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Sensitivity analysis of transient bioheat transfer with perfusion rate dependent on tissue injury

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The sensitivity analysis of transient temperature field in the tissue domain with respect to its thermophysical parameters is discussed. In particular, the influence of tissue specific heat, thermal conductivity, perfusion rate and metabolic heat source on the temperature distribution is considered. In order to determine the influence of variations of these parameters on temperature distribution the direct approach of sensitivity analysis is applied. Perfusion rate is treated as dependent on tissue injury which is estimated on the basis of Arrhenius integral. On the stage of numerical realization the boundary element method is used. In the final part of paper the results obtained are shown.

Keywords: bioheat transfer, Arrhenius scheme, tissue necrosis, boundary element method

1. Introduction

A rise in the temperature of biological tissue leads to changes in its domain. At first, when the temperature is moderate, that is from 37°C to 45–55°C, the blood vessels in the tissue become dilated without being thermally damaged. Higher temperatures cause immediate irreversible damage to the tissue. When the temperature reaches 60°C to 65°C, the proteins become denatured and tissue necrosis can be expected. After the temperature rises above 100°C, water in the tissue changes its phase from liquid to steam, increasing interstitial pressure until the pressure within the tissue exceeds the strength of confinement by the tissue architecture, resulting in explosive vaporization and thrombosis (shutting down of the vasculature). At over 150°C the proteins are broken down, releasing hydrogen, nitrogen and oxygen, and leaving a layer of carbonization [1, 6].

Thus, temperature elevation and thermal damage can dynamically change the thermal distribution during coagulation by altering thermophysical properties of tissue. Consequently, parameters applied in models of heat transfer in biological tissue domain can be regarded as temperature-dependent. A somewhat different concept based on this is the assumption that thermophysical parameters are dependent on the degree of tissue destruction. In this approach, temperature affects the values of parameters through Arrhenius injury integral, which means that the reaction rate increases exponentially with temperature. Special attention in this field is dedicated to the changes in perfusion that accompany necrosis [1, 6, 18, 19].

Knowledge of the value of the injury integral is also relevant to the point of determining the depth of tissue necrosis. It could be significant information in some thermal therapies, such as prostate hyperplasia or cancer thermotherapy [5, 18].

The course of the physical process is, as a rule, analyzed on the basis of a certain mathematical model. One of the problems connected with the application of such a model is the sensitivity of the solution with respect to the parameters appearing in the governing equations. The sensitivity information may be used, among others, to analyze the influence of the change of parameters on the final solution of the problem being considered [3, 13–16]. Additional tasks required to determine

the sensitivity functions result from differentiation of the assumed equation describing bioheat transfer with respect to the parameter, which means that the number of additional sensitivity tasks corresponds to the number of parameters with respect to which the sensitivity analysis is performed [4, 9].

In this paper the tissue is regarded as a homogeneous domain with perfusion rate coefficient dependent on tissue necrosis, while the remaining thermal parameters are regarded as constant values. The sensitivity analysis has been done with respect to thermal conductivity, volumetric specific heat, initial perfusion rate, and metabolic heat source.

The basic problems, but also the additional problems resulting from the sensitivity analysis, have been solved using the first scheme of boundary element method for transient heat diffusion.

2. Governing equation

Transient heat transfer in biological tissue domain is described by the Pennes equation in the form [1, 3, 5, 7, 8, 11–19]

$$x \in \Omega : c\dot{T} = \lambda T_{,ii} + c_B G_B \left(T_B - T\right) + Q_{\text{met}}, \tag{1}$$

where λ [W/(m K)] is the thermal conductivity, c [J/(m^3 K)] is the volumetric specific heat, G_B [(m^3 *blood*/s)/(m^3 *tissue*)] is the blood perfusion rate and Q_{met} [W/m^3] is the metabolic heat source. The parameters c_B [J/(m^3 K)] and T_B correspond to the volumetric specific heat of blood and the artery temperature, respectively, while $T = T(x,t)$ and $\dot{T}$ denotes a time derivative.

