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COMPUTER SIMULATION OF CYCLIC TEMPERATURE EFFECT ON THE ONCOLOGICAL NEOPLASM OF THE HUMAN SKIN

The paper presents the results of computer simulation of the temperature effect on the tumor of the human skin in a dynamic mode. The physical, mathematical and computer models of the human skin with oncological neoplasm (melanoma) were built with regard to thermophysical processes, blood circulation, heat exchange, metabolic processes and phase transition. As an example, the case is considered when a work tool is located on the tumor surface, the temperature of which changes cyclically according to a predetermined law in the temperature range $[-50 \div +50]$ °C. Temperature distributions in the tumor and various layers of human skin in the cooling and heating modes have been determined. The results obtained make it possible to predict the depth of freezing and heating of biological tissue, in particular a tumor, at a given temperature effect. Bibl. 59, Fig. 6, Tabl. 2.

Keywords: temperature effect, human skin, tumor, melanoma, dynamic mode, computer simulation.

Introduction

Cryodestruction [4 5, 8 27] and hyperthermia [28 32] of biological tissue are increasingly used to neutralize malignant and benign oncological neoplasms of the human skin [1 7]. When performing such procedures, it is important to control the temperature in the tumor, but there are still no tools to determine the temperature in the tumor during cryodestruction and hyperthermia. Thus, during the above procedures, the temperature in the tumor remains unknown, and, therefore, the destruction of oncological neoplasm remains an open question.

One of the methods for determining the temperature in a tumor with a given cyclic change in the temperature of the work tool is computer simulation [33 35]. However, in the computer models used so far, blood circulation, heat exchange, metabolic processes and other thermophysical processes are taken into account, but the phase transition in biological tissue is disregarded [36 38].

Therefore, *the purpose of this work* is computer simulation to determine the temperature in the tumor, taking into account the phase transitions.

Physical model

A physical model (Fig. 1) of the area of biological tissue of human skin is a structure of three skin layers (epidermis 1, dermis 2, subcutaneous layer 3), inner biological tissue 4 and tumor 5 which is characterized by thermophysical properties [33-35, 39-43], such as thermal conductivity κ_i , specific

heat C_i , density ρ_i , blood perfusion rate ω_{bi} , blood density ρ_b , blood temperature T_b , blood heat capacity C_b and specific heat release Q_{meti} due to metabolic processes and latent heat of phase transition L . The thermophysical properties of biological tissue of the skin and tumor in the normal [44-49] and frozen states [50, 51] are given in Tables 1, 2. In this paper, we use a 2D model with axial symmetry, because the proposed physical model is symmetric about the y-axis. Also, such a model allows increasing the speed of calculations without loss of accuracy [33-35, 39 – 43].

The corresponding layers of biological tissue 1-5 are considered as bulk heat sources q_i , where:

$$q_i = Q_{meti} + \rho_b \cdot C_b \cdot \omega_{bi} \cdot (T_b - T), \quad i = 1..5. \quad (1)$$

The geometric dimensions of each skin layer 1-4 are a_i , b_i , and of tumor (melanoma) are as follows: thickness b_5 and radius n . The skin surface accommodates a work tool 6 with thickness d and radius c . The temperatures at the boundaries of respective layers 1-5 and work tool 6 are T_1 , T_2 , T_3 , T_4 , T_5 , T_6 , T_7 . The temperature inside biological tissue is T_1 . The ambient temperature is T_9 . The surface of the human skin with temperature T_5 is in the state of heat exchange with the environment (heat transfer coefficient α and radiation coefficient ε) at temperature T_9 . The lateral surface of the skin is adiabatically insulated.

