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Mathematical Modeling in Cryobiology and Cryomedicine

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Abstract

We consider the two-dimensional boundary value problem of Stefan's type in a multi-connected domain with nonlinear heat sources arising in cryosurgery. A formulation of the problem for the case of two needle cryoinstruments cylindrical shape, fully embedded in biological tissue is showed. On this example, a method for investigation of such problems, reducing to the successive solution of two-dimensional problems in the areas of simpler forms is proposed. A feature article considered models is the fact that they take into account the actual effect observed spatial localization of heat.

Keywords

Models in Cryosurgery, Models in Cryomedicine, Stefan's Type Problems, Localization of Heat

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1. Introduction

The problem discussed below arise in the particular field of medicine known as cryosurgery, one of whose tasks is to destroy cells in the local, clearly limited amount of biological tissue occupied by a malignant tumor. Cryogenic temperatures used in practice are reaching $-150^{\circ}C$ and lower. Therefore, the corresponding mathematical models of biological tissue freezing should take into account the heat generated during the "water-to-ice" phase transition. Cryodestruction process is modeled by a nonlinear equation of thermal conductivity with the function of a heat source of a special form on the right. The source function is provided by a mathematical description of the observed in field effect of spatial localization of heat.

Currently, there are a large number of scientific publications (see [1-3] and references therein) dedicated to the mathematical models of biological tissue cryodesctruction. However, the vast majority of them use Pennes equation as the basis for mathematical models [4]:

$$\rho c \frac{\partial T}{\partial t} = \nabla \lambda \nabla T + c_b w (T_a - T) + q_{met} + Q^{ext} .$$

Here T, λ, c, ρ – temperature, coefficients of thermal conductivity, heat capacity and density of biological tissue; w - perfusion coefficient, c_b - heat capacity of the blood, T_a - temperature of arterial blood, q_{met}, Q^{ext} - heat which is allocated due to metabolic reactions and absorption of energy of an external source.

It assumes the linear dependence between inherent sources of heat in biological tissue and the temperature field. This assumption doesn't allow describing actually observed spatial localization of heat. In thermophysical meaning, functional dependence between heat sources and temperature should be limited, continuous and monotonically decreasing in the positive temperature range and limited and monotonically increasing in the range of negative temperatures.

Except the shortcoming stated above Pennes's model doesn't consider that fact that freezing of intercellular liquid happens

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much earlier, than freezing of intracellular liquid and heat corresponding to these two processes is allocated in different timepoints.

The models considered in the article, take into account the above features of the process of freezing of biological tissue.

Local freezing and destruction of biological tissue is performed by cryoprobes with different cooling surface shapes (spherical, flat, conical, and others). Cryoprobes can be located on the surface of the biological tissue, and (or) introduced into it. Location of the cryoprobe shape affects the area in which the problem is solved, and the type of boundary conditions.

In [5-8] a number of models for cryoinstruments with spherical, cylindrical and planar forms of the cooling surface are considered, with respect to the above features. However, except for some one-dimensional problems, these models have not been brought to the numerical calculations. In [9-11] the new productions of two-dimensional problems, the technique of numerical studies, as well as some results of computer calculations are given.

Much more urgent and complex tasks are associated with the simultaneous freezing of biological tissue by several cryoprobes. We propose a formulation of the problem for the case of two needle cryoprobes of cylindrical shape embedded in a biological tissue. In the case where more than two cryoprobes is used for freezing, formulation of the problem changes in terms of boundary conditions corresponding to the heat exchange between the biological tissue and cryoinstrument.

