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STATEMENT OF THE PROBLEM OF OPTIMIZATION AND CONTROL OF TISSUE TEMPERATURE DISTRIBUTION IN LOCAL HYPERTHERMIA OF MALIGNANT TUMORS

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We consider a model of thermal processes in treatment by local hyperthermia. The model is based on the classical nonlinear biothermal equation. We formulated a problem of optimization consisting of maximization of the mortality function of tumor cells and finding a control for which the temperature distribution in the tumor maximizes the therapeutic effect, while the injury function of healthy tissue is small.

1. Introduction. The main aim of treatment by local hyperthermia is to heat the tumor tissue to specific temperatures over its entire volume, provided that the heating of and thermal damage to the tissue remain small. Certain problems associated with simulation of thermal processes in hyperthermia have been considered, for example, in [1-3]. In [4], a procedure of optimization is suggested for a phase hyperthermal system. In this work the stationary classical biothermal equation is considered in a semi-infinite uniform region and, using Green's function, a solution of the problem for a four-element system is obtained.

For the vector q = (P_1, P_2, P_3, P_4, φ_1, φ_2, φ_3, and φ_4) the amplitude P_i and phase φ_i components of the i-th element are considered as controls. The optimization problem consists in finding a vector

$$\tilde{q} = (\tilde{P}_1, \tilde{P}_2, \tilde{P}_3, \tilde{P}_4, \tilde{\varphi}_1, \tilde{\varphi}_2, \tilde{\varphi}_3, \tilde{\varphi}_4) ,$$

for tumor tissue that minimizes the quadratic functional

$$\int\int\int (T_q(x) - T_0)^2 \, dx \tag{1.1}$$

for healthy tissue with the constraints

$$T_q(x) \le T_1 . \tag{1.2}$$

Actually, however, treatment by hyperthermia is not a stationary process. The damage and destruction of living tissue depend not only on the magnitude of the temperature but also on the duration of its action. Therefore, if the time of the action of a high temperature is rather small, the tissue is hardly damaged. Conversely, even a moderately high but long-lasting temperature can lead to the damage and destruction of healthy tissue.

In this connection, below we consider a nonstationary problem for the nonlinear biothermal equation. We introduce a damage function that is determined at each point of the tissue with allowance for the temperature history. This function is normalized so that it is equal to zero for healthy tissue and to unity for damaged tissue.

The optimization problem involves maximization of the mortality function of the tumor cells. In this case the value of the destruction function in healthy tissue must be small.

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2. Direct Problem. Let $\Omega \subset \mathbf{R}^n$, $n = 2, 3$ be a region filled with tissue, with tumor occupying the region $\Omega_1 \subset \Omega$ and a healthy tissue the region $\Omega \setminus \Omega_1$ (Fig. 1). We denote the boundaries of the Ω and Ω_1 regions by S and Γ and assume that the latter quantities are continuous according to Lipschits. Let $S_1 \subset S$ be the boundary between the tissue and the environment and $S_2 = S \setminus S_1$ the boundary between the region considered and the tissue located outside this region.

The temperature field T in the healthy tissue is described by the classical biothermal equation [5, 6]

$$a \frac{\partial T}{\partial t} = \sum_{i=1}^{n} \frac{\partial}{\partial x_i} \left(k \frac{\partial T}{\partial x_i} \right) - W (T - T_a) + Q \quad \text{in} \quad \Omega \times (0, N) . \tag{2.1}$$

The right-hand side of Eq. (2.1) determines the amount of heat passing through the tissue. The second term of Eq. (2.1) represents heat transfer due to blood circulation. We will consider boundary conditions of the following form:

$$T = T_1 \quad \text{over} \quad S_2 \times (0, N) , \tag{2.2}$$

$$k \frac{\partial T}{\partial \nu} = \beta (T_2 - T) \quad \text{over} \quad S_1 \times (0, N) . \tag{2.3}$$

We assume that the following initial temperature distribution is given:

$$T (x, 0) = T_0 (x) , \quad x \in \Omega . \tag{2.4}$$

In particular, it can be assumed that $T_0 = T_1 = T_a = \widetilde{C}$.

Let us assume that

$$T_a = \text{const} , \tag{2.5}$$

$$\{a, k\} \subset L_\infty (\Omega) , \tag{2.6}$$

$$a (x) \geq b_1 , \quad k (x) \geq b_2 \quad \text{almost everywhere in} \quad \Omega , \tag{2.7}$$

$$\beta \in L_\infty (S_1) , \ \beta (s) \geq b_3 \quad \text{almost everywhere over} \quad S_1 , \tag{2.8}$$

$$b_i = \text{const} > 0 \quad (i = \overline{1, 3}) . \tag{2.9}$$

Here and below we use cornventional notation for the functional spaces [7, 8]. Let $W = W(x, T)$ and the following conditions be satisfied:

$$W \in L_\infty (\Omega, C^1 (R)) , \tag{2.10}$$

$$\forall \ (x, \alpha) \in \Omega \times R , \quad 0 \leq W (x, \alpha) \leq b_4 , \tag{2.11}$$

$$\forall \ (x, \alpha) \in \Omega \times R , \quad \frac{\partial W}{\partial \alpha} (x, \alpha) \geq 0 , \tag{2.12}$$

where $b_4 = \text{const} > 0$. If $(x, t) \to \varphi(x, t)$ is a function defined in G_1, then we assume that $\varphi(t) = \langle x \to \varphi(x, t) \rangle$ and consider φ a function (or distribution) of t, taking values in the space of functions (or distributions) of x.