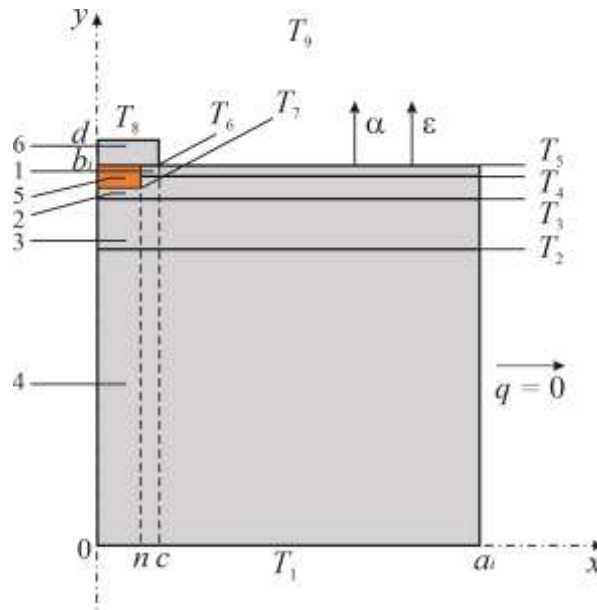


Fig.1. Physical 2D model of the human skin with a tumor: 1 – epidermis, 2 – dermis, 3 – subcutaneous layer, 4 – inner biological tissue, 5 – tumor (melanoma), 6 – work tool

Mathematical description

In the general form, the equation of heat exchange in biological tissue is as follows [52]:

$$C_i \cdot \frac{\partial T}{\partial t} = \nabla \cdot (\kappa_i \cdot \nabla T) + \rho_b \cdot C_b \cdot \omega_{bi} \cdot (T_b - T) + Q_{meti}, \quad i = 1..5, \quad (2)$$

where C_i , κ_i is specific heat and thermal conductivity of the respective skin layers and tumor, ρ_b is blood density, C_b is blood specific heat, ω_{bi} is blood perfusion of respective layers, T_b is blood temperature, T is temperature of biological tissue; Q_{meti} is heat released due to metabolic

processes in each layer.

The term on the left side of equation (2) is the rate of change of thermal energy contained in a unit volume of biological tissue. The three terms on the right part of this equation represent, respectively, the rate of change of thermal energy due to thermal conductivity, blood perfusion and metabolic heat.

Heat transfer equation in biological tissue (2) is solved with the corresponding boundary conditions. The temperature on the surface of work tool changes by the given dependence in the temperature range $T_8 = [-50 \div +50]^\circ\text{C}$. The temperature inside biological tissue is $T_1 = +37^\circ\text{C}$. The lateral surfaces of biological tissue are adiabatically insulated ($q = 0$), and the upper surface of the skin is in a state of heat exchange (heat transfer coefficient α and radiation coefficient ε) with the environment at temperature T_9 .

$$q_i(x, y, t) \Big|_{\substack{c \leq x \leq a \\ y = b_i}} = \alpha \cdot (T_9 - T_5) + \varepsilon \cdot \sigma \cdot (T_9^4 - T_5^4), \quad (3)$$

where $q_i(x, y, t)$ is heat flux density of the i -th layer of the skin and tumor, α is coefficient of convective heat exchange of the skin surface with the environment, ε is radiation coefficient, σ is the Boltzmann constant, T_5 is surface temperature of the human skin, T_9 is ambient temperature ($T_9 = +22^\circ\text{C}$).

At the initial moment of time $t = 0$ s, it is considered that the temperature in the entire volume of the skin is $T = T_b = +37^\circ\text{C}$, that is, the initial conditions for solving equation (2) are as follows:

$$T_i(x, y, 0) = T, \quad i = 1..5. \quad (4)$$

As a result of solving the initial boundary value problem (2) - (4), the distributions of temperature $T_i(x, y, t)$ and heat fluxes $q_i(x, y, t)$ in the corresponding layers of the skin and tumor at any time are determined.

During the freezing process, a phase change will occur in the cells at the freezing point, while there will be a loss of phase transition heat (L) and the temperature in these cells will not change. The phase transition in biological cells occurs in the temperature range $(-1 \div -8)^\circ\text{C}$. In the temperature range $(-1 \div -8)^\circ\text{C}$, when the cells are frozen, the heat of the phase transition is absorbed which in this work is simulated by adding the corresponding value of L to the heat capacity C [50, 51].

Freezing of the human skin causes vasoconstriction and freezing of blood, therefore the value of blood perfusion ω_{bi} tends to zero. In addition, cells will not be able to generate metabolic heat when frozen, and metabolic heat Q_{meti} will be zero at temperatures below zero.

