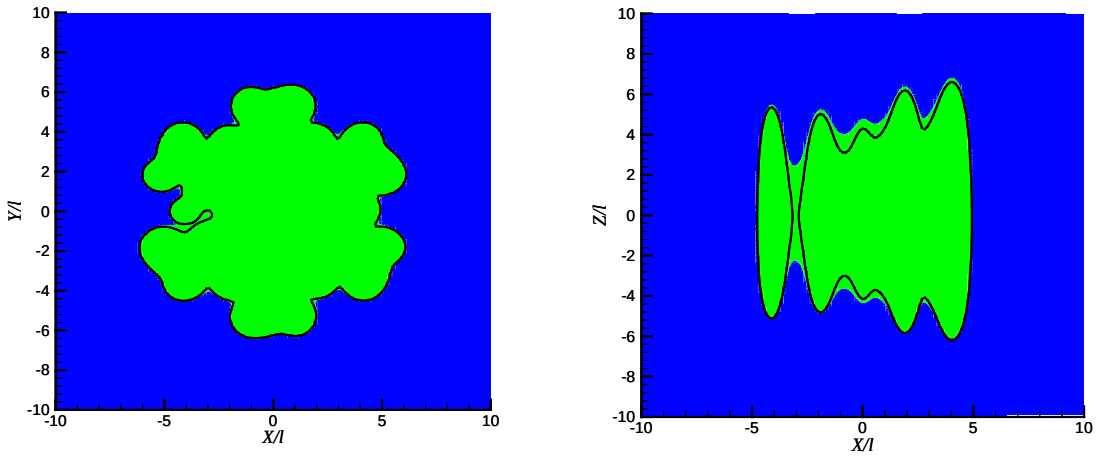

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Fig. 9. The boundary of the lesion area in the transverse plane $Z = 0$ (a) and in the longitudinal plane $Y = 0$ (b). The color field is case 1 and the line is case 3 (taking into account perfusion process)

6. Conclusion

The processes of heat propagation in biological tissue are considered within the paper. For the moderate intensities of focused ultrasound, the pressure field from a multi-element ultrasonic transducerwas calculated using the Rayleigh integral. The simulation of the thermal problemwas based on the numerical solution of the BHTE equation, which describes the spatial non-stationary process. Data were obtained on the dynamics of heat propagation in breast fat tissue for both a single pulse and a series of pulses.

To describe the dynamics of tissue heating / cooling by a single pulse, within the paper dimensionless scaling parameters which characterize the total energy of the pulse and the time of exposure were proposed. The influence of the parameters on the evolution of temperature distributions in the tissue was studied.It is shown that for large pulse durations, the process of heat conduction plays a significant role in reaching the maximum temperature and influence on the value of the thermal dose received by the tissue.

Within the paper the effect of a series of pulses on the tissue was also investigated. Two possible programs for processing a given volume of tissue were considered –"from the center" and "toward the center". For the considered range of ultrasound intensities and the pulse duration, it was shown that the "toward the center" program provides excessive heating of the central zone but is insufficient for full thermal ablation of the considering area. To obtain a continuous lesion area, the program "from the center" is preferable.Under moderate intensity

of ultrasound the perfusion process may leads to the presence of intact zones within ablation area and the failure of therapy plan.

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