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Mathematical Modeling of Biological Tissue Cryodestruction

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Abstract

New statements of one- and two-dimensional Stefan-type boundary problems with nonlinear heat sources arising in cryosurgery are considered in the paper. An effective method for their full research for cases of sufficiently extended cryoinstruments with a cylindrical shape of a cooling surface is offered. Some results of the computer simulation are present.

Keywords: mathematical modeling in cryosurgery, spatial localization of heat, the Stefan's type problem

Introduction

The development of cryogenic technology in the last decade gave rise to a new area of medicine – cryosurgery, which is focused on the destruction of cells in the local, precisely limited amount of biological tissue occupied by a malignant tumor. The theoretical basis of the exposure to low temperature on biological objects lies in physical processes of freezing water – the main component of cell structures for all living organisms. Cryosurgery enables the complete destruction of a predetermined amount of tissue and depending on the nature of the operation uses low temperature from -35 ° to -190 ° and below. It is clear that along with experimental studies mathematical modeling of thermal processes in freezing

biological tissue is one of the most actual areas of study for cryosurgery. A promising direction here is the development of effective methods for solving Stefan-type problems, which have distinctive features of spatial localization of the heat and the existence of stationary solutions.

Local freezing and destruction of biological tissue is implemented by cryoprobes with various shapes of cooling surface, most commonly – planar, cylindrical, semispherical, spherical and conical. They can be positioned at the surface of biological tissue or inserted into it. During the cryoprobe temperature decreasing, a nonstationary temperature field occurs in the tissue. Damage to tissue cells is the result of the phase changes, i.e. – freezing the biological tissue close to the cooling surface of the cryoprobe. Allocation of crystallization heat and unfrozen tissue inherent sources of heat (blood and lymph flow, metabolism, oxidative reactions) interfere the spread of the front freeze that leads to the actually observed spatial localization of thermal perturbations, and, with the steady heat removal – to the stabilization in time to the spatially localized steady state.

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]. 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. In [5,11] have been given one-dimensional and two-dimensional axisymmetric Stefan-type problems arising here for cryoinstruments with circular, spherical, hemispherical and cylindrical forms, disposed at the surface of biological tissue. There were stated inverse problems for field isotherms also, which are relevant in the case of monotonic dependence of the desired temperature field from one of the spatial coordinates (this does not hold in the case of cooling of biological tissue by several cryoinstruments at the same time). These models have been already taken into account the features of inherent biological tissue heat sources, but excepting some one-dimensional problems [6, 7] they were not brought to the numerical simulation.

In this paper we consider the specific two-dimensional Stefan-type problems arising in cryosurgery. An efficient method for the study of cryosurgery multidimensional problems with nonlinear heat sources is considered and some results of computer simulations are present. A problem of plane-parallel cryodestruction of biological tissue, which is a basis for solving of more complex multi-dimensional problems, is described in more detail.

1. The plane-parallel cryodestruction of biological tissue

With decreasing temperature of cryoprobe, a nonstationary temperature field $u(Q,t);\ \ Q:(x,y,z),$ occurs in the tissue. We assume that the biological tissue occupies the half-space $x>0$ and heat transfer from its surface $x=0$ is carried out by Newton's law. Then the determination of the temperature field in the biological tissue $u=u(x,t)$ is reduced to the solution of the following problem [6]:

$$\begin{aligned}
&\frac{\partial}{\partial x}\left(\lambda(u)\frac{\partial u}{\partial x}\right)-c(u)\rho(u)\frac{\partial u}{\partial t}=-w(u)-P\frac{dx_1}{dt}\delta(x-x_1)-\\
&-P_0\frac{dx_2}{dt}\delta(x-x_2),\quad x>0,\quad t>0,\\
&u(x,0)=\bar{u}=const,\quad x>0,\\
&\lambda(u)\frac{\partial u}{\partial x}-\alpha u=-\alpha u_A,\quad x=0,\ t>0,\\
&\lim_{x\to\infty}u(x,t)=\bar{u},\quad t>0,\\
&u(x_2(t),t)=u_2,\quad u(x_1(t),t)=u_1,\\
&x_1(t)=0,t\le t_1,x_2(t)=0,t\le t_2>t_1.
\end{aligned}\tag{1}$$

