Acta of Bioengineering and Biomechanics
Vol. 16, No. 4, 2014

Original paper
DOI: 10.5277/ABB-00075-2014-02

Hyperthermia process control induced by the electric field in order to destroy cancer

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Purpose: The paper presents numerical modeling of the artificial hyperthermia induced by the electric field in order to destroy the abnormal tissue. In particular, the possibility of process control in order to increase the temperature of only the tumor tissue was discussed. Due to the fact that the external electrodes which generate the additional heat, heat not only the area of the tumor, but also healthy tissue which surrounds the tumor, increasing the temperature inside the cancer is possible by introducing the paramagnetic nanoparticles into the interior. Additionally, the proper selection of voltage on the electrodes and the number of nanoparticles will enable optimal effect of hyperthermia treatment to be achieved.

Methods: The multiple reciprocity BEM is applied to solve the coupled problem connected with the biological tissue heating. In order to determine the appropriate values of the parameters the inverse problem has been formulated, connected with simultaneous identification of the voltage of the electrodes and the number of nanoparticles, which is solved using the evolutionary algorithm.

Results: The changes of the voltage of electrodes cause the changes of temperature in the entire domain considered, but the possibilities of temperature field control (e.g., concentration of maximum temperature at the central point of tumor) are rather unrealizable, because the maximum temperature we could observe in the neighbourhood of the electrodes.

Conclusions: The idea consisting in the introduction of nanoparticles to the tumor region (for the concentrated energy deposition at the target tissue) is very effective. We obtain the maximum temperature exactly in the tumor domain.

Key words: *nanoparticles, bioheat transfer, boundary element method, cancer destruction, evolutionary algorithm, hyperthermia*

1. Introduction

Hyperthermia can be described as controlled temperature increase of parts or the whole body for a specified period of time. Increasing the temperature is of the order of several degrees above the normal body temperature (in practice this increase is about 42–46 °C). Hyperthermia is a method that supports the treatment of cancer, but also is used as a physiological therapy that heals pains, strains, sprains, etc. It is usually caused by excessive exposure to heat [1]–[3]. Hyperthermia can also be created artificially by medical devices and it may be used as a therapeutic method to obtain an artificial increase in temperature of the certain types of cancer tissue [4]–[7]. The effectiveness of artificial hyperthermia depends on the temperature and time of exposure. Most of normal tissues at the temperature greater than 44 °C for 1 hour are irreversibly damaged. In the case of cancer treatment, induction of cancer cell necrosis is a desirable effect. The main problem associated with performing the hyperthermia treatment is appropriate orientation of artificial heat source. A significant limitation of hyperthermia method is its inability to heat specific regions. This implies a high risk of damage to the healthy tissue or heat dissipation around the tumor cells, which can lead to inadequate treatment of cancer [8]. Great efforts have recently been made to use magnetic nanoparticles for the concentrated heat deposition in the tumor region located inside the human body. The particles should be made from mate-

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Received: April 30th, 2014
Accepted for publication: May 8th, 2014

rial assuring the appropriate magnetic properties and biological compatibility. Here, the iron oxides magnetite (Fe_3O_4) and maghemite (γ–Fe_2O_3) can be applied [9]. It should be pointed out that the injection of nanoparticles to the human body belongs, most certainly, to the group of invasive interventions, but on the other hand, the effectiveness and precision of heating operation is essentially better than in the case of procedure neglecting the injection of the particles.

The present issue was the subject of discussion in many other publications [4]–[6], [9]–[13] and conference proceedings [14], [15]. In the previous publications, mainly the 2D problem is considered [4]–[6], [11]–[13]. Subjected to consideration was simplified geometrical model, both biological tissue (approximated by rectangle) and cancer (approximated by square) [4]–[6], [11], [13]. To solve the Pennes equation the classical algorithm of the Boundary Element Method (BEM) [4], [5], [11], Finite Element Method (FEM) [6], [12], [13] or Radial Basis Collocation Method (RBCM) [10] is used. The results of numerical calculations in which the nanoparticles in the tumor were modeled, in order to direct the increase of the temperature and achieve the effect of hyperthermia, are presented in [4], [8], [11], [12] for 2D tasks and in [14], [15] for 3D tasks. Most of the publications are related to the solution of direct problem [5], [6], [9], [12]–[14], while the solution of the inverse problem involving the identification of parameters associated with the nanoparticles or the voltage on the electrodes is shown in [4], [11], [15]. In [14], the 3D problem is presented, where the real shape of domain (tissue) is approximated by a rectangular prism, the tumor region is approximated by a cube and the direct problem is solved also using classical algorithm of the BEM.