Equation (1) is supplemented by boundary-initial conditions

$$\begin{cases} x \in \Gamma_1 : T(x,t) = T_0 \quad \text{or} \quad q(x,t) = -\lambda T_{,i} n_i = q_0, \\ x \in \Gamma_2 : q(x,t) = 0 \end{cases} \tag{2}$$

and

$$t = 0 : T = T_p. \tag{3}$$

According to the necrotic changes in tissue, the blood perfusion coefficient is defined as [1, 7]

$$G_B = G_B(\theta) = G_{B0} f(\theta), \tag{4}$$

where G_{B0} is the initial perfusion rate and θ corresponds to tissue injury integral [1, 6, 7, 19]

$$\theta(x) = \int_0^{t^F} A \exp\left[-\frac{\Delta E}{RT}\right] dt \tag{5}$$

where A is the pre-exponential factor [s^{-1}], ΔE is the activation energy [J/mole] and R is universal gas constant [J/(mole K)]. The criterion for complete tissue necrosis is [1, 6, 8, 19]

$$\theta(x) \geq 1 \tag{6}$$

In current work the function θ in Eq. (4) is assumed as a polynomial in a form [1]

$$f(\theta) = \sum_{j=1}^{3} m_j \theta^{j-1}, \tag{7}$$

where m_j are the coefficients.

Taking into account Eq. (4) the bioheat transfer equation (1) can be written as

$$x \in \Omega : c\dot{T} = \lambda T_{,ii} + Q_V, \tag{8}$$

where

$$Q_V = c_B G_{B0} f(\theta) \left(T_B - T\right) + Q_{\text{met}}. \tag{9}$$

3. Sensitivity analysis

To determine the influence of thermophysical parameters on the temperature distribution in tissue domain, the direct approach of sensitivity analysis has been applied [4, 9].

According to the rules of direct method Eq. (8) is differentiated with respect to thermophysical parameter p_s, where $s = \lambda$, c, G_{B0} or Q_{met}.

$$\frac{\partial c}{\partial p_s}\dot{T} + c\frac{\partial \dot{T}}{\partial p_s} = \frac{\partial \lambda}{\partial p_s}T_{,ii} + \lambda\frac{\partial T_{,ii}}{\partial p_s} + \frac{\partial}{\partial p_s}\left[c_B G_{B0} f(\theta)\left(T_B - T\right)\right] + \frac{\partial Q_{\mathrm{met}}}{\partial p_s}. \tag{10}$$

Because (cf. Eqs. (8) and (9))

$$T_{,ii} = \frac{1}{\lambda}\left[c\dot{T} - c_B G_B f(\theta)\left(T_B - T\right) - Q_{\mathrm{met}}\right] \tag{11}$$

so

$$\begin{aligned} c\dot{U}^s = {} & \lambda U^s_{,ii} + \frac{1}{\lambda}\frac{\partial \lambda}{\partial p_s}\left[c\dot{T} - c_B G_{B0} f(\theta)\left(T_B - T\right) - Q_{\mathrm{met}}\right] - \frac{\partial c}{\partial p_s}\dot{T} \\ & + \frac{\partial}{\partial p_s}\left[c_B G_{B0} f(\theta)\left(T_B - T\right)\right] + \frac{\partial Q_{\mathrm{met}}}{\partial p_s}, \end{aligned} \tag{12}$$

where

$$U^s = \frac{\partial T}{\partial p_s}, \tag{13}$$

while

$$\dot{U}^s = \frac{\partial U^s}{\partial t}, \qquad U^s_{,i} = \frac{\partial T_{,i}}{\partial p_s}. \tag{14}$$

Taking into account that (cf. Eq. (7))

$$\frac{\partial f(\theta)}{\partial p_s} = \left(m_2 + 2m_3\theta\right)\frac{\partial \theta}{\partial p_s}, \tag{15}$$

Eq. (12) is transformed into

$$\begin{aligned} c\dot{U}^s = {} & \lambda U^s_{,ii} - c_B G_{B0} f(\theta) U^s + \left[\frac{c}{\lambda}\frac{\partial \lambda}{\partial p_s} - \frac{\partial c}{\partial p_s}\right]\dot{T} \\ & + \left[\frac{c_B G_{B0} f(\theta)}{\lambda}\frac{\partial \lambda}{\partial p_s} - c_B f(\theta)\frac{\partial G_{B0}}{\partial p_s} - c_B G_{B0}\left(m_2 + 2m_3\theta\right)\frac{\partial \theta}{\partial p_s}\right]\left(T - T_B\right) \\ & - \frac{Q_{\mathrm{met}}}{\lambda}\frac{\partial \lambda}{\partial p_s} + \frac{\partial Q_{\mathrm{met}}}{\partial p_s}, \end{aligned} \tag{16}$$

where the variation of θ is calculated as (cf. Eq. (5))

$$\frac{\partial \theta}{\partial p_s} = \int_0^{t^F} A\frac{\Delta E U^s}{RT^2}\exp\left[-\frac{\Delta E}{RT}\right]dt. \tag{17}$$

