MODELLING OF THERMAL PROCESSES OCCURING IN THE TISSUE WITH A TUMOR WITH REGARD TO PARAMETER SENSITIVITY ANALYSIS

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Abstract. The numerical algorithm based on the multiple reciprocity boundary element method is used for the temperature field computations in the non-homogeneous domain of healthy tissue and the tumor region. The thermophysical parameters of tumor, in particular the perfusion rate, the metabolic heat source and the thermal conductivity are essentially bigger than for healthy tissue. From the mathematical point of view the problem is described by the system of two Poisson's equations supplemented by the adequate boundary conditions. The main subject of the paper is the sensitivity analysis of temperature distribution with respect to the thermal parameters of tumor region and healthy tissue. In the final part of the paper the examples of computations are shown.

1. Governing equations

From the mathematical point of view the heat transfer processes in the domain of healthy tissue with a tumor are described by the system of Pennes equations [1, 2]

$$x \in \Omega_e : \quad \lambda_e \nabla^2 T_e(x) + k_e \left[T_B - T_e(x) \right] + Q_{me} = 0 \tag{1}$$

where e = 1, 2 identifies the subdomains of healthy tissue and tumor (Fig. 1), λ_e is the thermal conductivity, $k_e = G_e c_B$ (G_e is the perfusion rate, c_B is the volumetric specific heat of blood), T_B is the blood temperature, Q_{me} is the metabolic heat source, T_e is the temperature.

On the surface between tissue and tumor the ideal thermal contact is assumed:

$$x \in \Gamma_c : \quad \begin{cases} T_1(x) = T_2(x) = T(x) \\ q_1(x) = -q_2(x) = q(x) \end{cases} \tag{2}$$

where $q_e(x) = -\lambda_e \partial T_e(x) / \partial n_e$ is the heat flux, $\partial T_e(x) / \partial n_e$ denotes the directional derivative at the boundary point considered, while n_e is the external unit normal vector.

Taking into account the shape of the domain, the symmetrical fragment is analyzed (as in Figure 1).

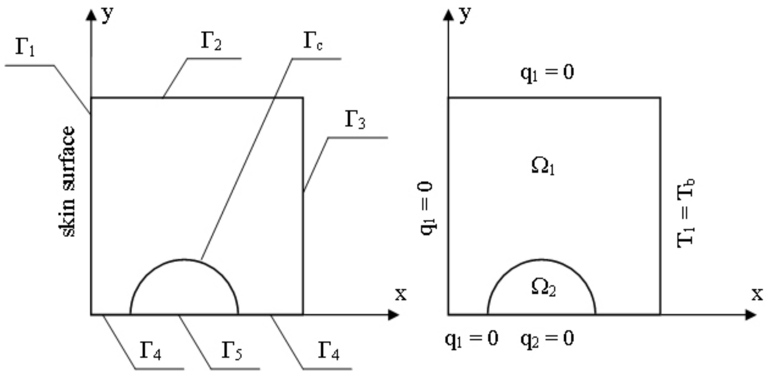

Fig. 1. Skin tissue with a tumor

On the remaining parts of the boundary the following conditions - c.f. Figure 1 can be accepted:

$$
\begin{aligned}
& x \in \Gamma_1 \cup \Gamma_2 \cup \Gamma_4 : && q_1(x) = 0 \\
& x \in \Gamma_3 : && T_1(x) = T_b \\
& x \in \Gamma_5 : && q_2(x) = 0
\end{aligned}
\tag{3}
$$

It should be pointed out that the adiabatic condition on the skin surface (Γ_1) allows to avoid the influence from the surrounding environment, which means that the skin is covered with an insulating material.

2. Parameter sensitivity analysis

In order to analyze the sensitivity of temperature field, the governing equations should be differentiated with respect to the healthy tissue and tumor region parameters (a direct approach [3, 4]), this means k_1, k_2, Q_{m1}, Q_{m2}, λ_1, λ_2 or T_B. The distinguished parameter we denote as z ($z = k_1$ or $z = k_2$ etc.).