Let $\widetilde{T}$ be a continuation of T_1 in G_1 and satisfy the conditions

$$\tilde{T} \in L_2((0, T);\ H^1(\Omega)), \tag{2.13}$$

$$\frac{\partial \tilde{T}}{\partial t} \in L_2((0, T);\ H^1(\Omega)^*), \tag{2.14}$$

$$\tilde{T}|_{G_2} = T_1 . \tag{2.15}$$

In particular, if $T_1(s, t) = C = \text{const}$ on G_2, then we can let

$$\tilde{T}(x, t) = C \ \forall\ (x, t) \in G_1 .$$

We assume that

$$Q \in L_2((0, N);\ X^*), \tag{2.16}$$

$$T_0 \in L_2(\Omega), \tag{2.17}$$

$$T_2 \in L_2((0, N);\ H^{-1/2}(S_1)). \tag{2.18}$$

Specifically, we can assume that $\forall\ x \in \Omega;\ T_0(x) = \hat{C}$. The function $T = \tilde{T} + T_a + \hat{T}$ will be called a generalized solution of problem (2.1)-(2.4) if $\hat{T}$ is a solution for the following problem:

$$\hat{T} \in L_2((0, T);\ X) \cap L_\infty((0, T);\ L_2(\Omega)), \tag{2.19}$$

$$\frac{\partial \hat{T}}{\partial T} \in L_2((0, T);\ X^*), \tag{2.20}$$

$$\left(a \frac{\partial \hat{T}}{\partial t}(t), h\right) + (L(t)\hat{T}(t), h) = (Q(t), h) - \left(a \frac{\partial \tilde{T}}{\partial t}(t), h\right) -$$
$$- \int_\Omega \sum_{i=1}^{n} k \frac{\partial \tilde{T}}{\partial x_i}(t) \frac{\partial h}{\partial x_i}\, dx - \int_{S_1} \beta(\tilde{T}(t) + T_a - T_2)\, h\, ds, \quad \forall\ h \in X, \tag{2.21}$$

$$\hat{T}(0) = T_0 - \tilde{T}(0) - T_a . \tag{2.22}$$

We can show that under condition (2.5)-(2.15) the operator is strictly monotonic. Using the results of [6, 7], we will prove the following theorem.

Theorem 2.1. *Let conditions (2.5)-(2.15) and (2.16)-(2.18) be satisfied. Then, there exists a unique solution of problem (2.19)-(2.22), where the function $(Q;\ T_2) \to T$, which determines the solution, is a continuous transform of*

$$G = L_2((0, N);\ X^*) \times L_2((0, N);\ H^{-1/2}(S_1))$$

to

$$V = \left\{ u \mid\ u \in L_2((0, T);\ H^1(\Omega));\ \frac{\partial u}{\partial t} \in L_2((0, T);\ (H^1(\Omega))^*) \right\}.$$

3. Problem of Optimization. Let us consider the function of the heat source power Q and the cooling-medium temperature T_2 as controls. The set of controls will be determined in the form

$$\mathrm{U} = \left\{ q \mid q = (Q, T_2) \in G \right\}.$$

From Theorem 2.1 it follows that for each $q \in \mathrm{U}$ there exists a unique generalized solution T_q of problem (2.1)-(2.4), where the function $q \to T_q$ is a continuous transform of U to V. For each $q \in \mathrm{U}$ we determine the damage function of the tissue at the point $x \in \Omega$

$$\Phi(q, x) = \int_0^N g(T_q(x, t), x)\, T_q(x, t)\, dt.$$

Here g is the influence function, which depends on temperature T and $x \in \Omega$. In our case $g(T_q(x, t), x)T_q(x, t)$ is the degree of tissue damage at a point $(x, t) \in G_1$. The function g is determined from an experiment and is equal to zero for $T \leq \tilde{C}$, while for $T > \tilde{C}$ it increases with an increase in T, $\tilde{C}$ = const > 0. For undamaged living tissue, $\Phi(q, x) = 0$ and the function g is normalized so that the equality $\Phi(q, x) = 0$ indicates the tissue damage in the vicinity of point x. We consider that:

$$g \in C(R \times \overline{\Omega}), \tag{3.1}$$

$$b_5 \geq g(\alpha, x) \geq 0, \quad \forall\, (\alpha, x) \in R \times \Omega, \tag{3.2}$$

$$b_5 = \text{const} > 0. \tag{3.3}$$

We assume that the region of the tumor Ω_1 is divided into n_1 small open areas ω_i such that

$$\omega_i \cap \omega_j = \varnothing \quad (i, j = \overline{1, n_1}\,;\ i \neq j), \quad \bigcup_{i=1}^{n_1} \overline{\omega}_i = \overline{\Omega}_1. \tag{3.4}$$