In the frozen state, the properties of biological tissue of the skin will have the following values (5)-(8), where $i = 1..4$:

$$C_i = \begin{cases} C_{i(1)} & T \geq -1^\circ\text{C} \\ \frac{L}{-1 - (-8)} + \frac{C_{i(1)} + C_{i(2)}}{2} & -8^\circ\text{C} \leq T \leq -1^\circ\text{C}, \\ C_{i(2)} & T \leq -8^\circ\text{C} \end{cases} \quad (5)$$

$$\kappa_i = \begin{cases} \kappa_{i(1)} & T \geq -1^\circ\text{C} \\ \frac{\kappa_{i(1)} + \kappa_{i(2)}}{2} & -8^\circ\text{C} \leq T \leq -1^\circ\text{C}, \\ \kappa_{i(2)} & T \leq -8^\circ\text{C} \end{cases} \quad (6)$$

$$Q_{met_i} = \begin{cases} Q_{met(i)} & T \geq -1^\circ\text{C} \\ 0 & -8^\circ\text{C} \leq T \leq -1^\circ\text{C}, \\ 0 & T \leq -8^\circ\text{C} \end{cases} \quad (7)$$

$$\omega_{b_i} = \begin{cases} \omega_{b(i)} & T \geq -1^\circ\text{C} \\ 0 & -8^\circ\text{C} \leq T \leq -1^\circ\text{C}. \\ 0 & T \leq -8^\circ\text{C} \end{cases} \quad (8)$$

Accordingly, the properties of tumor in the frozen state will have the following values (9)-(12):

$$C_5 = \begin{cases} C_{5(1)} & T \geq -1^\circ\text{C} \\ \frac{L}{-1 - (-8)} + \frac{C_{5(1)} + C_{5(2)}}{2} & -8^\circ\text{C} \leq T \leq -1^\circ\text{C}, \\ C_{5(2)} & T \leq -8^\circ\text{C} \end{cases} \quad (9)$$

$$\kappa_5 = \begin{cases} \kappa_{5(1)} & T \geq -1^\circ\text{C} \\ \frac{\kappa_{5(1)} + \kappa_{5(2)}}{2} & -8^\circ\text{C} \leq T \leq -1^\circ\text{C}, \\ \kappa_{5(2)} & T \leq -8^\circ\text{C} \end{cases} \quad (10)$$

$$Q_{met_5} = \begin{cases} Q_{met(5)} & T \geq -1^\circ\text{C} \\ 0 & -8^\circ\text{C} \leq T \leq -1^\circ\text{C}, \\ 0 & T \leq -8^\circ\text{C} \end{cases} \quad (11)$$

$$\omega_{b_5} = \begin{cases} \omega_{b(5)} & T \geq -1^\circ\text{C} \\ 0 & -8^\circ\text{C} \leq T \leq -1^\circ\text{C}. \\ 0 & T \leq -8^\circ\text{C} \end{cases} \quad (12)$$

Computer simulation example

To create a computer model, as an example, we used the following geometric dimensions of the skin – the thickness of epidermis $b_1=0.08$ mm, dermis $b_2=2$ mm, subcutaneous layer $b_3=10$ mm, inner tissue $b_4=30$ mm, radius $a_i=20$ mm ($i=1..4$) and tumor (melanoma) – thickness $b_5 = 1$ mm and radius $n = 2$ mm [53, 54]. The surface of the skin accommodates a work tool 6, which is a copper probe in the form of a round disc. Its geometrical dimensions are as follows: thickness $d = 1$ mm and radius $c = 3$ mm. This model does not take into account the thermal contact resistance between the work tool and the human skin, since it is estimated to be insignificant and makes $R_c = 2 \cdot 10^{-3} \text{ m}^2 \cdot \text{K/W}$ [55]. The temperature inside the biological tissue is $T_1 = +37^\circ\text{C}$. The ambient temperature is $T_9 = +22^\circ\text{C}$. As an example, this paper considers the case when the temperature of the work tool varies according to a given dependence in the temperature range of $T_8 = [-50 \div +50]^\circ\text{C}$. However, it is noteworthy that the developed computer model makes it possible to consider the cases when the temperature of work tool $T_f(t)$ varies in any temperature range or according to any predetermined function. The thermophysical properties of biological tissue of the human skin and tissue in the normal and frozen states are given in Tables 1, 2 [44 – 49].

Table 1.