In this article, the complex shape of the object analyzed close to the fragment of the human hand is considered [15]. Since the solution of the Pennes equation using the classical approach of BEM requires the discretization of both the boundaries and the interior area. With complexity of the geometry, the discretization of the interior is quite problematic, therefore on the stage of numerical computations the multiple reciprocity BEM (MRBEM) is used, which requires only the boundaries discretization.

So, in the paper, a 3D electromagnetic field and temperature one induced by two external electrodes in the biological tissue containing a cancer with magnetic nanoparticles, as shown in Fig. 1, are considered. The aim of investigations is to determine the electric potential of the electrodes relative to the ground assuring the temperature at the nodes located in the tumor region greater than the temperature which cause the necrosis. The more complex task concerns the simultaneous identification of electric potential and the number of particles introduced to a tumor region.

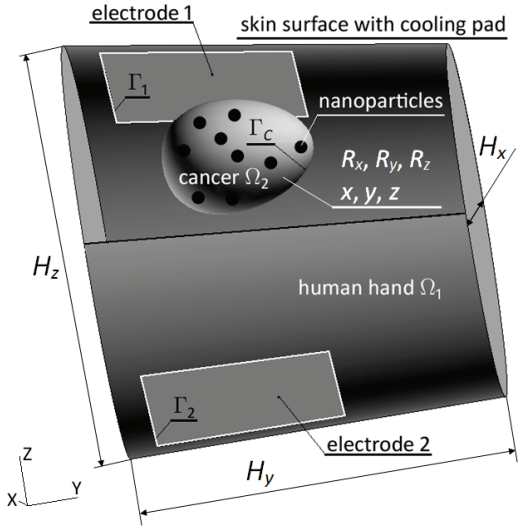

Fig. 1. Hyperthermia system

2. Materials and methods

2.1. Electromagnetic field

Because the wavelength of the radio frequency (RF) current in tissues is much greater than depth of a human body, the quasistatic electric field approximation can be applied. The quasistatic electric field is irrotational, so the electric potential can be introduced. The potential $\varphi_e(x, y, z)$ inside the healthy tissue (e = 1) and tumor region (e = 2) is described by the system of Laplace equations

$$(x,y,z) \in \Omega_e : \quad \varepsilon_e \nabla^2 \varphi_e(x,y,z) = 0 \tag{1}$$

where ε_e [$C^2/(Nm^2)$] is the dielectric permittivity of sub-domains Ω_e. At the interface Γ_c of the tumor and healthy tissue (Fig. 1) the ideal electric contact is assumed

$$(x,y,z) \in \Gamma_c : \begin{cases} \varphi_1(x,y,z) = \varphi_2(x,y,z), \\ -\varepsilon_1 \dfrac{\partial \varphi_1(x,y,z)}{\partial n} = -\varepsilon_2 \dfrac{\partial \varphi_2(x,y,z)}{\partial n}. \end{cases} \tag{2}$$

On the external surface of tissue being in contact with the electrodes the following condition is given

$$(x,y,z)\in\Gamma_1:\ \varphi_1(x,y,z)=U,$$
$$(x,y,z)\in\Gamma_2:\ \varphi_2(x,y,z)=-U, \tag{3}$$

where U [V] is the electric potential of the electrode relative to the ground. On the remaining external boundary of tissue the ideal electric isolation is assumed: $\varepsilon_1\partial\varphi_1(x, y, z)/\partial n = 0$.