Denoting that

$$k = c_B G_{B0} f(\theta), \tag{18}$$

Eq. (16) takes a form

$$c\dot{U}^s = \lambda U^s_{,ii} + Q^s_V, \tag{19}$$

where sensitivity source function $Q_V^s$is defined as

$$Q_V^s = -kU^s + \left(\frac{c}{\lambda}\frac{\partial\lambda}{\partial p_s} - \frac{\partial c}{\partial p_s}\right)\dot{T} - \frac{Q_{\text{met}}}{\lambda}\frac{\partial\lambda}{\partial p_s} + \frac{\partial Q_{\text{met}}}{\partial p_s} + \left[\frac{k}{\lambda}\frac{\partial\lambda}{\partial p_s} - c_B f(\theta)\frac{\partial G_{B0}}{\partial p_s} - c_B G_{B0}\frac{\partial f(\theta)}{\partial p_s}\right](T - T_B)\,. \tag{20}$$

In particular, we have

$$Q_V^\lambda = -kU^\lambda + \frac{c}{\lambda}\dot{T} - \frac{Q_{\text{met}}}{\lambda} + \left[\frac{k}{\lambda} - c_B G_{B0}\left(m_2 + 2m_3\theta\right)\frac{\partial\theta}{\partial\lambda}\right](T - T_B) \tag{21}$$

and

$$Q_V^c = -kU^c - \dot{T} - c_B G_{B0}\left(m_2 + 2m_3\theta\right)(T - T_B)\frac{\partial\theta}{\partial c}, \tag{22}$$

while

$$Q_V^{G_{B0}} = -kU^{G_{B0}} - \left[c_B f(\theta) + c_B G_{B0}\left(m_2 + 2m_3\theta\right)\frac{\partial\theta}{\partial G_{B0}}\right](T - T_B) \tag{23}$$

and

$$Q_V^{Q_{\text{met}}} = -kU^{Q_{\text{met}}} - c_B G_{B0}\left(m_2 + 2m_3\theta\right)(T - T_B)\frac{\partial\theta}{\partial Q_{\text{met}}} + 1. \tag{24}$$

Equation (19) is supplemented by boundary conditions in the form [4, 8, 15, 16]

$$\begin{cases} x \in \Gamma_1 : U^s(x,t) = U_0^s = 0 \quad \text{or} \quad Q^s(x,t) = Q_0^s = -\dfrac{1}{\lambda}\dfrac{\partial\lambda}{\partial p_s}q_0, \\ x \in \Gamma_2 : Q^s(x,t) = 0, \end{cases} \tag{25}$$

where

$$Q^s = -\lambda U^s_{,i} n_i \tag{26}$$

and the initial distribution of sensitivity is assumed as

$$t = 0 : U^s = 0. \tag{27}$$

4. Boundary element method

The primary and also the additional problem resulting from the sensitivity analysis have been solved using the first scheme of the BEM for 1D transient heat diffusion [2, 10]. So, the following equations are considered

$$c\dot{F} = \lambda F_{,ii} + S \tag{28}$$

where $F = F(x,t)$ denotes the temperature T or function U resulting from the sensitivity analysis, $S = S(x,t)$ are the source functions described by the Eq. (9) for the primary problem or by Eq. (20) (or Eqs. (21)– (24)) for the sensitivity problems with respect to p_s.