*Thermophysical properties of biological tissue of the human skin
and tumor in the normal state [44 – 49]*

Layers of biological tissue	Epidermis	Dermis	Subcutaneous layer	Internal tissue	Tumor (melanoma)
Specific heat, C ($\text{J} \cdot \text{kg}^{-1} \cdot \text{K}^{-1}$)	3590	3300	2500	4000	3852
Thermal conductivity, κ ($\text{W} \cdot \text{m}^{-1} \cdot \text{K}^{-1}$)	0.24	0.45	0.19	0.5	0.558
Density, ρ ($\text{kg} \cdot \text{m}^{-3}$)	1200	1200	1000	1000	1030
Metabolism, Q_{met} (W/m^3)	368	368	368	368	3680
Blood perfusion rate, ω_b ($\text{ml}/\text{s} \cdot \text{ml}$)	0	0.0005	0.0005	0.0005	0.0063
Blood density, ρ_b ($\text{kg} \cdot \text{m}^{-3}$)	1060	1060	1060	1060	1060
Blood heat capacity, C_b ($\text{J} \cdot \text{kg}^{-1} \cdot \text{K}^{-1}$)	3770	3770	3770	3770	3770

Table 2

Thermophysical properties of biological tissue of the human skin in the frozen state [50, 51]

Thermophysical properties of biological tissue	Value	Measurement units
Heat capacity of frozen biological tissue (C_2)	1800	$\text{J}/\text{m}^3 \cdot ^\circ\text{C}$
Thermal conductivity of frozen biological tissue (κ_2)	2	$\text{W}/\text{m} \cdot ^\circ\text{C}$
Latent heat of phase transition (L)	$250 \cdot 10^3$	J/m^3
Upper temperature of phase transition (T_1)	-1	$^\circ\text{C}$
Lower temperature of phase transition (T_2)	-8	$^\circ\text{C}$

Thus, a three-dimensional computer model of the human skin with oncological neoplasms (melanoma) was created. To construct a computer model, the Comsol Multiphysics software package was used [56], which makes it possible to simulate thermophysical processes in biological tissue, taking into account blood circulation, heat exchange, metabolic processes and phase transition.

The distribution of temperatures and heat flux densities in biological tissue was calculated by the finite element method, the essence of which is that the object under study is divided into a large number of finite elements and in each of them a function value is sought for that satisfies given second-order differential equations with the corresponding boundary conditions. The accuracy of solving the formulated problem depends on the level of partitioning and is ensured by the use of a large number of finite elements [56] and is $T = \pm 0.1$ $^\circ\text{C}$.

Computer simulation results

According to the known methods of cryodestruction and hyperthermia of biological tissue [11, 31, 57-59], the cooling rate should be at least $(40-50)^\circ\text{C}/\text{min}$, and the heating rate $(20-25)^\circ\text{C}/\text{min}$. Therefore, in this paper, as an example, we consider the case in which the temperature of the work tool $T_f(t)$ varies in the range $[-50 \div +50]^\circ\text{C}$ as follows (Fig. 2, graph 1). First, cryodestruction of the tumor is carried out with a cooled work tool at a temperature of $T = -50^\circ\text{C}$ for $t = 30$ s, then the temperature of the work tool changes from -50°C to $+50^\circ\text{C}$ for the next 240 s (note that in this case when the temperature changes, the freezing of the tumor continues to grow for a few more seconds), following which a heated work tool is used to conduct tumor hyperthermia at a temperature of $T = +50^\circ\text{C}$ for $t = 30$ s. The subsequent decrease in temperature to $T = -50^\circ\text{C}$ occurs within 120 s, and then this temperature effect is repeated cyclically to achieve tumor destruction.