For the function q $\in \mathrm{U}$ we determine the extent of damage in ω_i

$$\Phi_i(q) = (\text{mes}\, \omega_i)^{-1} \times \int_{\omega_i} \int_0^N g(T_q(x, t), x)\, T_q(x, t)\, dx\, dt \tag{3.5}$$

and the objective functional

$$\Psi_0(q) = \sum_{i=1}^{n_1} (\Phi_i(q) - 1)^2. \tag{3.6}$$

It is obvious that minimization of functional Φ_0 is equivalent to maximization of tumor damage. Similarly, we divide the region of healthy tissue $\Omega \backslash \Omega_1$ into n_2 small open areas χ_i such that

$$\chi_i \cap \chi_j = \varnothing \quad (i, j = \overline{1, n_2}\,;\ i \neq j),$$

$$\bigcup_{i=1}^{n_2} \overline{\chi}_i = \overline{\Omega} \setminus \Omega_1. \tag{3.7}$$

The damage extent in χ_i is:

$$\Psi_i(q) = (\text{mes}\, \chi_i)^{-1} \times \int_{\chi_i} \int_0^N g(T_q(x, t), x)\, T_q(x, t)\, dx\, dt. \tag{3.8}$$

Let us determine the set of admissible controls

$$\mathrm{U}_{\alpha\delta} = \Big\{ q \mid q = (Q, T_2) \in \mathrm{U} ,$$

$$\| Q \|_{L_2(G_1)} + \left\| \frac{\partial Q}{\partial t} \right\|_{L_2(G_1)} \le c_1 , \quad \| T_2 \|_{L_2(G_2)} + \left\| \frac{\partial T_2}{\partial t} \right\|_{L_2(G_2)} \le c_2 ,$$

$$\Psi (q) \le l_i , \quad i = \overline{1, n_2} , \ c_i = \text{const} > 0 , \quad i = 1, 2 ; \quad l_i = \text{const} > 0 , \quad i = \overline{1, n_2} \Big\} . \tag{3.9}$$

The constants l_i are constraints on the damage of healthy tissue, $l_i < 1$. The problem of optimization consists in finding q_0 such that

$$q_0 \in \mathrm{U}_{\alpha\delta} , \quad \Psi_0 (q_0) = \inf_{q \in \mathrm{U}_{\alpha\delta}} \Psi_0 (q) . \tag{3.10}$$

Theorem 3.1. *Let us assume that the conditions of Theorem 2.1 and Eqs. (3.3)-(3.5) are valid. Let Ψ_0 be an objective functional and U_{ad} be a nonempty set defined by relations (3.4)-(3.9). Then a solution of problem (3.10) exists.*

Proof. Applying Theorem 2, we verify that Ψ_i are continuous on U. Next, using general theorems on compactness [8], we prove that U_{ad} is compact in U. Theorem 3.1 follows from the Weierstrass theorem.

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NOTATION

T_q, solution of the biothermal equation for the vector q; T_0, temperature required for therapeutic effect (43°C), T_1, maximum temperature allowable for healthy tissue (41°C); t, time; $x = (x_1, x_2, \ldots, x_n)$, point of the region Ω; $a = a_1\rho$, where a_1 is the specific heat, ρ is the density; k, specific thermal conductivity; w, value of blood perfusion; T_a, temperature of arterial blood; Q, power of a heat source of any physical nature providing tissue heating; N, duration of treatment; $\partial T / \partial \nu$, derivative in the direction of the unit normal ν to S_1; T_2, temperature of the cooling medium; β, heat transfer coefficient; $\widetilde{C}$, normal (physiological) temperature of healthy tissue; Y, Y^* are the Banach space and a space conjugate with it; $G_1 = \Omega \times (0, N)$, $G_2 = S_2 \times (0, N)$, $X = \{ u \mid u \in H^1(\Omega), u|_{S_1} = 0 \}$; $L = \{ L(t), t \in [0, N] \}$ is a set of operators mapping the space X into X^* in the following manner:

$$(L(t)(u), h) = \int_\Omega \left(\sum_{i=1}^{n} k \frac{\partial u}{\partial x_i} \frac{\partial h}{\partial x_i} + W(., u + \widetilde{T}(t) + T_a)(u + \widetilde{T}(t) h \right) dx + \int_{S_1} \beta u h \, ds ,$$

$$\{ u, h \} \subset X .$$

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