At first, we introduce the time grid

$$0 = t^0 < t^1 < \ldots < t^{f-1} < t^f < \ldots < \infty, \qquad \Delta t = t^f - t^{f-1}. \tag{29}$$

If the first scheme of the BEM is taken into account then the boundary integral equations corresponding to transition $t^{f-1} \to t^f$ are of the form [2, 10]

$$F(\xi,t^f)+\left[\frac{1}{c}\int_{t^{f-1}}^{f} F^*(\xi,x,t^f,t)J(x,t)\,dt\right]_{x=0}^{x=L}=\left[\frac{1}{c}\int_{t^{f-1}}^{f} J^*(\xi,x,t^f,t)F(x,t)\,dt\right]_{x=0}^{x=L} + \int_0^L F^*(\xi,x,t^f,t^{f-1})F(x,t^{f-1})\,dx+\frac{1}{c}\int_0^L S(x,t^{f-1})\int_{t^{f-1}}^{t^f} F^*(\xi,x,t^f,t)\,dt\,dx, \tag{30}$$

where F^* are the fundamental solutions given by formulas

$$F^*(\xi,x,t^f,t)=\frac{1}{2\sqrt{\pi a(t^f-t)}}\exp\left[-\frac{(x-\xi)^2}{4a(t^f-t)}\right], \tag{31}$$

where ξ is the point in which the concentrated heat source is applied and $a=\lambda/c$.

The heat fluxes resulting from the fundamental solutions are equal to

$$J^*(\xi,x,t^f,t)=-\lambda F^*_{,i}n_i=\frac{\lambda(x-\xi)}{4\sqrt{\pi}[a(t^f-t)]^{3/2}}\exp\left[-\frac{(x-\xi)^2}{4a(t^f-t)}\right], \tag{32}$$

while $J^*(x,t)=-\lambda F^*_{,i}n_i$.

Assuming that for $t\in\left[t^{f-1},t^f\right]: F(x,t)=F(x,t^f)$ and $J(x,t)=J(x,t^f)$ we have the following form of Eqs. (30)

$$F(\xi,t^f)+g(\xi,L)J(L,t^f)-g(\xi,0)J(0,t^f)=h(\xi,L)F(L,t^f)-h(\xi,0)F(0,t^f)+p(\xi)+z(\xi), \tag{33}$$

where

$$h(\xi,x)=\frac{1}{c}\int_{t^{f-1}}^{t^f} J^*(\xi,x,t^f,t)\,dt=\frac{\operatorname{sgn}(x-\xi)}{2}\operatorname{erfc}\left(\frac{|x-\xi|}{2\sqrt{a\Delta t}}\right) \tag{34}$$

and

$$g(\xi,x)=\frac{1}{c}\int_{t^{f-1}}^{t^f} F^*(\xi,x,t^f,t)\,dt=\frac{\Delta t}{\sqrt{\pi\lambda c}}\exp\left[-\frac{(x-\xi)^2}{4a\Delta t}\right]-\frac{|x-\xi|}{2\lambda}\operatorname{erfc}\left(\frac{|x-\xi|}{2\sqrt{a\Delta t}}\right), \tag{35}$$

while

$$p(\xi)=\int_0^L F^*(\xi,x,t^f,t^{f-1})F(x,t^{f-1})\,dx=\frac{1}{2\sqrt{\pi a\Delta t}}\int_0^L \exp\left[-\frac{(x-\xi)^2}{4a\Delta t}\right]F(x,t^{f-1})\,dx. \tag{36}$$

At the same time

$$z(\xi)=\int_0^L S(x,t^{f-1})g(\xi,x)\,dx. \tag{37}$$

For $\xi \to 0^+$ and $\xi \to L^-$ for each domain considered one obtains the system of equations

$$\begin{bmatrix} g_{11} & g_{12}\\ g_{21} & g_{22}\end{bmatrix}\begin{bmatrix} J(0,t^f)\\ J(L,t^f)\end{bmatrix}=\begin{bmatrix} h_{11} & h_{12}\\ h_{21} & h_{22}\end{bmatrix}\begin{bmatrix} F(0,t^f)\\ F(L,t^f)\end{bmatrix}+\begin{bmatrix} p(0)\\ p(L)\end{bmatrix}+\begin{bmatrix} z(0)\\ z(L)\end{bmatrix}. \tag{38}$$

The solution of Eq. (38) determines the boundary temperatures and heat fluxes in the primary problem or their equivalents in sensitivity problems for time t^f for $x\in\Gamma_1,\Gamma_2$ and next the temperatures or sensitivity functions at the internal points can be found using the formula

$$F(\xi,t^f)=h(\xi,L)F(L,t^f)-h(\xi,0)F(0,t^f)-g(\xi,L)J(L,t^f)+g(\xi,0)J(0,t^f)+p(\xi)+z(\xi). \tag{39}$$