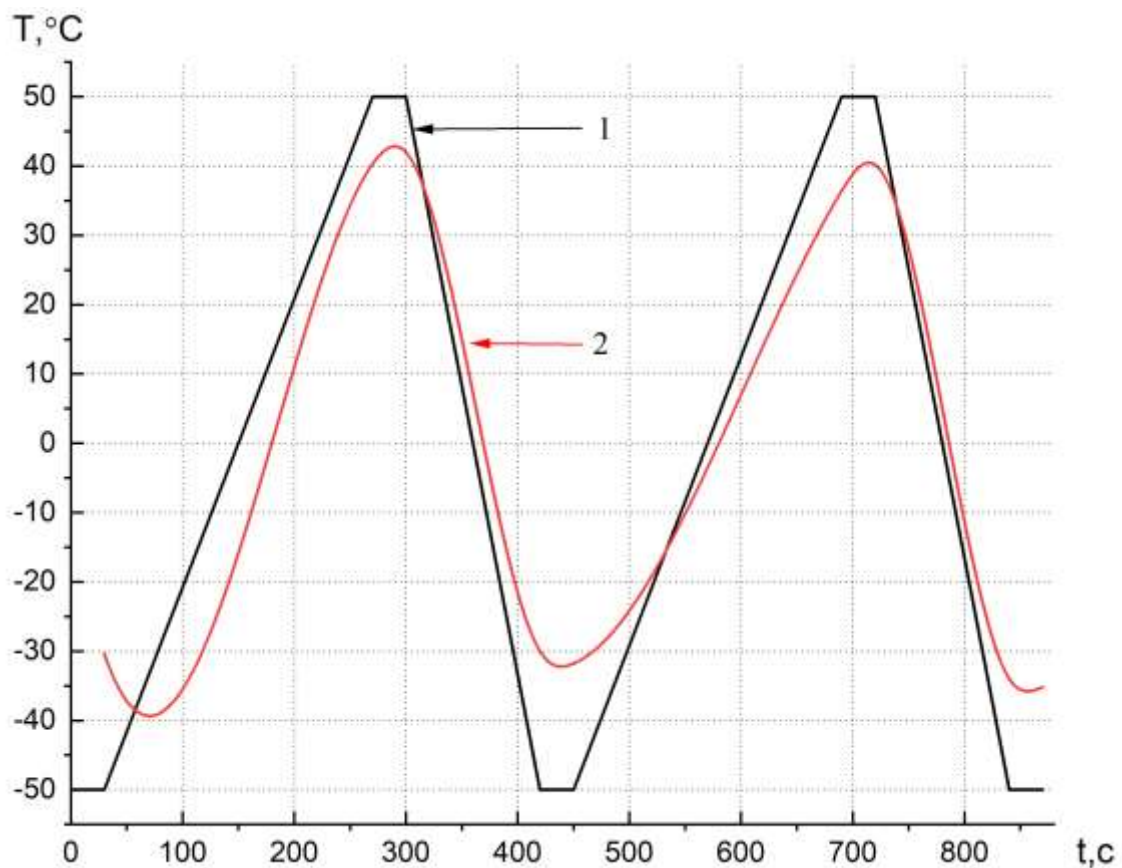


Fig.2. The plots of work tool temperature (1) and tumor temperature (2) versus time. The tumor temperature was taken at the depth of 1 mm from the skin surface along the Oy axis.

With the help of computer simulation, the temperature distribution in the tumor was determined at different points in time with the corresponding specified cyclic change in the temperature of the work tool. The results of computer simulation, namely the temperature in the tumor at a depth of 1 mm from the skin surface on the Oy axis, are shown in plot 2, Fig.2.

Figs.3-6 show the temperature distributions in the cross-section of the skin with the tumor the surface of which accommodates a work tool the temperature of which changes cyclically according to the above dependence in the temperature range of $[-50 \div +50]^\circ\text{C}$.