The electric field inside the tissue is determined by equation

$$\boldsymbol{E}_e(x,y,z)=-\nabla\varphi_e(x,y,z)$$
$$=-\left[\frac{\partial\varphi_e(x,y,z)}{\partial x}\ \frac{\partial\varphi_e(x,y,z)}{\partial y}\ \frac{\partial\varphi_e(x,y,z)}{\partial z}\right]^T. \tag{4}$$

Heat generation Q_1 [W/m^3] due to the electromagnetic dissipated power in healthy tissue depends on the conductivity σ_1 [S/m] and the electric field $\mathbf{E}_1$ [9]

$$Q_1(x,y,z)=\frac{\sigma_1|\mathbf{E}_1(x,y,z)|^2}{2}. \tag{5}$$

The tumor region with embedded magnetic particles is treated as a composite and due to the assumed homogeneity of Ω_2 the mean value of electrical conductivity σ_2 of this sub-domain can be approximated as $1/\sigma_2 = (1 - \Theta)/\sigma_2' + \Theta/\sigma_3$, where σ_2', σ_3 are the electrical conductivities of tumor and particles, respectively, and $\Theta = n\frac{4}{3}\pi r^3/V_t$ is the concentration of particles (n is the number of particles, r is the radius of particle, V_t is the tumor volume).

The amplitude of the magnetic field intensity can be expressed as [9]

$$|\mathbf{H}(x,y,z)|=\frac{1}{1+N(\chi)}\frac{|\mathbf{E}_2(x,y,z)|}{\mu_0\pi f R} \tag{6}$$

where $\mu_0 = 4\pi\cdot10^{-7}$ [Tm/A] is the dielectric constant permeability of free space, f [Hz] is the frequency of electromagnetic field, R [m] is the radius of the magnetic induction loop, $N(\chi)$ is the demagnetizing factor ($N(\chi) = 1/3$ for a spherical composite) and χ (here: $\chi = \chi' + i\chi''$ [8]) is the susceptibility of the magnetic nanoparticles. Heat generation by superparamagnetism (SPM) is given by [9]

$$P_{SPM}(x,y,z)=\mu_0\pi f\chi''|\mathbf{H}(x,y,z)|^2 \tag{7}$$

and then for $(x, y, z) \in \Omega_2$ one has

$$Q_2(x,y,z)=\Theta P_{SPM}(x,y,z)+(1-\Theta)\frac{\sigma_2|\mathbf{E}_2(x,y,z)|^2}{2}. \tag{8}$$

2.2. Temperature field

The temperature field in the healthy tissue and the tumor region with embedded magnetic nanoparticles for the steady state problem is described by the system of Pennes equations [5], [9], [10], [16]

$$\lambda_e\nabla^2T_e(x,y,z)+k_e[T_B-T_e(x,y,z)]$$
$$+Q_{\text{met }e}+Q_e^E(x,y,z)=0, \tag{9}$$

e = 1, 2 correspond to the healthy tissue and tumor region, respectively, T_e denotes temperature, λ_e [W/(mK)] is the thermal conductivity, $k_e = G_{Be}c_B$ (G_{Be} [1/s] is the perfusion rate, c_B [J/(m^{3}K)] is the volumetric specific heat of blood), T_B is the supplying arterial blood temperature, $Q_{\text{met }e}$ [W/m^3] is the metabolic heat source, $Q_e^E(x, y, z)$ [W/m^3] is the heat source connected with the electromagnetic field action. It should be pointed out that thermal conductivity λ_2 of tumor region with nanoparticles can be calculated as follows: $1/\lambda_2 = (1 - \Theta)/\lambda_2' + \Theta/\lambda_3$, where λ_2', λ_3 are the thermal conductivities of tumor and nanoparticles, respectively.

At the interface Γ_c between the tumor and healthy tissue the ideal contact is assumed

$$(x,y,z)\in\Gamma_c:\begin{cases}T_1(x,y,z)=T_2(x,y,z),\\ -\lambda_1\dfrac{\partial T_1(x,y,z)}{\partial n}=-\lambda_2\dfrac{\partial T_2(x,y,z)}{\partial n}.\end{cases} \tag{10}$$

At the skin surface (c.f. Fig. 1) of tissue domain the convection condition can be accepted, which is simulated that the skin tissue is covered by a cooling layer (cooling pad)

$$-\lambda_1\partial T_1(x,y,z)/\partial n=\alpha_w[T_1(x,y,z)-T_w] \tag{11}$$

where α_w [W/(m^{2}K)] is the heat transfer coefficient between the skin surface and the cooling water, T_w is the cooling water temperature. On the remaining boundaries the adiabatic condition

$$-\lambda_1\partial T_1/\partial n=0 \tag{12}$$

can be taken into account. This condition results from the consideration that at the positions far from the center of the domain the temperature field is almost not affected by the external heating [10].

