Journal of Engineering Physics and Thermophysics, Vol. 74, No. 3, 2001

THERMOPHYSICAL INTRAOPERATIONAL ESTIMATES FOR THE DESTRUCTION ZONE OF TUMOR TISSUE IN INTERSTITIAL THERMOTHERAPY

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UDC 576.8.06+616.006.097+616.33.002.44

The authors developed models of intraoperational selection of the optimum regime for realization of thermotherapy of tumors and determination of the degree of their destruction based on successive fixation of the times of relaxation of their temperature to the arterial one. The models and evaluations of such times are based on the proposed mechanism of destruction of a tumor in local heating that is reduced to thermal regimes ensuring minimization, up to cessation, of the blood flow in the tissue, which causes its subsequent self-destruction.

For thermal medicinal technologies, such as local hyperthermia and thermotherapy, substantiation of the mechanisms of their action on malignant tissue is still an unsolved fundamental problem. Clearly, it is only on this basis that the optimum thermal regimes of clinical realization of such technologies that must ensure effective treatment and preservation of healthy tissues around the tumor can be developed. This is particularly important in the treatment of cerebral (brain) structures.

Practically all the existing publications of clinical applications of the indicated methods and their modifications, regardless of the type of physical field used for heating and its possible biospecific bioeffects, proceed, as a rule, from primary information on only the anatomical location of a tumor, more rarely on its size as well, without account for its physiological and biophysical properties.

In the overwhelming majority of numerous investigations of thermal processes in local hyperthermia and thermotherapy, researchers take into account just the initial intensity (or power) of the physical heat source and the duration of heating, which are not related to the properties of a concrete tumor, as a rule. All such values of operating conditions, most frequently not changing during the thermosession, are essentially carried over from one publication to another and rarely differ by more than 10–20%, especially in cases of the action on tissues of the same kind (for example, cerebral tissues). The current situation explains the disappointment in the obtained results of treatment by the methods of local hyperthermia and thermotherapy.

The concept (proposed in [1]) of a thermal mechanism of destruction of tumor tissue even at hyperthermal temperatures foremost because of the sclerosis or destruction of its vascular system makes it possible to perform evaluations for intraoperational selection and monitoring of the regimes of interstitial therapy under clinical conditions [2].

The thermophysical model developed below confirms the realization of approaches whose substantiation is related to the nonstationary changes in the perfusion of tissue in its heating. The simplest description of the situation can be reduced to a nonstationary two-layer model with a moving interface between the destroyed tissue with decreasing bloodfilling in the process of its heating (to be specific its source is assumed to be a laser [3] in what follows, which, however, is not a limitation of the approaches developed below) and the perfused tissue whose blood flow was formed as a result of the development of a tumor. Such a model can be reduced to solution of the equations of biological heat transfer in active inhomogeneous media as temperature responses of the tissue to a short-duration local thermal action.

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 1062-0125/01/7403-0656$25.00

Let us consider first the simplest, very idealized model for nonstationary propagation of heat in the case of its interstitial supply to a homogeneously perfusion medium and restrict ourselves to the solution of a heat-conduction equation with one space variable; the equation will be represented in the form

$$a\,\frac{\partial^2 u}{\partial x^2} = \frac{\partial u}{\partial t} \tag{1}$$

with boundary and initial conditions

$$\left.\frac{\partial u}{\partial x}\right|_{x=0} = 0\,; \quad u\,|_{x\to\infty} = 0\,; \quad u\,(x,\, t=0) = \Phi\,(x)\,. \tag{2}$$

In the representation of (1) and (2), we took into account that $c_b \approx c$ and $\rho_b \approx \rho$ and adopted the following notation:

$$a = \frac{\chi}{\rho c}\,, \quad \Theta = \frac{T - T_a}{T_a}\,, \quad u\,(x,\, t) = \Theta\,(x,\, t)\,\exp\,(\rho\omega t)\,, \quad \Phi\,(x) = T_a\,(\varphi\,(x) + 1)\,. \tag{3}$$