Here $\lambda=\lambda(u),\ c=c(u),\ \rho=\rho(u)$ – coefficients of thermal conductivity, heat capacity and density of biological tissue, respectively; $w=w(u)$ – heat sources; $x_1=x_1(t)$ and $x_2=x_2(t)$ – coordinates of freezing isotherm $u=u_1$ and cryodestruction isotherm $u=u_2;\ P=\rho_1\Lambda_в,\ P_0=\rho_2\Lambda_в;\ \Lambda_в$ – latent heat of crystallization for water; ρ_1,ρ_2 - densities of extracellular and intracellular water in a volume unit of biological tissue; $\delta(x)$ - Dirac delta-function, $\bar{u}=const$ - initial temperature; α - heat exchange coefficient between tissue and cryoinstrument freezing surface; $u_A=u_A(t)$ - temperature of freezing surface of plane cryoinstrument (applicator); t_1 и t_2 – time moments when biological tissue surface $x=0$ is cooled to freezing temperature $u(0,t_1)=u_1$ and cryodestruction temperature $u(0,t_2)=u_2$ respectively. We should define the temperature filed $u(x,t)$ and coordinates $x_1=x_1(t),\ x_2=x_2(t).$

The observed effect of spatial localization of heat allows us to proceed to the solution of the problem (1) in a bounded domain. As shown in [6], it is required that function $w=w(u)$ should have feature of order $(\bar{u}-u)^{\gamma}$, where $0<\gamma<1,$ at the point $u=\bar{u}$.

When heat exchange coefficient $(\lambda(u)\neq 0)$ value is non-zero, integrability condition is transferred to the functional dependence of the heat source from

temperature $\int_u^{\bar{u}} w(u)\,du \sim (\bar{u}-u)^{2\gamma}$, which implies the order of vanishing of heat source in point $u=\bar{u}$: $w(u)\sim(\bar{u}-u)^{2\gamma-1}$, $1/2\le\gamma\le 1$. Condition $\gamma\ge 1/2$ is caused by the requirement of continuity and boundedness of functional dependence of heat source from temperature.

In computer simulation in this paper we considered power dependence [6] $w_1(u)=w_0(\bar{u}-u)^{\beta}$, $u\le u\le\bar{u}$, $0\le\beta=2\gamma-1<1$, logarithmic dependence of heat source from temperature $w_2(u)=w_0\,ln(\bar{u}-u)$, and dependence

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

Functions $w_1(u), w_2(u)$ do not satisfy above requirements in full, but the results of computer simulation show that they are practically suitable for modeling the process of freezing live biological tissue. Parameters w_0 and β here should be found experimentally. A number of particular values of these parameters are determined in [9].

As for the problem (1) we can conclude that when $x\to\infty$ the boundary condition can be replaced by following

$$u(x_в,t)=\bar{u},\quad t>0, \tag{2}$$

where $x_в$ - determined constant, without loss of accuracy of the described process.

Solution method.

For solution of problem (1) we will use method described in [9, 12] and based on preliminary smoothing of coefficients. Note that functions $c(u),\rho(u),\lambda(u)$ have discontinuity of the first kind at points $u=u_1$, $u=u_2$. On other sections of domain we will consider them sufficiently smooth. Let's introduce specific enthalpy following [12]:

$$H(u)=\int_0^u c(\xi)\rho(\xi)\,d\xi+P\eta(u-u_1)+P_0\eta(u-u_2) \tag{3}$$

Now problem (1) with (2) can be written as follows:

$$\frac{\partial}{\partial x}\left(\lambda(u)\frac{\partial u}{\partial x}\right)-\frac{\partial H(u)}{\partial t}=-\omega(u),\quad x_в>x>0,\ t>0 \tag{4}$$

$$u(x,0)=\bar{u}=const,\quad x_в\ge x\ge 0,$$

$$\lambda(u)\frac{\partial u}{\partial x}-\alpha u=-\alpha u_A,\ x=0,\ t>0,$$

$$u(x_в,t)=\bar{u},\quad t>0.$$

Here $\eta(x)$ - Heaviside function. Derivative of $H(u)$ in $u = u_1$ and $u = u_2$ goes to infinity, and $H(u)$ in $u = u_1$ and $u = u_2$ have discontinuity of the first kind respectively with jumps:

$$H(u_1 + 0) - H(u_1 - 0) = P$$

$$H(u_2 + 0) - H(u_2 - 0) = P_0$$

Thereby, the direct application of finite difference schemes to the equation (4) doesn't give good results in simulation. For making finite difference schemes here practically efficient for (4), it is expedient to smoothing functions $H(u)$ и $\lambda(u)$ (we used zero-order smoothing [10]). After smoothing, we proceed to differentiation of the smoothed function $\widetilde{H}(u)$ and equation (4) will be written as

$$\frac{\partial}{\partial x}\left(\widetilde{\lambda}(u)\frac{\partial u}{\partial x}\right) - \widetilde{H}'(u)\frac{\partial u}{\partial t} = -w(u), \quad 0 < x < x_в, \quad t > 0. \tag{5}$$

Adding initial and boundary conditions to (5)

$$u(x,0) = \overline{u} = const, \qquad 0 \le x \le x_в \tag{6}$$

$$\lambda(u)\frac{\partial u}{\partial x} - \alpha u = -\alpha u_A, \quad x = 0, \quad t > 0,$$

$$u(x_в, t) = \overline{u}, \quad t > 0,$$

we obtain the boundary problem (5), (6). Its solution under define conditions on the given functions and smoothness [12] tends to the solution of (1).