2.3. Inverse problem

The inverse problem which will be discussed consists in the identification of electric potential U of the electrodes and number of nanoparticles embedded in tumor under the assumption that the temperature at the nodes located in this region is equal to T_h, for T_h = 42 °C and 44 °C. The final temperature field inside the tumor corresponding to the optimum value of identified parameter is heterogeneous, of course. The following criterion is considered

$$\sum_{i=1}^{M}(T_i - T_h)^2 \to \text{MIN} \tag{13}$$

where T_i are the nodal temperatures located inside the tumor and resulting from numerical solution of direct boundary problem for assumed value of potential U and number of nanoparticles n and M is the number of nodes located inside the tumor.

To identify the electric potential U and number of nanoparticles n the evolutionary algorithm has been applied [17], [18]. The functional (13) is minimized due to the unknown parameters of the process control hyperthermia. Chromosome which genes contain the information about the identified parameters is defined as follows

$$\mathbf{p} = [U \quad n]^T \tag{14}$$

where U and n are the genes containing information about the electric potential and number of nanoparticles, respectively.

The genes representing the possible solutions (parameters value) are obtained during operation of the evolutionary algorithm, within the constraints imposed

$$U^L \le U \le U^H, \quad n^L \le n \le n^H \tag{15}$$

where L and H denote the minimum and maximum value of the limitations imposed on the parameters identified.

Operation of an evolutionary algorithm starts with a generating of starting population. This population consists of S chromosomes $\mathbf{p}^s$, s = 1, 2, ..., S, generated in a random way in accordance with the limitations imposed by (15). For each chromosome, which is a potential solution, the direct problem is solved by equations (1)–(3), (9)–(12) using the boundary element method. The next step in the EA is a calculation of the fitness function (13) for each chromosome. In order to create the next generation the chromosomes are subjected to evolutionary operators [17], [18]:

- arithmetic crossover – which creates new chromosome with genes which are the linear combination of two randomly chosen chromosomes,
- uniform mutation – which changes the genes values in chromosome by choosing the new ones in random way,
- nonuniform mutation – which changes the genes values in chromosome using the Gauss distribution, the amplitude of such mutation in each generation is equal $\sigma = 1/pop$, where pop is number of generation,
- cloning – which makes possible the passage of the best chromosome to the next population without necessity of participation in the process of selection.

Application of the selection operator allows to create a new generation of chromosomes. The process is repeated until the chromosome, for which the value of the fitness function is zero, is found or after the achieving the assumed number of generations.

In Fig. 2 the scheme of evolutionary algorithm is presented.

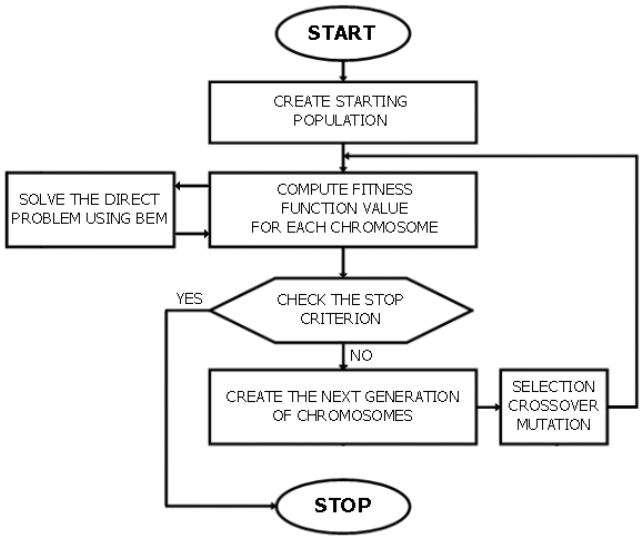

Fig. 2. Flow chart of evolutionary algorithm

Table 1. Evolutionary algorithm parameters

Number of generations	Number of chromosomes	Probability of uniform mutation	Probability of nonuniform mutation	Probability of arithmetic crossover	Probability of cloning
100	50	30%	20%	60%	10%

In Table 1, the parameters of evolutionary algorithm used in computations are collected.