At first, the equation (1) is differentiated with respect to z and then

$$
\frac{\partial \lambda_e}{\partial z} \nabla^2 T_e + \lambda_e \frac{\partial}{\partial z}\left(\nabla^2 T_e\right) + \frac{\partial k_e}{\partial z}\left(T_B - T_e\right) + k_e \left(\frac{\partial T_B}{\partial z} - \frac{\partial T_e}{\partial z}\right) + \frac{\partial Q_{me}}{\partial z} = 0 \tag{4}
$$

From equation (1) results that

$$
\nabla^2 T_e = -\frac{k_e}{\lambda_e}\left(T_B - T_e\right) - \frac{Q_{me}}{\lambda_e} \tag{5}
$$

and then

$$\lambda_e \nabla^2 U_e(x) - \frac{\partial \lambda_e}{\partial z}\left[\frac{k_e}{\lambda_e}\left[T_B - T_e(x)\right] + \frac{Q_{me}}{\lambda_e}\right] + \frac{\partial k_e}{\partial z}\left[T_B - T_e(x)\right] + k_e\left[\frac{\partial T_B}{\partial z} - U_e(x)\right] + \frac{\partial Q_{me}}{\partial z} = 0 \tag{6}$$

where $U_e(x) = \partial T_e(x)/\partial z$ is the sensitivity function.

Because

$$\frac{\partial q_e}{\partial z} = -\frac{\partial}{\partial z}\left(\lambda_e \frac{\partial T_e}{\partial n_e}\right) = -\frac{\partial \lambda_e}{\partial z}\frac{\partial T_e}{\partial n_e} - \lambda_e \frac{\partial}{\partial n_e}\left(\frac{\partial T_e}{\partial z}\right) = \frac{1}{\lambda_e}\frac{\partial \lambda_e}{\partial z} q_e - \lambda_e \frac{\partial U_e}{\partial n_e} \tag{7}$$

so the differentiation of boundary condition (2) leads to the following formula

$$x \in \Gamma_c: \quad \begin{cases} \dfrac{\partial T_1}{\partial z} = \dfrac{\partial T_2}{\partial z} = \dfrac{\partial T}{\partial z} \\ \dfrac{1}{\lambda_1}\dfrac{\partial \lambda_1}{\partial z} q_1 - \lambda_1 \dfrac{\partial U_1}{\partial n_1} = -\dfrac{1}{\lambda_2}\dfrac{\partial \lambda_2}{\partial z} q_2 + \lambda_2 \dfrac{\partial U_2}{\partial n_2} \end{cases} \tag{8}$$

or (c.f. equation (2))

$$x \in \Gamma_c: \quad \begin{cases} U_1(x) = U_2(x) = U(x) \\ W_1(x) = -W_2(x) - \left(\dfrac{1}{\lambda_1}\dfrac{\partial \lambda_1}{\partial z} - \dfrac{1}{\lambda_2}\dfrac{\partial \lambda_2}{\partial z}\right) q(x) \end{cases} \tag{9}$$

where $W_e(x) = -\lambda_e \partial U_e(x)/\partial n_e$.
Finally, the remaining boundary conditions (3) are differentiated with respect to z

$$\begin{aligned} &x \in \Gamma_1 \cup \Gamma_2 \cup \Gamma_4: && W_1(x) = 0 \\ &x \in \Gamma_3: && U_1(x) = 0 \\ &x \in \Gamma_5: && W_2(x) = 0 \end{aligned} \tag{10}$$

3. Solution of basic problem using the multiple reciprocity BEM

The basic problem and additional problems connected with the sensitivity analysis have been solved using the multiple reciprocity boundary element method. At first, the algorithm will be presented for the equation describing the temperature distribution in the healthy tissue

$$x \in \Omega: \quad \lambda \nabla^2 T(x) - kT(x) + Q = 0 \tag{11}$$

where λ is the thermal conductivity, k is the perfusion coefficient and $Q = kT_B + Q_m$ (Q_m is the constant metabolic heat source).

The standard boundary element method leads to the following integral equation [5, 6]

$$\begin{gathered} B(\xi)T(\xi) + \int_\Gamma V_0^*(\xi, x) q(x) \mathrm{d}\Gamma = \\ \int_\Gamma Z_0^*(\xi, x) T(x) \mathrm{d}\Gamma + \int_\Omega \left[-kT(x) + Q\right] V_0^*(\xi, x) \mathrm{d}\Omega \end{gathered} \tag{12}$$

where ξ is the observation point, $B(\xi) \in (0, 1]$, $V_0^*(\xi, x)$ is the fundamental solution

$$V_0^*(\xi, x) = \frac{1}{2\pi\lambda} \ln \frac{1}{r} \tag{13}$$

r is the distance between the points ξ and x, while

$$Z_0^*(\xi, x) = -\lambda \frac{\partial V_0^*(\xi, x)}{\partial n}, \qquad q(x) = -\lambda \frac{\partial T(x)}{\partial n} \tag{14}$$