Applying the Laplace transformation and using the Green functions, we represent the final solution as follows:

$$\frac{\Theta\,(t)}{\Theta\,(0)} = \frac{1}{1 - \dfrac{1}{\mu}\sqrt{\dfrac{\rho\omega}{a}}}\left[\operatorname{erfc}\,(\sqrt{\rho\omega t}\,) - \frac{1}{\mu}\sqrt{\frac{\rho\omega}{a}}\,\exp\,((\mu^2 a - \rho\omega)\,t)\,\operatorname{erfc}\,(\mu\,\sqrt{at}\,)\right], \tag{4}$$

$$\operatorname{erfc}\,(y) = \frac{2}{\sqrt{\pi}}\int_y^\infty \exp\,(-t^2)\,dt\,,$$

if the initial temperature distribution $\Phi(x)$ which is unknown in heating of the tissue with its undefinable, in essence, characteristics can be approximated in the form of a sum of two exponents:

$$\Phi\,(x) = A\,\exp\left(-\sqrt{\frac{\rho\omega}{a}}\;x\right) + B\,\exp\,(-\mu x)\,, \tag{5}$$

where μ is a parameter similar in meaning to the coefficient of extinction of light in the biotissue whose value has already been discussed in [4]. Formally, the solution (4) is a change with time in the temperature Θ relative to its original value at the point $x = 0$. By determining these values of the changing temperature during a limited time interval we can evaluate the influence of the parameters ω for μ = const and μ for ω = const or of simultaneously changing ω and μ on the relaxation time τ_{rel}, which corresponds to the time of an *e*-fold decrease in the relative temperature Θ.

For a more real two-layer thermophysical model of tissue in its local short-duration heating the system of equations, in the notation (3), has the form

$$a\,\frac{\partial^2 \Theta_1}{\partial x^2} = \frac{\partial \Theta_1}{\partial t}\,, \quad x \in [0,\, l]\,; \quad a\,\frac{\partial^2 \Theta_2}{\partial x^2} - \rho\omega\Theta_2 = \frac{\partial \Theta_2}{\partial t}\,, \quad x \in (l,\, \infty)\,;$$

$$\left.\frac{\partial \Theta_1}{\partial x}\right|_{x=0} = 0\,; \quad \Theta_2\,|_{x\to\infty} = 0\,; \quad \Theta_1\,|_{t=0} = \psi_1\,(x)\,; \quad \Theta_2\,|_{t=0} = \psi_2\,(x)\,; \tag{6}$$

$$\Theta_1\big|_{x=l} = \Theta_2\big|_{x=l}; \quad \left.\frac{\partial\Theta_1}{\partial x}\right|_{x=l} = \left.\frac{\partial\Theta_2}{\partial x}\right|_{x=l}.$$

It is assumed in representation (6) that the length of the first layer (the index i = 1) that determines a tissue with a system of blood flow destroyed in its thermal heating and a single mechanism of heat transfer in it, i.e., heat conduction, is l. Although this quantity is not constant and increases as the tumor is destroyed, the rate of such increase can be quite low [4]; therefore, we can disregard the change in l in the case of short-duration heating and corresponding cooling. With such representations the properties of the second layer (the index i = 2) correspond to a perfused tissue with another blood flow-related mechanism of heat transfer. In (6), we have also used the assumption that the thermophysical constants of the tissues of both layers are equal, which agrees with the literature data [4].

In solve (6) we use the Laplace transformation and obtain the solution for the transforms of the sought functions (they are marked below by a horizontal overscribed bar; $t \div s$) by the method of Green cell functions G_{ij}, i, j = 1, 2, for multilayer media [5]. Finally, for the most important temperature distribution in the first layer when x = 0 in the space of transforms we obtain

$$\overline{\Theta}_1(0, s) = \int_0^l \overline{G}_{11}^*(0, \xi, s)\, \psi_1(\xi)\, d\xi + \int_l^\infty \overline{G}_{12}(0, \xi, s)\, \psi_2(\xi)\, d\xi. \tag{7}$$