2. Formulation of the Problem

We assume that the axis OZ is parallel to the axis of cryoprobes. Due to the fact that each of cryoinstruments has axial symmetry, the process of cryodestruction of biological tissue can be described by the following two-dimensional Stefan's type problem:

$$\frac{\partial}{\partial x}\left[\lambda(u)\frac{\partial u}{\partial x}\right]+\frac{\partial}{\partial y}\left[\lambda(u)\frac{\partial u}{\partial y}\right]+c(u)\rho(u)\frac{\partial u}{\partial t}=$$

$$=-w(u)+P\frac{\partial u}{\partial t}\delta(u-u_1)+P_0\frac{\partial u}{\partial t}\delta(u-u_2),$$

$$(x,y)\in\Omega\setminus\bar{\gamma}_1\setminus\bar{\gamma}_2,\ t>0,$$

$$u(x,y,0)=\bar{u}=\text{const},\quad (x,y)\in\Omega,$$

$$\lambda(u)\frac{\partial u}{\partial n_1}-\alpha u=\alpha u_3,\qquad (x,y)\in\gamma_1,\ t>0,$$

$$\lambda(u)\frac{\partial u}{\partial n_2}-\alpha u=\alpha u_4,\qquad (x,y)\in\gamma_2,\ t>0,$$

$$u(a,y,t)=u(0,y,t)=\bar{u},\qquad y\in[0,b],\quad t>0,$$

$$u(x,b,t)=u(x,0,t)=\bar{u},\quad x\in[0,a],\quad t>0,$$

$$u(x,y_1(x,t),t)=u_1,\ x\in[0,a],\quad t>0,$$

$$u(x,y_2(x,t),t)=u_2,\quad x\in[0,a],\quad t>0,$$

$$y_1(x,t)=0,\qquad x\in[0,a],\quad t\le t_1,$$

$$y_2(x,t)=0,\qquad x\in[0,a],\quad t\le t_2>t_1.$$

Here $\Omega=\{(x,y):\ 0<x<a,\ 0<y<b\}$; γ_1,γ_2 -circles corresponding to cryoinstruments cooling surfaces (can be with different radii, see Fig. 1); $u_3=u_3(t)$, $u_4=u_4(t)$ - the temperatures of the cooling surfaces; $\lambda(u)$, $c(u)$, $\rho(u)$ - thermal conductivity, heat capacity and density of the biological tissue, respectively; $\bar{u}$ - the temperature of the biological tissue to which has not yet reached the cold; $P=\rho_1\Lambda_в$, $P_0=\rho_2\Lambda_в$; $\Lambda_в$ – the latent heat of crystallization of water; ρ_1,ρ_2 - arrays of extracellular and intracellular water in a unit volume of biological tissue; α - heat transfer coefficient for cryoinstrument and biological tissue; t_1,t_2 -moments of time in which the biological tissue is cooled to freezing u_1 and cryodestruction u_2 temperatures; $\vec{n}_1,\vec{n}_2$ - vectors of inner normals to the γ_1,γ_2 circles, respectively; $w(u)$ - a known function of heat sources; $\delta(x)$ - the Dirac delta function .

Determination is to be a function of temperature $u=u(x,y,t)$, and a pair of insulated surfaces $y_1(x,t)$, $y_2(x,t)$, on which the temperatures of the biological tissue are u_1,u_2 , respectively, a,b - constants, characterized in that the temperature of the rectangle is considered constant and equal $\bar{u}$.

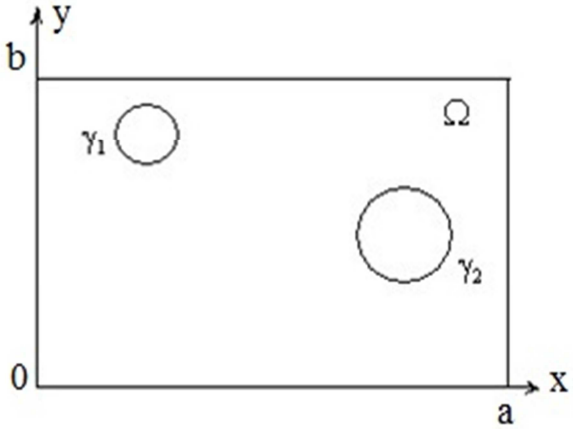

Figure 1. The domain in which the problem is solved.