The heat flux resulting from fundamental solution can be calculated analytically

$$Z_0^*(\xi, x) = \frac{d}{2\pi r^2}, \qquad d = (x_1 - \xi_1)\cos\alpha_1 + (x_2 - \xi_2)\cos\alpha_2 \tag{15}$$

where $\cos\alpha_1$, $\cos\alpha_2$ are the directional cosines of the normal outward vector n.
The last component in equation (12) we denote by I. In multiple reciprocity method the domain integral I is transformed into equivalent boundary integrals [7, 8]

$$I = \sum_{l=1}^{\infty} \left(\frac{k}{\lambda}\right)^{l-1} \int_\Gamma \left[-\frac{Q}{\lambda} + \frac{k}{\lambda} T(x)\right] Z_l^*(\xi, x) \mathrm{d}\Gamma - \sum_{l=1}^{\infty} \left(\frac{k}{\lambda}\right)^{l} \int_\Gamma V_l^*(\xi, x) q(x) \mathrm{d}\Gamma \tag{16}$$

where

$$V_l^*(\xi, x) = \frac{1}{2\pi\lambda} r^{2l} \left(A_l \ln\frac{1}{r} + B_l\right), \qquad l = 1, 2, 3, \ldots \tag{17}$$

while:

$$\begin{aligned} &A_0 = 1, \quad A_l = \frac{A_{l-1}}{4l^2}, && l = 1, 2, 3, \ldots \\ &B_0 = 0, \quad B_l = \frac{1}{4l^2}\left(\frac{A_{l-1}}{l} + B_{l-1}\right), && l = 1, 2, 3, \ldots \end{aligned} \tag{18}$$

and

$$Z_l^*\left(\xi, x\right) = \frac{d}{2\pi} r^{2l-2} \left[A_l - 2l\left(A_l \ln\frac{1}{r} + B_l \right) \right] \tag{19}$$

In numerical realization, the boundary Γ is divided into N boundary elements Γ_j, $j = 1, 2, ..., N$. If the constant elements are used, then one obtains the following system of algebraic equations (c.f. equations (12), (16))

$$\sum_{j=1}^{N} G_{ij} q_j = \sum_{j=1}^{N} H_{ij} T_j + R_i, \quad i = 1,\ 2,\ ..., N \tag{20}$$

where

$$G_{ij} = \sum_{l=0}^{\infty} \left(\frac{k}{\lambda} \right)^l \int_{\Gamma_j} V_l^*\left(\xi^i, x\right) \mathrm{d}\Gamma_j \tag{21}$$

and

$$H_{ij} = \sum_{l=0}^{\infty} \left(\frac{k}{\lambda} \right)^l \left[\int_{\Gamma_j} Z_l^*\left(\xi^i, x\right) \mathrm{d}\Gamma_j - \frac{1}{2}\delta_{ij} \right] \tag{22}$$

δ_{ij} is the Kronecker delta, while

$$R_i = -\frac{Q}{\lambda} \sum_{j=1}^{N} \left[\sum_{l=1}^{\infty} \left(\frac{k}{\lambda} \right)^{l-1} \int_{\Gamma} Z_l^*\left(\xi^i, x\right) \mathrm{d}\Gamma_j \right] \tag{23}$$

The system of equations (20) can be written in the matrix form

$$\mathbf{Gq} = \mathbf{HT} + \mathbf{R} \tag{24}$$

from which the 'missing' boundary values T_j or q_j can be found.
Next, the internal values of temperature T are obtained on the basis of formula

$$T_i = \sum_{j=1}^{N} H_{ij} T_j - \sum_{j=1}^{N} G_{ij} q_j + R_i \tag{25}$$

For the needs of further considerations concerning the temperature field calculation in the system healthy tissue - tumor region the following denotations are introduced (c.f. Figure 1):

- $\mathbf{T}_1$, $\mathbf{q}_1$ are the vectors of functions T and q on the surface $\Gamma_1 \cup \Gamma_2 \cup \Gamma_3 \cup \Gamma_4$ of domain Ω_1,
- $\mathbf{T}_2$, $\mathbf{q}_2$ are the vectors of functions T and q on the surface Γ_5 of domain Ω_2,
- $\mathbf{T}_{c1}$, $\mathbf{T}_{c2}$, $\mathbf{q}_{c1}$, $\mathbf{q}_{c2}$ are the vectors of functions T and q on the surface Γ_c between domains Ω_1 and Ω_2.