The system of equations for the Green functions has the form

$$a\frac{d^2\overline{G}_{11}}{dx^2} - s\overline{G}_{11} = 0; \quad a\frac{d^2\overline{G}_{11}^*}{dx^2} - s\overline{G}_{11}^* = 0; \quad a\frac{d^2\overline{G}_{21}}{dx^2} - (s+\rho\omega)\,\overline{G}_{21} = 0; \quad a\frac{d^2\overline{G}_{12}}{dx^2} - s\overline{G}_{12} = 0;$$

$$a\frac{d^2\overline{G}_{22}}{dx^2} - (s+\rho\omega)\,\overline{G}_{22} = 0; \quad a\frac{d^2\overline{G}_{22}^*}{dx^2} - (s+\rho\omega)\,\overline{G}_{22}^* = 0; \quad \overline{G}_{11}\big|_{\xi=x} = \overline{G}_{11}^*\big|_{\xi=x}; \quad \overline{G}_{22}\big|_{\xi=x} = \overline{G}_{22}^*\big|_{\xi=x};$$

$$\frac{d\overline{G}_{11}}{dx} - \frac{d\overline{G}_{11}^*}{dx}\bigg|_{\xi=x} = -\frac{1}{a}; \quad \frac{d\overline{G}_{22}}{dx} - \frac{d\overline{G}_{22}^*}{dx}\bigg|_{\xi=x} = -\frac{1}{a}; \quad \frac{d\overline{G}_{11}^*}{dx}\bigg|_{x=0} = 0; \quad \frac{d\overline{G}_{12}}{dx}\bigg|_{x=0} = 0; \quad \overline{G}_{21}\big|_{x=\infty} = 0;$$

$$\overline{G}_{22}\big|_{x=\infty} = 0; \quad \overline{G}_{11}\big|_{x=l} = \overline{G}_{21}\big|_{x=l}; \quad \overline{G}_{12}\big|_{x=l} = \overline{G}_{22}^*\big|_{x=l}; \quad \frac{d\overline{G}_{11}}{dx}\bigg|_{x=l} = \frac{d\overline{G}_{21}}{dx}\bigg|_{x=l}; \quad \frac{d\overline{G}_{12}}{dx}\bigg|_{x=l} = \frac{d\overline{G}_{22}^*}{dx}\bigg|_{x=l}. \tag{8}$$

Its solution for the functions of interest is

$$\overline{G}_{11}^* = \frac{1}{\sqrt{sa}} \frac{\cosh\left(\sqrt{\frac{s}{a}}\,(\xi - l)\right) - \sqrt{\frac{s+\rho\omega}{s}}\,\sinh\left(\sqrt{\frac{s}{a}}\,(\xi - l)\right)}{\sinh\left(\sqrt{\frac{s}{a}}\,l\right) + \sqrt{\frac{s+\rho\omega}{s}}\,\cosh\left(\sqrt{\frac{s}{a}}\,l\right)} \cosh\left(\sqrt{\frac{s}{a}}\,x\right), \tag{9}$$

$$\overline{G}_{12} = \frac{1}{\sqrt{sa}} \frac{\cosh\left(\sqrt{\frac{s}{a}}\,x\right)\exp\left(-\sqrt{\frac{s+\rho\omega}{s}}\,(\xi - l)\right)}{\sinh\left(\sqrt{\frac{s}{a}}\,l\right) + \sqrt{\frac{s+\rho\omega}{s}}\,\cosh\left(\sqrt{\frac{s}{a}}\,l\right)}. \tag{10}$$

It is obvious that the functions of the initial temperature distributions $\psi_1(x)$ and $\psi_2(x)$ for the process of interstitial thermotherapy are unknown, as a rule, and are actually undefinable under the conditions of clinical use. Therefore, we use here the approximation proposed above but with the replacement of the perfusion-dependent coefficient $\sqrt{\rho\omega/a}$ by an empirical μ_1:

$$\psi(x) = A\exp(-\mu_1 x) + B\exp(-\mu_2 x) \approx A\exp(-\mu_1 x), \quad x \in [0, \infty). \tag{11}$$

The introduction of the coefficient μ_1, just as of μ earlier, makes it possible to perform evaluations of the times of relaxation of the heated-tissue temperature to the arterial one within the framework of the proposed approach, for which precisely these times are the only quantities measurable in the process of interstitial thermotherapy. Determination of the concrete values of μ and μ_1 is essentially the solution of classical problems of decoding the response-signals received by any physical system to the external action and will be the topic of subsequent reports. However, it is noteworthy that determination of similar characteristics of the original tissue and of the tissue changing in heating greatly complicates the practical selection of optimum conditions for realization of hyperthermal and thermotherapeutic technologies, which ultimately creates the still existing constant uncertainty in the efficiency of such methods of treatment. It is precisely from these considerations that the approach developed, whose model is presented here, makes it possible to eliminate the need for additional measurements.