5. Results

At the stage of numerical computations, the following values of tissue parameters have been assumed: $\lambda = 0.75\,\mathrm{W/(mK)}$, $c = 3\,\mathrm{MJ/(m^3K)}$, $G_{B0} = 0.00125\,\mathrm{m^3}$ *blood*/s/($\mathrm{m^3}$ *tissue*), $Q_{\mathrm{met}} = 245\,\mathrm{W/m^3}$ and $L = 35\,\mathrm{mm}$, while for the blood $c_B = 3.9962\,\mathrm{MJ/(m^3K)}$ and $T_B = 37^{\circ}\mathrm{C}$ [8, 18]. The parameters of Arrhenius injury integral are: $A = 3.1\times10^{98}\,\mathrm{s^{-1}}$, $\Delta E = 6.27\times10^{5}\,\mathrm{J/mole}$ and $R = 8.314\,\mathrm{J/(mole\,K)}$, and the coefficients appearing in the $f(\theta)$ function are as follows [1]:

$$\begin{aligned} &0 < \theta \le 0.1 : m_1 = 1, \quad m_2 = 25, \quad m_3 = -260, \\ &0.1 < \theta \le 1 : m_1 = 1, \quad m_2 = -1, \quad m_3 = 0. \end{aligned} \tag{40}$$

The values of these coefficients for the interval from 0 to 0.1 respond to the increase of perfusion rate caused by vasodilatation, while for interval from 0.1 to 1 they reflect blood flow decrease as the vasculature begins to shut down (thrombosis).

Tissue domain has been divided into 100 elements and the time step $\Delta t = 0.5\,\mathrm{s}$.

Sensitivity analysis has been done with regard to parameters λ, c, G_{B0} and Q_{met}, that means four additional problems have been calculated.

As an example, the solution obtained for the boundary condition on Γ_1 (tissue surface) assumed as

$$x \in \Gamma_1 : q(x,t) = q_0 = 3000\,\mathrm{W/m^2}, \tag{41}$$

while the initial distribution of temperature has been assumed as the constant temperature $T_p = 37^{\circ}\mathrm{C}$.

In Fig. 1 the temperature distribution in the tissue domain is presented. The two next figures concern results connected with tissue damage. Figure 2 shows the distribution of perfusion coefficient for different times. The effect of tissue necrosis corresponds to left hand side of the peak where value of perfusion coefficient fall down to zero, and on the right side of the peak is visible increase of perfusion rate caused by vasodilation. In Fig. 3 the profiles of injury integrals are shown.