Using above notations, one obtains the following systems of equations:
– for the healthy tissue domain

$$\begin{bmatrix}\mathbf{G}_1 & \mathbf{G}_{c1}\end{bmatrix}\begin{bmatrix}\mathbf{q}_1\\ \mathbf{q}_{c1}\end{bmatrix}=\begin{bmatrix}\mathbf{H}_1 & \mathbf{H}_{c1}\end{bmatrix}\begin{bmatrix}\mathbf{T}_1\\ \mathbf{T}_{c1}\end{bmatrix}+\mathbf{R}_1 \tag{26}$$

– for the tumor region

$$\begin{bmatrix}\mathbf{G}_{c2} & \mathbf{G}_2\end{bmatrix}\begin{bmatrix}\mathbf{q}_{c2}\\ \mathbf{q}_2\end{bmatrix}=\begin{bmatrix}\mathbf{H}_{c2} & \mathbf{H}_2\end{bmatrix}\begin{bmatrix}\mathbf{T}_{c2}\\ \mathbf{T}_2\end{bmatrix}+\mathbf{R}_2 \tag{27}$$

The condition (2) written in the form

$$x\in\Gamma_c: \quad \begin{cases}\mathbf{T}_{c1}=\mathbf{T}_{c2}=\mathbf{T}\\ \mathbf{q}_1=-\mathbf{q}_{c2}=\mathbf{q}\end{cases} \tag{28}$$

should be introduced to the equations (26), (27) and then

$$\begin{bmatrix}\mathbf{G}_1 & -\mathbf{H}_{c1} & \mathbf{G}_{c1} & \mathbf{0}\\ \mathbf{0} & -\mathbf{H}_{c2} & -\mathbf{G}_{c1} & \mathbf{G}_2\end{bmatrix}\begin{bmatrix}\mathbf{q}_1\\ \mathbf{T}\\ \mathbf{q}\\ \mathbf{q}_2\end{bmatrix}=\begin{bmatrix}\mathbf{H}_1 & \mathbf{0}\\ \mathbf{0} & \mathbf{H}_2\end{bmatrix}\begin{bmatrix}\mathbf{T}_1\\ \mathbf{T}_2\end{bmatrix}+\begin{bmatrix}\mathbf{R}_1\\ \mathbf{R}_2\end{bmatrix} \tag{29}$$

In order to solve the system of equations (29), the remaining boundary conditions (3) should be taken into account.

The internal values of T_1 and T_2 can be determined on the basis of formulas of type (25), for Ω_1 and Ω_2, separately.

4. Solution of sensitivity problem using the multiple reciprocity BEM

At first, the algorithm will be presented for equation describing the distribution of sensitivity function in the healthy tissue

$$\lambda\nabla^2U(x)-kU(x)+wT(x)+S=0 \tag{30}$$

where (c.f. equation (6)):

$$\begin{gathered}w=\frac{\partial\lambda}{\partial z}\frac{k}{\lambda}-\frac{\partial k}{\partial z}\\ S=-\frac{\partial\lambda}{\partial z}\left(\frac{k}{\lambda}T_B+\frac{Q_m}{\lambda}\right)+\frac{\partial k}{\partial z}T_B+k\frac{\partial T_B}{\partial z}+\frac{\partial Q_m}{\partial z}\end{gathered} \tag{31}$$

As previously, the standard BEM leads to the following integral equation

$$
\begin{gathered}
B(\xi)U(\xi)+\int_{\Gamma} V_0^*(\xi, x)W(x)\,\mathrm{d}\Gamma = \\
\int_{\Gamma} Z_0^*(\xi, x)U(x)\,\mathrm{d}\Gamma+\int_{\Omega}\left[-kU(x)+wT(x)+S\right]V_0^*(\xi, x)\,\mathrm{d}\Omega
\end{gathered}
\tag{32}
$$

where $W(x)=-\lambda\partial U(x)/\partial n$.