3. Solution Method

Direct construction of a difference scheme for the problem stated above is difficult to determine, especially if cooling is done by several cryoinstruments. In this regard, it is possible to divide the process of solving the original problem to a consecutive solution of the following subtasks (1) and (2):

$$\frac{\partial}{\partial x}\left[\lambda(v_1)\frac{\partial v_1}{\partial x}\right]+\frac{\partial}{\partial y}\left[\lambda(v_1)\frac{\partial v_1}{\partial y}\right]+c(v_1)\rho(v_1)\frac{\partial v_1}{\partial t}=$$
$$=-w(v_1)+P\frac{\partial v_1}{\partial t}\delta(v_1-u_1)+P_0\frac{\partial v_1}{\partial t}\delta(v_1-u_2),$$
$$(x,y)\in\Omega\setminus\overline{\gamma}_1,\ t>0,$$

$$v_1(x,y,0)=\overline{u}=\text{const},\quad (x,y)\in\Omega\setminus\overline{\gamma}_1,$$

$$\lambda(v_1)\frac{\partial v_1}{\partial n_1}-\alpha v_1=\alpha u_3,\qquad (x,y)\in\gamma_1,\ t>0,$$

$$\begin{aligned} &v_1(a,y,t)=v_1(0,y,t)=\overline{u},\qquad y\in[0,b],\quad t>0,\\ &v_1(x,b,t)=v_1(x,0,t)=\overline{u},\quad x\in[0,a],\quad t>0, \end{aligned}\tag{1}$$

$$v_1(x,y_1(x,t),t)=u_1,\ x\in[0,a],\quad t>0,$$
$$v_1(x,y_2(x,t),t)=u_2,\ x\in[0,a],\quad t>0,$$

$$y_1(x,t)=0,\qquad x\in[0,a],\quad t\le t_1,$$
$$y_2(x,t)=0,\qquad x\in[0,a],\quad t\le t_2>t_1.$$

$$\frac{\partial}{\partial x}\left[\lambda(v_2)\frac{\partial v_2}{\partial x}\right]+\frac{\partial}{\partial y}\left[\lambda(v_2)\frac{\partial v_2}{\partial y}\right]+c(v_2)\rho(v_2)\frac{\partial v_2}{\partial t}=$$
$$=-w(v_2)+P\frac{\partial v_2}{\partial t}\delta(v_2-u_1)+P_0\frac{\partial v_2}{\partial t}\delta(v_2-u_2),$$
$$(x,y)\in\Omega\setminus\overline{\gamma}_2,\ 0<t<t^*,$$

$$v_2(x,y,t^*)=v_1(x,y,t^*),\quad (x,y)\in\Omega\setminus\overline{\gamma}_2,$$

$$\lambda(v_2)\frac{\partial v_2}{\partial n_2}-\alpha v_2=\alpha u_4,\qquad (x,y)\in\gamma_2,\ 0<t<t^*,$$

$$\begin{aligned} &v_2(a,y,t)=v_2(0,y,t)=\overline{u},\qquad y\in[0,b],\quad 0<t<t^*,\\ &v_2(x,b,t)=v_2(x,0,t)=\overline{u},\quad x\in[0,a],\quad 0<t<t^*, \end{aligned}\tag{2}$$

$$v_2(x,y_1(x,t),t)=u_1,\ x\in[0,a],\quad 0<t<t^*,$$
$$v_2(x,y_2(x,t),t)=u_2,\ x\in[0,a],\quad 0<t<t^*,$$

$$y_1(x,t)=0,\qquad x\in[0,a],\quad t\le t_1,$$
$$y_2(x,t)=0,\qquad x\in[0,a],\quad t\le t_2>t_1,$$

where t^* is the time point to which the cooling process of biological tissue deals within the problem (1). To avoid double indices denote that constants t_1, t_2, as well as surfaces $y_1(x,t), y_2(x,t)$ remain the same, although their numerical values in different tasks will vary.

In general, the number of subtasks to be solved corresponds to the number of cylindrical cryoprobes introduced into the tissue. If the biological tissue is cooled by n cryoprobes over time t^*, than $v_n(x,y,t)$ will give an approximate solution of the original problem.