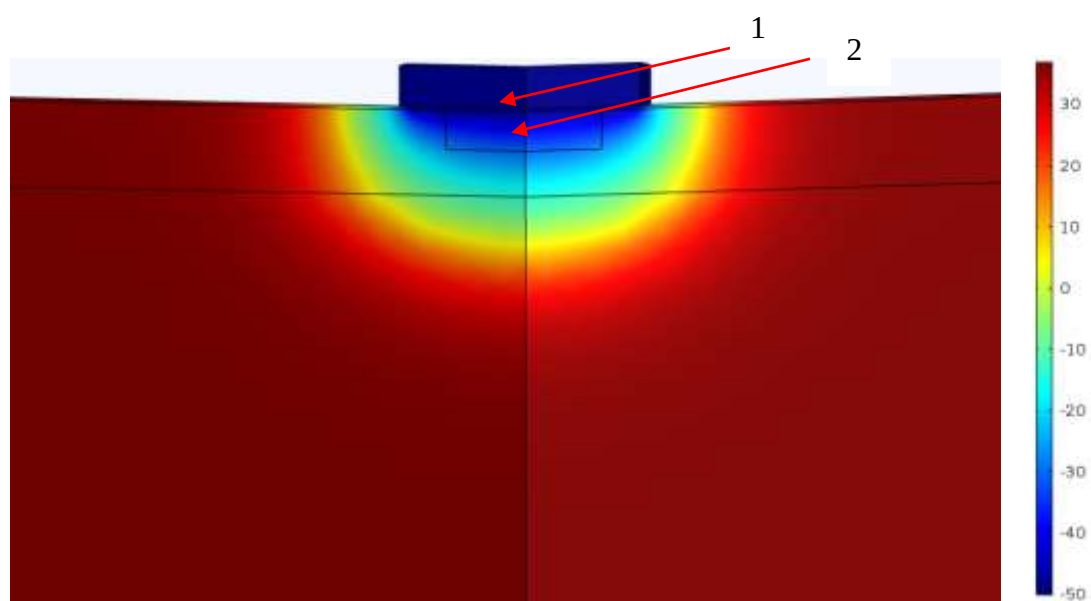


Fig.3. Distribution of temperature in the cross-section of the skin with a tumor the surface of which accommodates a work tool at a temperature of $T=50^{\circ}\text{C}$ at point of time $t=30\text{ s}$

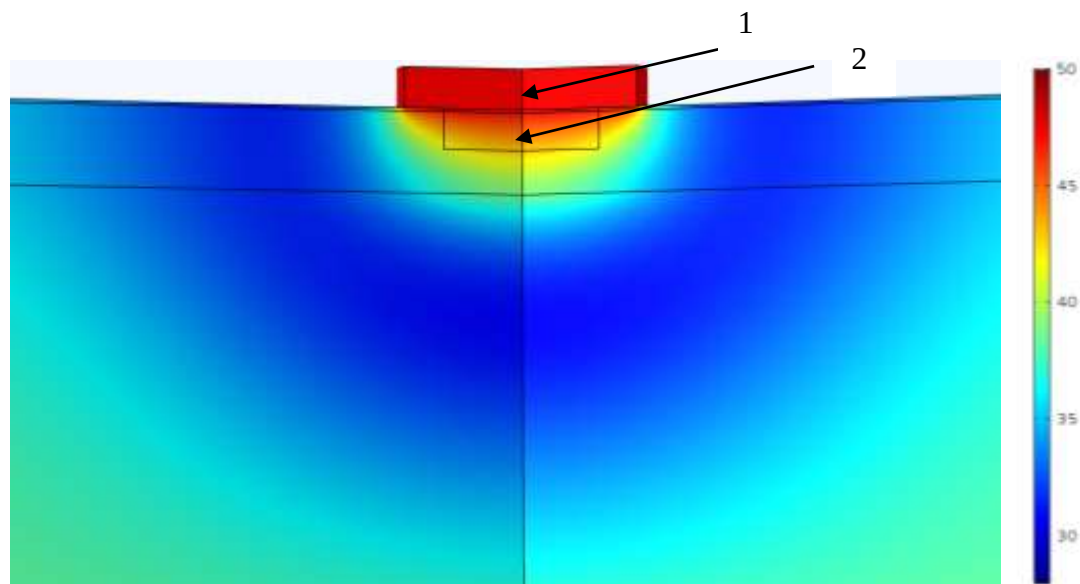


Fig.4. Distribution of temperature in the cross-section of the skin with a tumor the surface of which accommodates a work tool at a temperature of $T=+50^{\circ}\text{C}$ at point of time $t=300\text{ s}$