The last component in equation (32) (denoted by J) can be transformed into the following series of boundary integrals only [8]

$$
\begin{gathered}
J=\sum_{l=1}^{\infty}\left(\frac{k}{\lambda}\right)^{l-1}\int_{\Gamma}\left[\frac{k}{\lambda}U(x)-\frac{wl}{\lambda}T(x)-\frac{S}{\lambda}\right]Z_l^*(\xi,x)\,\mathrm{d}\Gamma+ \\
Q\sum_{l=2}^{\infty}\frac{w}{\lambda^2}(l-1)\left(\frac{k}{\lambda}\right)^{l-2}\int_{\Gamma} Z_l^*(\xi,x)\,\mathrm{d}\Gamma+\sum_{l=1}^{\infty}\left(\frac{k}{\lambda}\right)^{l-1}\int_{\Gamma}\left[\frac{wl}{\lambda}q(x)-\frac{k}{\lambda}W(x)\right]V_l^*(\xi,x)\,\mathrm{d}\Gamma
\end{gathered}
\tag{33}
$$

On the stage of numerical computations one obtains the system of algebraic equations (i= 1, 2, ..., N)

$$
\sum_{j=1}^{N} G_{ij}W_j=\sum_{j=1}^{N} H_{ij}U_j+\sum_{j=1}^{N}\left(\hat{G}_{ij}q_j-\hat{H}_{ij}T_j\right)+\hat{R}_i \tag{34}
$$

or

$$
\mathbf{GW}=\mathbf{HU}+\hat{\mathbf{G}}\mathbf{q}-\hat{\mathbf{H}}\mathbf{T}+\hat{\mathbf{R}} \tag{35}
$$

where

$$
\hat{G}_{ij}=\frac{w}{\lambda}\sum_{l=1}^{\infty} l\left(\frac{k}{\lambda}\right)^{l-1}\int_{\Gamma_j} V_l^*\left(\xi^i, x\right)\mathrm{d}\Gamma_j \tag{36}
$$

and

$$
\hat{H}_{ij}=\frac{w}{\lambda}\sum_{l=1}^{\infty} l\left(\frac{k}{\lambda}\right)^{l-1}\int_{\Gamma_j} Z_l^*\left(\xi^i, x\right)\mathrm{d}\Gamma_j \tag{37}
$$

while

$$
\hat{R}_i=-\frac{S}{\lambda}\sum_{j=1}^{N}\left[\sum_{l=1}^{\infty}\left(\frac{k}{\lambda}\right)^{l-1}\int_{\Gamma_j} Z_l^*\left(\xi^i,x\right)\mathrm{d}\Gamma_j\right]+\frac{wQ}{\lambda^2}\sum_{j=1}^{N}\left[\sum_{l=2}^{\infty}(l-1)\left(\frac{k}{\lambda}\right)^{l-2}\int_{\Gamma_j} Z_l^*\left(\xi^i,x\right)\mathrm{d}\Gamma_j\right] \tag{38}
$$

If we consider the calculations of sensitivity function in the system healthy tissue - tumor region then the following systems of equations should be taken into account:

– for the healthy tissue domain

$$\begin{bmatrix} \mathbf{G}_1 & \mathbf{G}_{c1} \end{bmatrix} \begin{bmatrix} \mathbf{W}_1 \\ \mathbf{W}_{c1} \end{bmatrix} = \begin{bmatrix} \mathbf{H}_1 & \mathbf{H}_{c1} \end{bmatrix} \begin{bmatrix} \mathbf{U}_1 \\ \mathbf{U}_{c1} \end{bmatrix} + \hat{\mathbf{G}}_1 \mathbf{q}_1 + \hat{\mathbf{G}}_{c1} \mathbf{q} - \hat{\mathbf{H}}_1 \mathbf{T}_1 - \hat{\mathbf{H}}_{c1} \mathbf{T} + \hat{\mathbf{R}}_1 \tag{39}$$

– for the tumor region

$$\begin{bmatrix} \mathbf{G}_{c2} & \mathbf{G}_2 \end{bmatrix} \begin{bmatrix} \mathbf{W}_{c2} \\ \mathbf{W}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{H}_{c2} & \mathbf{H}_2 \end{bmatrix} \begin{bmatrix} \mathbf{U}_{c2} \\ \mathbf{U}_2 \end{bmatrix} + \hat{\mathbf{G}}_2 \mathbf{q}_2 + \hat{\mathbf{G}}_{c2} \mathbf{q} - \hat{\mathbf{H}}_2 \mathbf{T}_2 - \hat{\mathbf{H}}_{c2} \mathbf{T} + \hat{\mathbf{R}}_2 \tag{40}$$