To solve each of subtasks are applied local one-dimensional method, described in detail in [13]. To find the value of the grid function on the $(k+1)$-th time step from the known value of the k-th time step it is necessary to consistently solve two series of one-dimensional problems, respectively, for any coordinates. Each task is a nonlinear algebraic system of equations with tridiagonal matrix, and sweep method in conjunction with any iterative method can be used for its solution (discussed in detail in [9]). When determine the grid function using iterative method, coefficients c, ρ, λ can be taken at the previous iteration. Iterative process convergence related issues considered earlier in [12].

We described an algorithm for solving the problem for only one iteration of the time, i.e. when the time step size is equal t^*. If the process of cooling the biological tissue is made by n cylindrical cryoprobes for a certain period of time, than this time interval should be divided into intervals of t^* value.

At each such time interval n subtasks is solved by a method described above, then the next step in time is taken. Function $v_n(x,y,t)$ corresponding to the last iteration is given us an approximate solution of the original problem.

Thus, finding an approximate solution of the original problem in a multiply connected domain is reduced to the serial finding of approximate solutions for simple two-dimensional problems.

4. Conclusions and Results

It is clear that the described method is applicable in the case of multiple simultaneous cooling biotissue by cryoinstruments with various shapes of the cooling surface. At the same time, to avoid any problems with the construction of computational grid, in our opinion, it is more expedient to use the rectangular coordinates.

For ensuring spatial localization of heat, nonlinear function of heat sources has to satisfy to the certain properties described in [9].

In computer simulation we considered power dependence $w_1(u) = w_0(\overline{u} - u)^{\beta}$, $0 \le u \le \overline{u}$, $0 \le \beta < 1$, logarithmic dependence of heat source from temperature

$w_2(u) = w_0 \ln(\bar{u} - u)$, and dependence

$$w_3(u) = \begin{cases} w_0(\bar{u} - u)^{\beta}, & 0 \le u \le \bar{u}, \\ -\dfrac{w_0 \bar{u}^{\beta}}{u_A}(u - u_A), & u_A \le u < 0, \\ 0, & u < u_A, \end{cases}$$

$u_A = u_A(t)$ - temperature of freezing surface of cryoinstrument (applicator), $\bar{u} = \text{const}$ - initial temperature of biological tissue.

Results of computer simulation show that these functions are practically suitable for modeling the process of freezing live biological tissue. Parameters w_0 and β here should be found experimentally.

Calculation results for cooling of biological tissue by one cylindrical tool shown in [11].

The simulations were performed for the following values of thermophysical properties of biological tissue.

$$\lambda_1 = 0.56 \frac{W}{m \cdot {}^{\circ}C}, \lambda_2 = \lambda_3 = 2.22 \frac{W}{m \cdot {}^{\circ}C},$$

$$w_0 = 48.5 \cdot 10^3 \frac{W}{m^3 \cdot {}^{\circ}C}, \; c_1 \cdot \rho_1 = 3.6 \cdot 10^6 \frac{W \cdot s}{m^3 \cdot {}^{\circ}C},$$

$$u_A = -90, \bar{u} = 36.7., \; c_3 \cdot \rho_3 = 1.08 \cdot 10^6 \frac{W \cdot s}{m^3 \cdot {}^{\circ}C},$$

$$P = 300 \cdot 10^6 \frac{W \cdot s}{m^3}, \; P_0 = 0.3 \cdot P, \; \alpha = 100 \div 2 \cdot 10^5 \frac{W}{m^2 \cdot {}^{\circ}C},$$

Indexes 1, 2, 3 refer to the chilled, frozen and affected by cryodestruction areas of biotissue respectively.

Stabilization to limit state occurs in about 6 minutes. Radii of cryodestruction, freezing and influence of the cold zones are equal to 9 mm, 17 mm and 34 mm respectively (calculations correspond to the cooling of tissue by tool with radius 0.75 mm)

Comparison of the results shows a similar character of dynamics for freezing and cryodestruction isotherms for all three types of heat sources. Note that the second functional dependency contains only one experimentally determined parameter.

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