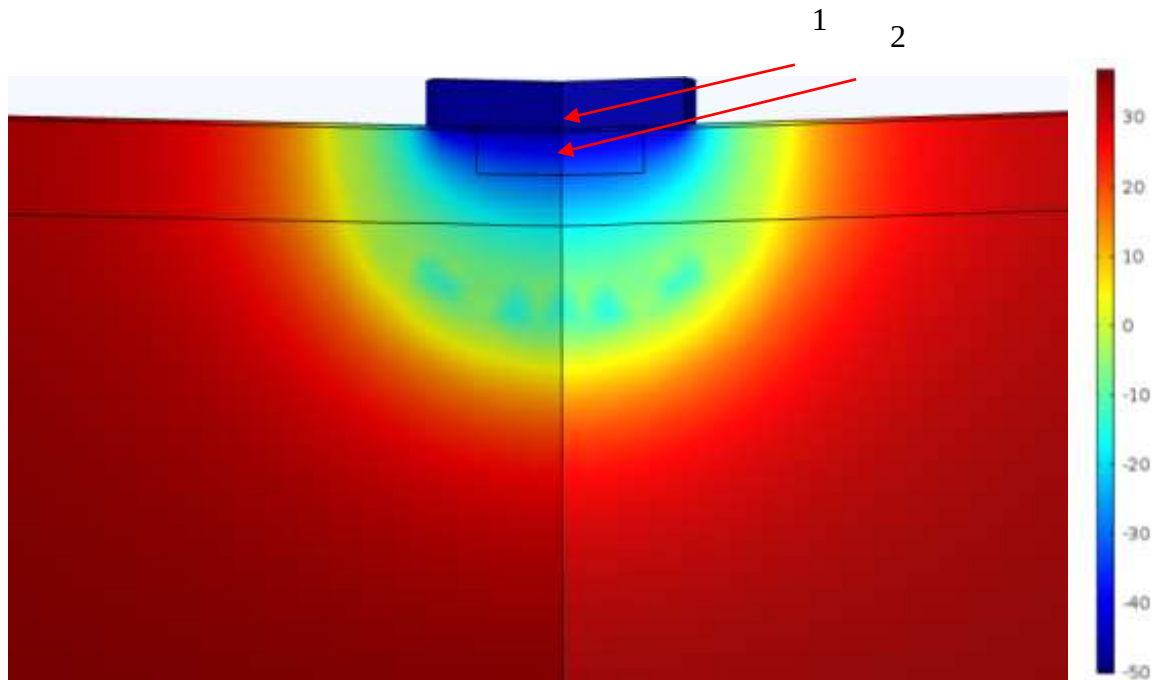


Fig.5. Distribution of temperature in the cross-section of the skin with a tumor the surface of which accommodates a work tool at a temperature of $T = -50^{\circ}\text{C}$ at point of time $t = 450\text{ s}$

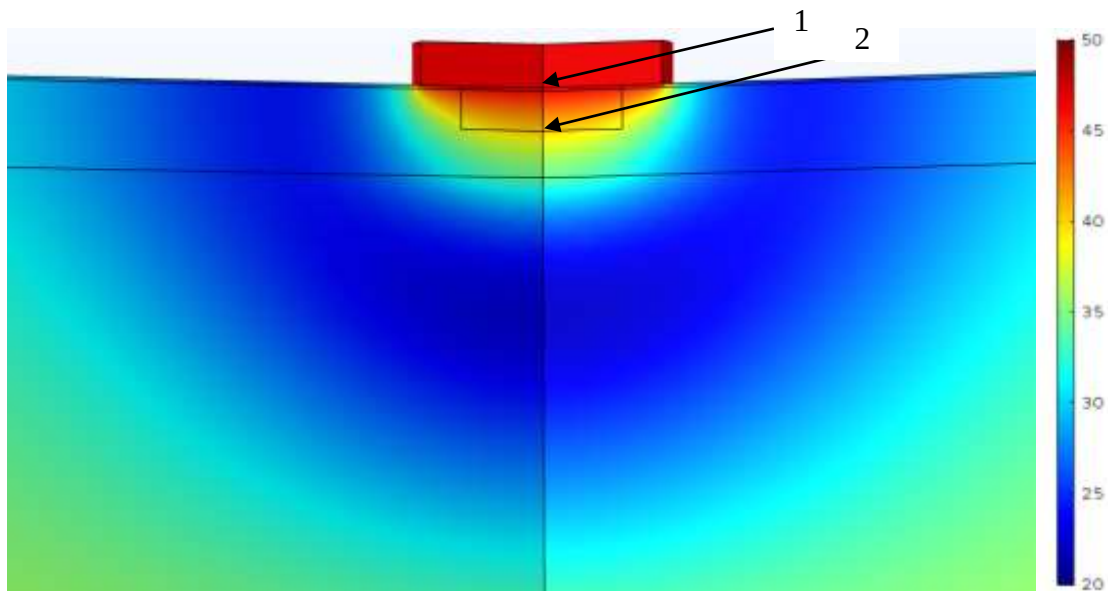


Fig.6. Distribution of temperature in the cross-section of the skin with a tumor the surface of which accommodates a work tool at a temperature of $T = +50^{\circ}\text{C}$ at point of time $t = 720\text{ s}$