The condition (9) written in the form

$$x \in \Gamma_c : \quad \begin{cases} \mathbf{U}_{c1} = \mathbf{U}_{c2} = \mathbf{U} \\ \mathbf{W}_{c2} = -\mathbf{W}_{c1} - \left(\dfrac{1}{\lambda_1} \dfrac{\partial \lambda_1}{\partial z} - \dfrac{1}{\lambda_2} \dfrac{\partial \lambda_2}{\partial z} \right) \mathbf{q} \end{cases} \tag{41}$$

should be introduced to the system (39), (40) and then

$$\begin{gathered} \begin{bmatrix} \mathbf{G}_1 & -\mathbf{H}_{c1} & \mathbf{G}_{c1} & \mathbf{0} \\ \mathbf{0} & -\mathbf{H}_{c2} & -\mathbf{G}_{c2} & \mathbf{G}_2 \end{bmatrix} \begin{bmatrix} \mathbf{W}_1 \\ \mathbf{U} \\ \mathbf{W}_{c1} \\ \mathbf{W}_2 \end{bmatrix} = \begin{bmatrix} \mathbf{H}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{H}_2 \end{bmatrix} \begin{bmatrix} \mathbf{U}_1 \\ \mathbf{U}_2 \end{bmatrix} + \\ \begin{bmatrix} \hat{\mathbf{G}}_1 \mathbf{q}_1 + \hat{\mathbf{G}}_{c1} \mathbf{q} - \hat{\mathbf{H}}_1 \mathbf{T}_1 - \hat{\mathbf{H}}_{c1} \mathbf{T} \\ \hat{\mathbf{G}}_2 \mathbf{q}_2 + \hat{\mathbf{G}}_{c2} \mathbf{q} - \hat{\mathbf{H}}_2 \mathbf{T}_2 - \hat{\mathbf{H}}_{c2} \mathbf{T} \end{bmatrix} + \begin{bmatrix} \hat{\mathbf{R}}_1 \\ \hat{\mathbf{R}}_2 \end{bmatrix} \end{gathered} \tag{42}$$

In order to solve the system of equations (42), the remaining boundary conditions (10) should be taken into account.

5. Results of computations

The domain of biological tissue of dimensions 0.03 × 0.03 m has been considered. The radius of tumor region equals 0.006 m, the position of its center (0.014, 0). The following thermophysical parameters have been assumed: λ_1 = 0.5 W/mK, λ_2 = 0.6 W/mK, k_1 = 1998.1 W/m^{3}K, k_2 = 7992.4 W/m^{3}K,

Q_{m1} = 420 W/m^3, Q_{m2} = 4200 W/m^3, blood temperature T_B = 37°C. On the arbitrary assumed internal boundary Γ_3 the temperature T_b = 37°C can be accepted.

In Figure 2 the discretization of boundary and the position of internal nodes are shown. Figure 3 illustrates the temperature distribution in the domain considered. In Figures 4-7 the distribution of sensitivity function $\Delta Q_{me} \cdot \partial T/\partial Q_{me}$ and $\Delta k_e \cdot \partial T/\partial k_e$ for e = 1, 2, for $\Delta Q_{me} = 0.2Q_{me}$, $\Delta k_e = 0.2k_e$ are shown.