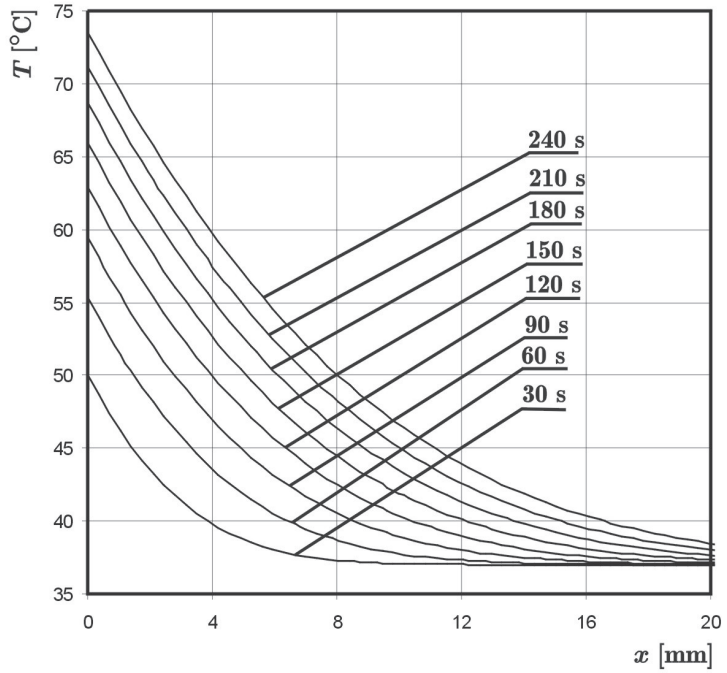

Fig. 1. Profiles of temperature

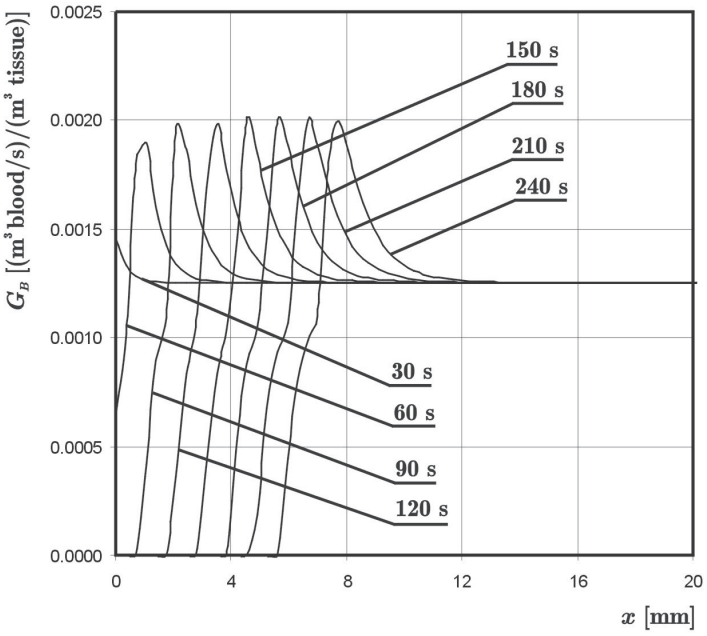

Fig. 2. Profiles of perfusion rate G_B

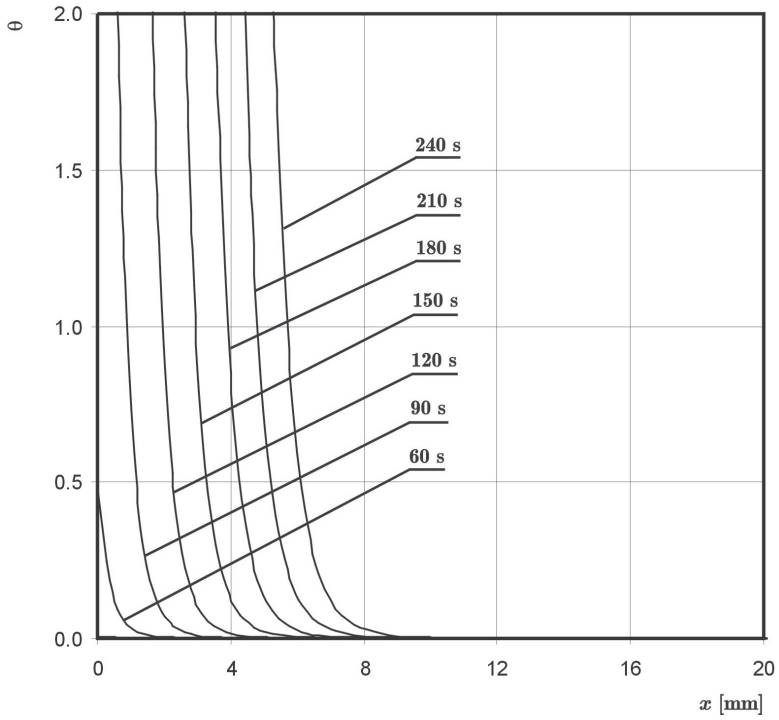

Fig. 3. Profiles of injury integral

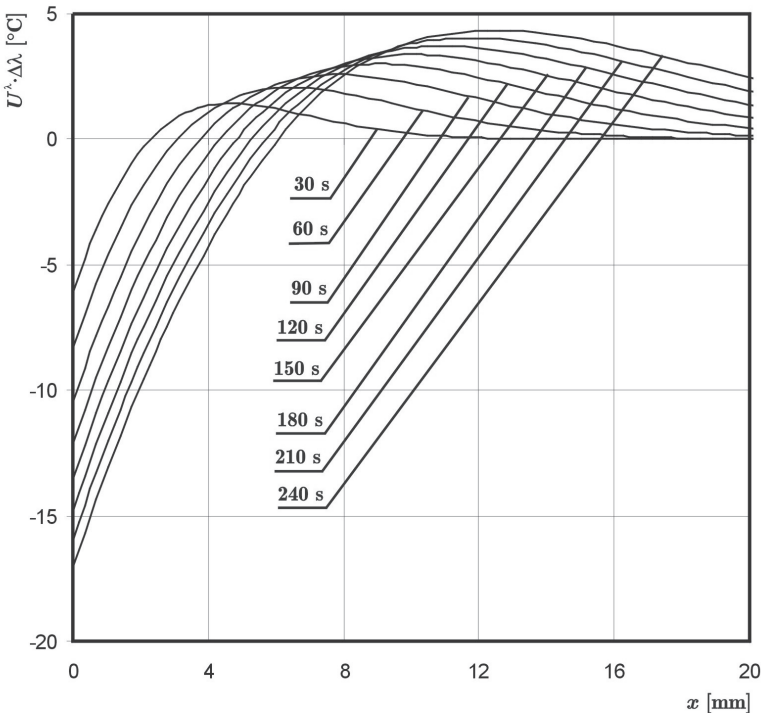

Fig. 4. Profiles of sensitivity function with respect to λ

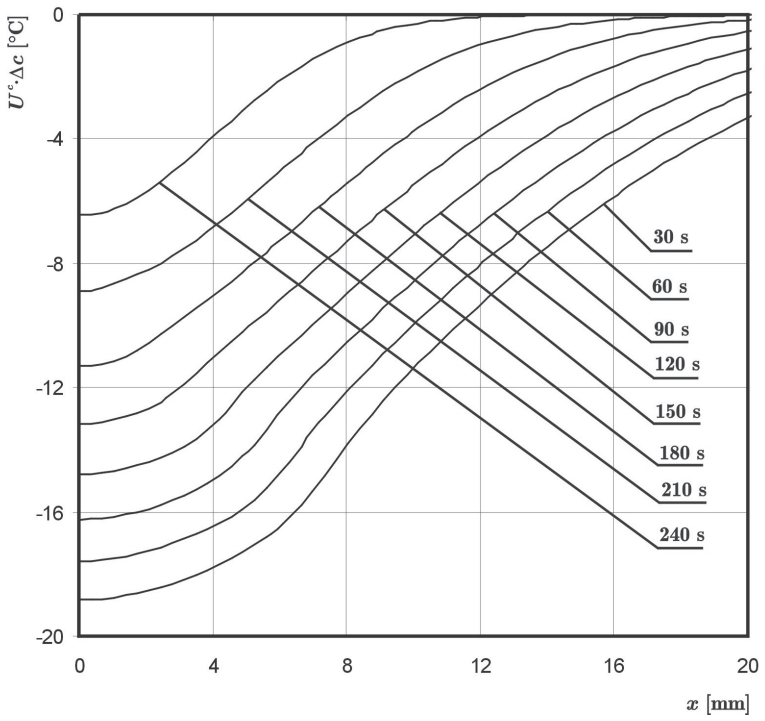

Fig. 5. Profiles of sensitivity function with respect to c

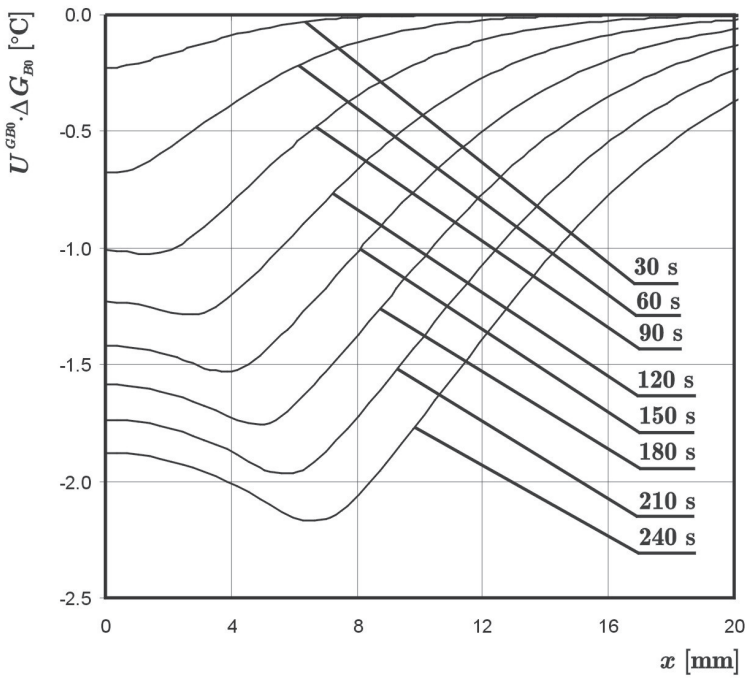

Fig. 6. Profiles of sensitivity function with respect to G_{B0}

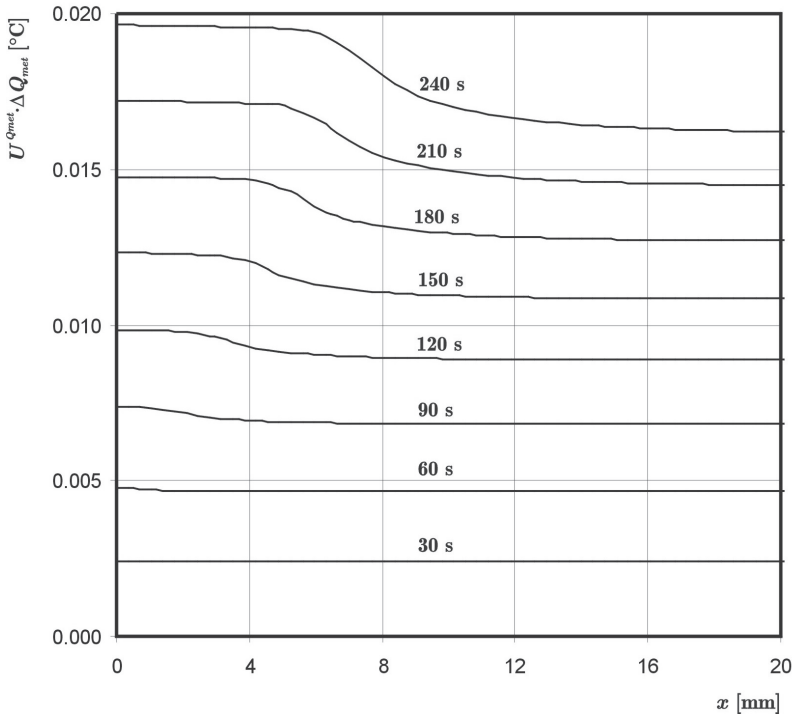

Fig. 7. Profiles of sensitivity function with respect to Q_{met}

Figures 4 to 7 present the profiles of sensitivity function for successive thermophysical parameters of tissue. The values on those figures are multiplied by: $\Delta\lambda = 0.25\,\mathrm{W/(mK)}$, $\Delta c = 1\,\mathrm{MJ/(m^3K)}$, $\Delta G_{B0} = 0.0004\,\mathrm{m^3}$ *blood*/s/($\mathrm{m^3}$ *tissue*), $\Delta Q_{\mathrm{met}} = 80\,\mathrm{W/m^3}$.

6. Conclusions