From Fig .3, 4 it is seen that at $t = 30\text{ s}$ the skin tumor (melanoma) is cooled at point 1 to a temperature of -48.8°C , and at point 2 to -30.5°C (it should be noted that when changing temperature from -50°C to $+50^{\circ}\text{C}$ freezing of the tumor at point 2 continues to increase to a temperature of $T = -31.3^{\circ}\text{C}$ for $t = 4\text{ s}$). And at $t = 300\text{ s}$ the temperature at point 1 of the tumor rises to $+49.9^{\circ}\text{C}$, and at point 2 of the tumor the temperature is $+42.8^{\circ}\text{C}$. Since the tumor is in direct contact with the work tool, the

temperature at point 1 of the tumor will be close to the temperature of the work tool.

Subsequently, with repeated cyclic temperature exposure (Figs. 5, 6), it is observed that at $t = 450$ s after cooling, the temperature at point 1 of the tumor reaches 49.4°C , at point 2 of the tumor the temperature is -32.3°C . At $t = 720$ s, the temperature at point 1 of the tumor rises to $+48.6^{\circ}\text{C}$, and at point 2 of the tumor the temperature is $+40.1^{\circ}\text{C}$.

It is established that taking into account the phase transition increases the accuracy of determining the temperature in the tumor at $\Delta T = 6^{\circ}\text{C}$ and the depth of freezing (heating) by $\Delta h = 0.8$ mm.

The obtained results make it possible to determine the depth of freezing and heating of the skin layers, in particular the tumor, at a given cyclic temperature effect to achieve maximum efficiency during cryodestruction and hyperthermia. The developed computer model in dynamic mode allows determining at any time the temperature distributions in different layers of the skin and tumor with a predetermined arbitrary function of temperature change of the work tool with time $T_f(t)$.

Conclusions

1. A computer model was developed to determine the temperature in the tumor, taking into account the phase transitions in the dynamic mode for any given cyclic change in the temperature of the work tool.
2. Using computer simulations, it was found that taking into account the phase transitions increases the accuracy of determining the temperature in the tumor by $\Delta T = 6^{\circ}\text{C}$ and the depth of freezing (heating) by $\Delta h = 0.8$ mm.

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КОМП'ЮТЕРНЕ МОДЕЛЮВАННЯ ЦИКЛІЧНОГО ТЕМПЕРАТУРНОГО ВПЛИВУ НА ОНКОЛОГІЧНЕ НОВОУТВОРЕННЯ ШКІРИ ЛЮДИНИ

У роботі наведено результати комп'ютерного моделювання температурного впливу на пухлину шкіри у динамічному режимі. Побудовано фізичну, математичну і комп'ютерну моделі шкіри з онкологічним новоутворенням (меланомаю) із врахуванням теплофізичних процесів, кровообігу, теплообміну, процесів метаболізму та фазового переходу. Як приклад, розглянуто випадок, коли на поверхні пухлини знаходиться робочий інструмент, температура якого змінюється циклічно за наперед заданою залежністю у діапазоні температур $[-50 \div +50]$ °C. Визначено розподіли температури у пухлині та у різних шарах шкіри в режимах охолодження і нагріву. Отримані результати дають можливість визначати глибину промерзання і прогріву біологічної тканини, зокрема пухлини, при заданому температурному впливі. Бібл.59, рис. 6, табл. 2.

Ключові слова: температурний вплив, шкіра людини, пухлина, меланома, динамічний режим, комп'ютерне моделювання.

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В работе приведены результаты компьютерного моделирования температурного воздействия на опухоль кожи в динамическом режиме. Построены физическая, математическая и компьютерная модели кожи с онкологическим новообразованием (меланомой) с учетом теплофизических процессов, кровообращения, теплообмена, процессов метаболизма и фазового перехода. В качестве примера, рассмотрен случай, когда на поверхности опухоли находится рабочий инструмент, температура которого изменяется циклически по заранее заданной зависимости в диапазоне температур $[-50 \div +50]$ °C. Определены распределения температуры в опухоли и в различных слоях кожи в режимах охлаждения и нагрева. Полученные результаты дают возможность определять глубину промерзания и прогрева биологической ткани, в частности опухоли, при заданном температурном воздействии. Библ. 59, рис. 6, табл. 2.

Ключевые слова: температурное воздействие, кожа человека, опухоль, меланома, динамический режим, компьютерное моделирование.

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