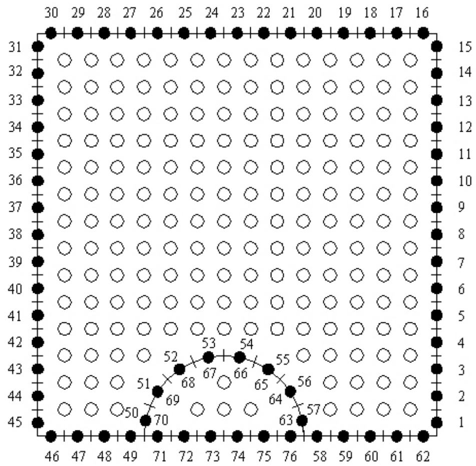

Fig. 2. Discretization

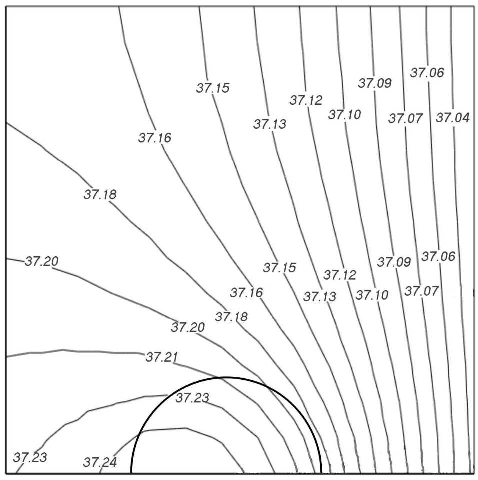

Fig. 3. Temperature distribution

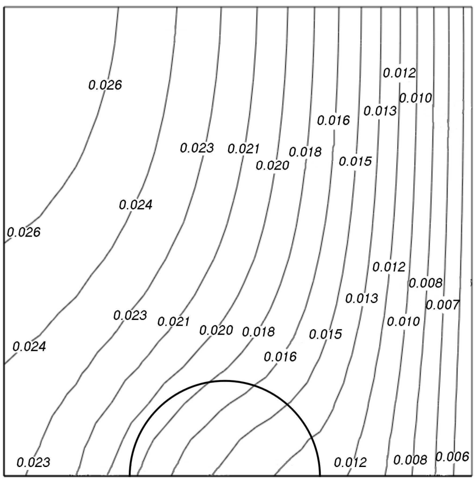

Fig. 4. Distribution of function $\Delta Q_{m1} \cdot \partial T/\partial Q_{m1}$

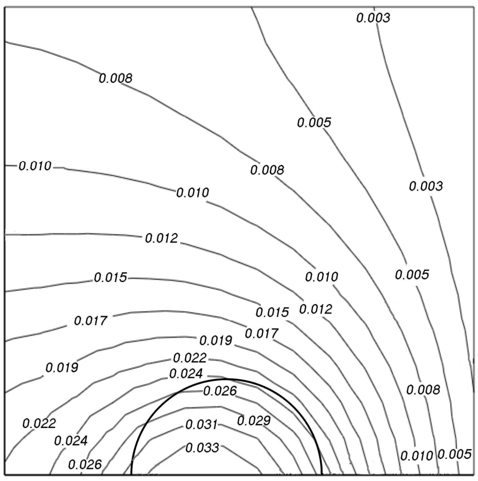

Fig. 5. Distribution of function $\Delta Q_{m2} \cdot \partial T/\partial Q_{m2}$

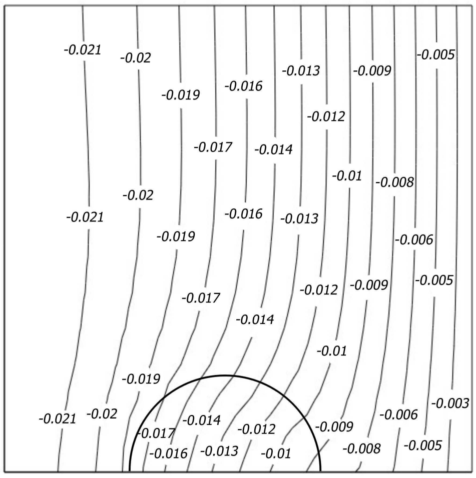

Fig. 6. Distribution of function $\Delta k_1 \cdot \partial T/\partial k_1$

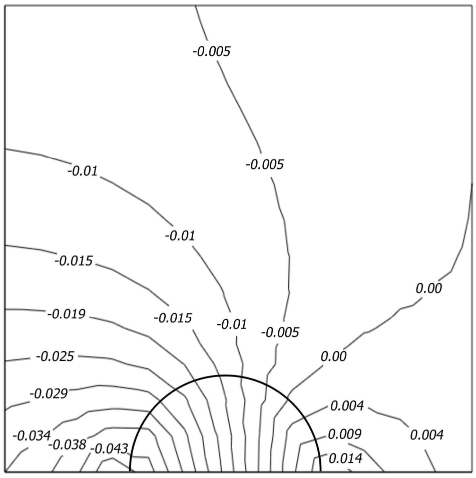

Fig. 7. Distribution of function $\Delta k_2 \cdot \partial T/\partial k_2$

Summing up, the sensitivity analysis allows, among others, to estimate the changes of temperature due to a changes of the parameters considered. It is visible, that perturbations of thermal parameters of tumor region cause the greater changes of temperature than the perturbations of thermal parameters of healthy tissue subdomain.

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