Turning back to determination of the function $\psi(x)$, we can finally write the expression for $\overline{\Theta}_1(0, s)$ as follows:

$$\overline{\Theta}_1(0, s) = \frac{1}{\sqrt{sa}} \frac{A}{\sinh\left(l\sqrt{\frac{s}{a}}\right) + \sqrt{\frac{s+\rho\omega}{s}}\cosh\left(l\sqrt{\frac{s}{a}}\right)} \left(\frac{1 - \sqrt{\frac{s+\rho\omega}{s}}}{2} \frac{\exp(-\mu_1 l) - \exp\left(l\sqrt{\frac{s}{a}}\right)}{\sqrt{\frac{s}{a}} - \mu_1} - \right.$$

$$\left. - \frac{1 + \sqrt{\frac{s+\rho\omega}{s}}}{2} \frac{\exp(-\mu_1 l) + \exp\left(l\sqrt{\frac{s}{a}}\right)}{\sqrt{\frac{s}{a}} + \mu_1} + \frac{\exp(-\mu_1 l)}{\sqrt{\frac{s+\rho\omega}{a}} + \mu_1} \right). \tag{12}$$

In order to obtain the inverse transform for (12), we draw on the fact that $l/\sqrt{a}$ is rather high. Having expanded the expression $\frac{1}{\sinh(l\sqrt{\frac{s}{a}}) + \sqrt{\frac{s+\rho\omega}{s}}\cosh(l\sqrt{\frac{s}{a}})}$ in functions $\exp(-lj\sqrt{\frac{s}{a}})$, j = 0, 1, 2, ... near $\exp(-l\sqrt{\frac{s}{a}})$ = 0 and having restricted ourselves to the first two terms, we obtain

$$\overline{\Theta}_1(0, s) =$$

$$= \frac{1}{\sqrt{s}} \frac{\sqrt{s} - \sqrt{s+\rho\omega}}{\sqrt{s} + \sqrt{s+\rho\omega}} \frac{1}{\sqrt{s} - \mu_1\sqrt{a}} \exp\left(-l\sqrt{\frac{s}{a}}\right)\left(\exp(-\mu_1 l) - \exp\left(-l\sqrt{\frac{s}{a}}\right)\right) + \frac{1}{\sqrt{s} + \mu_1\sqrt{a}} \times$$

$$\times \frac{1}{\sqrt{s}}\left(1 - \exp(-\mu_1 l)\exp\left(-l\sqrt{\frac{s}{a}}\right)\right) + \frac{2}{\sqrt{s} + \sqrt{s+\rho\omega}} \frac{1}{\mu_1\sqrt{a} + \sqrt{s+\rho\omega}} \exp(-\mu_1 l)\exp\left(-l\sqrt{\frac{s}{a}}\right). \tag{13}$$

The temperature distribution in the tissue at $x = 0$ in the space of inverse transforms will finally take the form

$$\frac{\Theta_1(t)}{\Theta_1(0)} = -\frac{\rho\omega}{4}\exp(-\mu_1 l)\exp\left(-\frac{\rho\omega t}{4}\right)I_1(t) + \exp(-\mu_1 l)\,I_2(t) + \frac{\rho\omega}{4}\exp\left(-\frac{\rho\omega t}{4}\right)I_3(t) +$$

$$+ \operatorname{erfc}(\mu_1\sqrt{at})\exp(\mu_1^2 at) - \operatorname{erfc}\left(\frac{l^2}{2a\sqrt{t}} + \mu_1\sqrt{at}\right)\exp\left(\mu_1 l\left(\frac{l}{\sqrt{a}} - 1\right)\right)\exp(\mu_1^2 at)\,; \qquad (14)$$

$$I_1(t) = \int_0^t (t-u)\exp\left(\frac{\rho\omega u}{4}\right)\left(\frac{l}{2u\sqrt{\pi a u}} + \mu_1\sqrt{\frac{a}{\pi u}}\right)\exp\left(-\frac{l^2}{4au}\right)du +$$

$$+ \int_0^t \mu_1^2\, a\operatorname{erfc}\left(\frac{l}{2\sqrt{au}} - \mu_1\sqrt{au}\right)\exp(-\mu_1 l)\exp(\mu_1^2 au)\,du\,; \qquad (15)$$

$$I_2(t) = \int_0^t \exp(-\rho\omega u)\left(\frac{1}{\sqrt{\pi u}} - \mu_1\sqrt{a}\exp(\mu_1^2 au)\operatorname{erfc}(\mu_1\sqrt{au})\right)\frac{1}{\sqrt{\pi(t-u)}}\exp\left(-\frac{l^2}{4a(t-u)}\right)du\,; \qquad (16)$$