Assuming that the value of heat flux on the external surface of a tissue results in a maximum level below 75°C, there is no water phase change. The negative effects of heating have a visible impact on perfusion rate. The process of necrosis begins after 76 seconds and causes changes in perfusion rate; both the drop of perfusion to zero corresponding to the left side of the peak and the increase of perfusion rate caused by vasodilation on the right side of the peak are clearly visible. On the basis of the knowledge of Arrhenius integral profiles (Fig. 3) and the criterion for tissue necrosis (cf. Eq. (6)) the depth of complete tissue damage after 240 seconds was determined to be equal to 5.6 mm.

The profiles of the sensitivity functions show that thermal conductivity and volumetric specific heat have the most substantial impact on temperature levels. The results obtained for sensitivity with respect to initial perfusion rate delineate the change of temperature by about 2°C down for the change of initial perfusion on $\Delta G_{B0} = 0.0004\,\mathrm{m^3}$ *blood*/s/($\mathrm{m^3}$ *tissue*), and denote a decrease of temperatures with an increase of initial perfusion. According to temperature-dependent injury integral formulation (cf. Eq. (5)) greater values of initial perfusion rate cause a decrease of the depth of necrosis as well.

The proposed model is closer to the real conditions of an ablation process in living tissue than the classical Pennes equation with constant values of thermal parameters. However, the thermal wave model of bioheat transfer could be also taken into account. Application of Arrhenius integral injury formulation in such a kind of problems seems to be quite a convenient tool to obtain additional information about the process considered. It should be pointed out that the presented model could be also considered with phase change taken into account, similarly to that presented in [1]. On the stage of sensitivity analysis using the adjoint approach is also possible.

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