A finite difference scheme is considered for the problem (5), (6) further. Nonlinear relatively the grid function, three-point equation can be solved by an iterative method (ex., Newton's method), and each of the iterations can be found by the sweep formula.

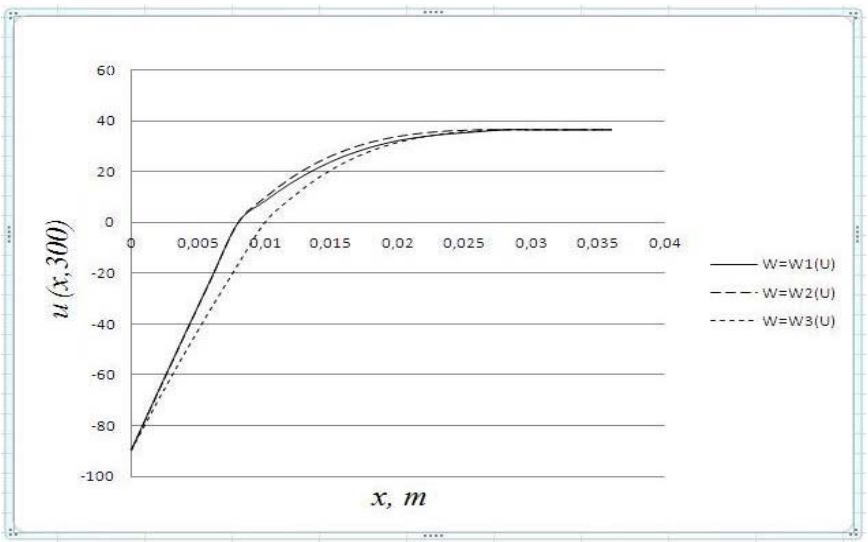

Figure1. Graph of temperature of biological tissue on the coordinate after 300 seconds for different source functions, degree Celsius-degree, ^0C .

Temperature distribution $u(x,t)$ for all three functional dependencies at the time moments $t = 300$ seconds is shown on Figure 1. At this moment movement of freezing front is greatly slowed, as it is showed by simulation.

The simulations were performed for the following values of thermo-physical properties of biological tissue.

$$\lambda_1 = 0.56\frac{W}{m\cdot{}^\circ C}, \qquad \lambda_2 = \lambda_3 = 2.22\frac{W}{m\cdot{}^\circ C}, w_0 = 48.5\cdot 10^3\frac{W}{m^3\cdot{}^\circ C},$$

$$c_1\cdot\rho_1 = 3.6\cdot 10^6\frac{W\cdot s}{m^3\cdot{}^\circ C}, \qquad c_2\cdot\rho_2 = 2.01\cdot 10^6\frac{W\cdot s}{m^3\cdot{}^\circ C},$$

$$c_3\cdot\rho_3 = 1.08\cdot 10^6\frac{W\cdot s}{m^3\cdot{}^\circ C}, \ \mathrm{P} = 300\cdot 10^6\frac{W\cdot s}{m^3}, \qquad P_0 = 0.3\cdot P,$$

$$\alpha = 100 \div 2\cdot 10^5\frac{W}{m^2\cdot{}^\circ C}, \quad u_A = -90, \bar{u} = 36.7.$$

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

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.

Mathematical models of biological tissue cryodestruction are considered further, which are represented by two-dimensional three-phase boundary problems of Stefan type.