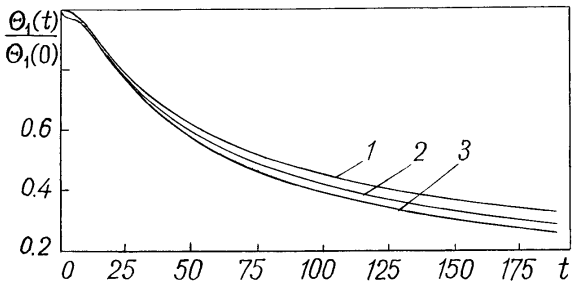
$$I_3(t) = \int_0^t (t-u)\exp\left(\frac{\rho\omega u}{4}\right)\left(\frac{l}{u\sqrt{\pi a u}} + \mu_1\sqrt{\frac{a}{\pi u}}\right)\exp\left(-\frac{l^2}{au}\right)du +$$

$$+ \int_0^t \mu_1^2\, a\operatorname{erfc}\left(\frac{l}{\sqrt{au}} - \mu_1\sqrt{au}\right)\exp(-2l\mu_1)\exp(\mu_1^2 au)\,du\,. \qquad (17)$$

In deriving (14)-(17), use was made of the approximation $\sqrt{s+\rho\omega} \approx \sqrt{s}\left(1 + \frac{\rho\omega}{2s}\right)$ and of the table of inverse Laplace transforms [6]. It can be shown that the expression for $\Theta_1(t)$ holds for small values of t, namely, for the times of heating or cooling to the arterial temperature $t \le 2\tau_{rel}$.

Thus, we have obtained a formula for the values of the temperature recorded at the point $x = 0$ as functions of the changes in the bloodfilling (perfusion) of the tissue ω on its segment of length l (for a one-dimensional problem). It is obvious that the established interrelation confirms the possibility of evaluating the evolution of ω and l by the measured values of T_1 ($x = 0$) and τ_{rel}. The values of ω that are necessary in such an indirect manner and decrease during the session of thermotherapy determine the degree of destruction of a tumor in accordance with [1, 7, 8] in the selected regimes of action [2]. Minimization of the blood flow up to its cessation causes further destruction of neoplastic tissue [9]. It is precisely on these ideas that one direction in the chemotherapy of oncological diseases is being intensely developed today; this direction can lead to the development of preparations that inhibit the angiogenesis of a tumor [7]. The physiological substantiation of the destruction of tissue in such a process is quite obvious.

The model developed here qualitatively confirms the mechanism of hyperthermia and thermotherapy [10] which is reduced to such regimes of realization of these technologies that will ensure minimization of the blood flow in the tumor. It is quite obvious that this local purposeful action of heat (even without taking



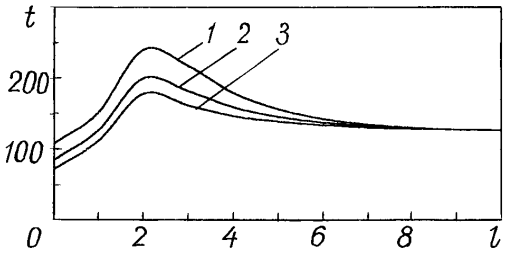


Fig. 1. Dependence of $\Theta_1(t)/\Theta_1(0)$ at $x = 0$ on the values of the blood flow in the second layer with $l = 1$ mm and $\mu = 0.333$ mm^{-1}: 1, 2, and 3) for $\omega = 0.1$, 0.3, and 0.5 (all in ml/(g·min)). t, sec.

Fig. 2. Relaxation time of the temperature vs. values of l for different values of ω and $\mu = 0.333$ mm^{-1}: 1, 2, and 3) notation is the same as in Fig. 1. l, mm.

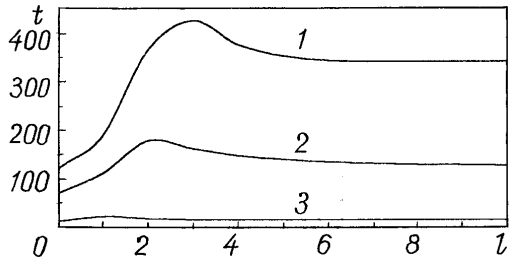


Fig. 3. Relaxation time of the temperature vs. values of l with $\omega = 0.5$ ml/(g·min): 1, 2, and 3) for μ_1 equal to 0.2, 0.333, and 1 (all in mm^{-1}).

into account possible biospecific effects of its source) is more efficient and safe than the use of medicinal preparations that inhibit the blood flow of a tumor and are still absent from the worldwide pharmaceutical market. It is also of importance that the thermal regimes can in essence be realized in such a manner that they will turn out to be much more noninvasive for the tissues surrounding the tumor, which is particularly important, for example, in neurooncology.

Taking into account the mechanism proposed and the models developed, we analyze the obtained results and perform certain evaluations.

Under the conditions of clinical use of thermotherapeutic technologies, it is most simple technically to measure the relaxation times τ_{rel}. Therefore, we calculate these times from formulas (4)–(5) for a single-layer model (τ^{I}_{rel}) and formulas (14)–(17) for a two-layer model (τ^{II}_{rel}); we set $\rho = 10^3$ kg/m^3, $c = 4200$ J/(kg·^{o}C), and $a = (1/9)\cdot 10^{-6}$ m^2/sec [11]. Calculation results make it possible to draw the following conclusions:

1. As μ increases, the relaxation times of the temperature decrease, and the most sharply for τ^{II}_{rel}.

2. With increase in the perfusion of tissues τ^{I}_{rel} decreases rapidly, as was noted in [12], too, and vice versa. However, for τ^{II}_{rel} this dependence on the values of the blood flow is not so expressive (Fig. 1), which indicates the decrease in the influence of perfusion on the temperature in the first layer.

3. The dependences of τ^{II}_{rel} on the values of the thickness l of the first layer for different ω (Fig. 2) and μ_1 (Fig. 3) are not monotonic, which rather indicates the changes in μ_1 during the thermosession. Upon attainment of a certain critical value of l, τ^{II}_{rel} becomes stabilized, which suggests that the steady-state temperature in the first layer is independent of the values of the blood flow in the second one. For the practice of thermotherapeutic technologies, this means that it is impossible to detect large values of the thickness (volumes) of destruction of the blood flow of tissues in the selected regime, and it must be changed if any part

of the tumor remains undestroyed. By virtue of the developed mechanism of thermotherapy this governs the cessation of further destruction of the tumor itself.

Thus, we have developed models of intraoperational selection of the optimum regime for realization of tumor thermotherapy and determination of the degree of destruction of such heated tissues which are based on successive fixation of the times of relaxation of their temperature to the arterial one with the disconnected heat source. The models and the performed evaluations of such times are based on the proposed mechanism of destruction of a tumor in local heating that is reduced to thermal regimes ensuring minimization, up to cessation, of the blood flow in the tissue, which causes its further self-destruction. The developed procedure requires no additional, usually almost inaccessible, knowledge of the parameters of laser radiation and its interaction with tissue and operates with just two parameters that are easily determined under clinical conditions as well. Although the model developed here is formulated and calculated for one-dimensional situations, its generalization to two- and three-dimensional cases is quite transparent. Calculations are also possible for such conditions where other physical fields are used as the heat source. Finally, in photodynamic therapy, the destroyed volumes of the tumor can also be evaluated based on the model proposed and on the use of a measured-out supply of heat sufficient for an increase in the temperature above the arterial one in the tissue.

NOTATION

x, ξ, space coordinates; t, time, l, thickness of the destroyed layer; ρ and c, density and specific heat of the tissue, respectively; ρ_b and c_b, density and specific heat of the blood, respectively; χ, thermal conductivity; a, thermal diffusivity of the tissue; T, temperature; T_a, arterial temperature; ω, blood flow; $\varphi(x)$, $\psi_1(x)$, and $\psi_2(x)$, initial temperature distributions in the biotissue; μ, μ_1, μ_2, A, and B, empirical coefficients; G and G^*, Green functions; τ_{rel}, time of temperature relaxation. Subscripts: b, refers to the blood; i, number of the layer; i, j, number of the Green cell function.

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