2. The case of sufficiently extended cryoinstrument of cylindrical shape

Now let's consider a cryoinstrument being of cylindrical shape and located on the surface of the biological tissue. Then the area in which we seek the temperature distribution will take the form of semicircle. When the cooling surface of cryoinstrument has a rather large length, neglecting edge effects at the ends (axis $0Z$ is parallel to the axis of the tool) we obtain a two-dimensional initial-boundary problem of Stefan type. Formulation of the problem in polar coordinates will be following:

$$\frac{1}{r}\frac{\partial}{\partial r}\left(r\,\lambda(u)\frac{\partial u}{\partial r}\right) + \frac{1}{r^2}\frac{\partial}{\partial\varphi}\left(\lambda(u)\frac{\partial u}{\partial\varphi}\right) - c(u)\rho(u)\frac{\partial u}{\partial t} =$$

$$= -w(u) + P\frac{\partial u}{\partial t}\delta(u-u_1) + P_0\frac{\partial u}{\partial t}\delta(u-u_2), \quad 0<\varphi<\pi, \quad r_0<r<R,$$

$$u(r,\varphi,0) = \bar{u} = const, \quad r_0 \le r \le R, \quad 0 \le \varphi \le \pi,$$

$$\lambda(u)\frac{\partial u}{\partial r} - \alpha u = -\alpha u_A, \quad r = r_0, \ 0 \le \varphi \le \pi, \ t > 0,$$
$$u(r,\varphi,t) = \bar{u}, \qquad r = R, \ 0 \le \varphi \le \pi, \ t > 0,$$
$$\lambda(u)\frac{1}{r}\frac{\partial u}{\partial \varphi} - \gamma u = -\gamma u_c, \ r_0 \le r \le R, \quad \varphi = 0, \ t > 0,$$
$$-\lambda(u)\frac{1}{r}\frac{\partial u}{\partial \varphi} - \gamma u = -\gamma u_c, \ r_0 \le r \le R, \quad \varphi = \pi, \ t > 0,$$
$$\left.\begin{aligned} u(r,\varphi_1(r,t),t) = u_1, \\ u(r,\varphi_2(r,t),t) = u_2, \end{aligned}\right\},$$

where r - polar radius, φ - polar angle.

Functions $u(r,\varphi,t)$, $\varphi_1(r,t)$, $\varphi_2(r,t)$. should be defined. Here R - a constant, such as when $r > R$; the temperature of biological tissue is constant and equal to $\bar{u}$.

After smoothing of discontinuous functions, the problem is solved by local one-dimensional method [13], where a number of one-dimensional problems, like discussed above in p.1, is solved in each direction.

In the case of sufficiently extended cylindrical cryoinstrument fully embedded in biological tissue, an area in which we seek a solution of the problem will be ring-shaped.

Statement of the problem will be changed a bit, namely:

1) no boundary conditions corresponding to heat exchange with the environment;
2) a periodicity condition corresponding equality of temperature when $\varphi = 0$ and $\varphi = 2\pi$ appears.

Due to the fact that the formulation of the problem appear periodicity conditions, in its simulation by local one-dimensional method in the φ direction, it is appropriate to apply the method of cyclic sweep, since the corresponding matrix for the system of linear equations will not be tridiagonal.

3. Results of computer simulation for problems described in p. 2

We can say about results obtained for those problems following:

1) results are quite consistent with the results obtained for other two-dimensional problems considered earlier by the author, as well as with the results obtained by other authors when considering the one-dimensional non-stationary Stefan-type problems arising in cryosurgery;
2) the effect of spatial localization of heat enables to pass from problem for an unbounded domain to problem for a domain with the known boundaries;

3) analysis of the calculations made it possible to trace stabilization of the temperature field and the field of isotherms to the ultimate steady state;
4) an association between the steps in time and space is found, which means that the difference schemes are conditionally stable;
5) under initial data $r_0 = 1_{mm}$, $u_A = -90^0 C$, $\beta = 0.5$, following results were found: stabilization to limiting steady state is reached after about 6 minutes; for cryoinstrument, located on the surface of biological tissue radius of the affected area is around 16 mm, radius of freezing biotissue zone $\approx$ 19 mm, radius of cooled biotissue zone $\approx$ 35 mm. For cryoinstrument fully embedded in the biological tissue, corresponding values are $\approx$ 14 mm, 17 mm и 30 mm. A smaller areas in the second case caused by the absence of contact with a low temperature environment ($u_c = 20^\circ C$ was used for simulations).

Conclusion

Summing up, the following are most important aspects of Stefan-type problems arising in cryosurgery:
1. One of the most important features of the abovementioned Stefan-type problems is actually observed effect of spatial localization of heat, which is associated with the presence of nonlinear biological heat sources of a special kind. Although this effect complicates the mathematical model (a nonlinear term, depended on the desired temperature field, appears in equation), it also allows to move from statements of problems in an unbounded domain to problems in bounded domain.
2. Nonlinear heat sources depend on the numerical parameters that must be determined experimentally. This is an additional and quite complicated task.
3. The methodology of computation with preliminary smoothing of discontinuous functions is independent of the dimension of the problem and can be used without any change for solving three-dimensional problems.
4. The link between the steps in time and space, found in the simulations, shows that the constructed difference schemes are conditionally stable.

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