2.4. Boundary element method – electric field

The boundary integral equations corresponding to equations (1) can be expressed as [10], [16], [19], [20]

$$B_e(\xi_1,\xi_2,\xi_3)\varphi_e(\xi_1,\xi_2,\xi_3) + \iint_\Gamma \psi_e(x,y,z)\varphi_e^*(\xi_1,\xi_2,\xi_3,x,y,z)d\Gamma = \iint_\Gamma \varphi_e(x,y,z)\psi_e^*(\xi_1,\xi_2,\xi_3,x,y,z)d\Gamma \quad (16)$$

where (ξ_1, ξ_2, ξ_3) is the observation point, the coefficient $B_e(\xi_1, \xi_2, \xi_3)$ is dependent on the location of source point (ξ_1, ξ_2, ξ_3), $\psi_e(x, y, z) = -\varepsilon_e \partial\varphi_e(x, y, z)/\partial_n$.

Fundamental solutions of the problem discussed have the following form

$$\varphi_e^*(\xi_1,\xi_2,\xi_3,x,y,z) = \frac{1}{4\pi\varepsilon_e r} \quad (17)$$

where r is the distance between points (ξ_1, ξ_2, ξ_3) and (x, y, z). Differentiating the function $\varphi_e^*(\xi_1, \xi_2, \xi_3, x, y, z)$ with respect to the outward normal $\mathbf{n} = [\cos\alpha\ \cos\beta\ \cos\gamma]$ the function $\psi_e^*(\xi_1, \xi_2, \xi_3, x, y, z)$ is obtained

$$\psi_e^*(\xi_1,\xi_2,\xi_3,x,y,z) = -\varepsilon_e \frac{\partial\varphi_e^*(\xi_1,\xi_2,\xi_3,x,y,z)}{\partial n} = \frac{d}{4\pi r^3} \quad (18)$$

where

$$d = (x-\xi_1)\cos\alpha + (y-\xi_2)\cos\beta + (z-\xi_3)\cos\gamma. \quad (19)$$

The boundaries of the domains are divided into $N_1 = 723$ and $N_2 = 198$ boundary elements as shown in Fig. 3.

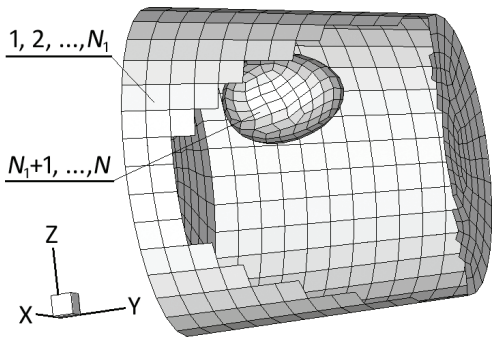

Fig. 3. Boundary elements

The method of solving the problem using the boundary element method can be found in [5], [10], [19], [21]–[23].

2.5. Boundary element method – temperature field

The Pennes equation (9) can be written in the form

$$(x,y,z) \in \Omega_e: \quad \lambda_e \nabla^2 T_e(x,y,z) + Q_e(x,y,z) = 0 \quad (20)$$

where

$$Q_e(x,y,z) = \Omega_{\text{perf } e} + Q_{\text{met } e} + Q_e^E(x,y,z) \quad (21)$$

where $Q_{\text{perf } e}$, $Q_{\text{met } e}$, $Q_e^E(x,y,z)$ are the heat sources connected with perfusion, metabolism and electromagnetic dissipated power, respectively.

To obtain the temperature field the multiple reciprocity boundary element method has been applied. This variant of the BEM allows one to avoid the discretization of domain interior. So, the boundary integral equations corresponding to equations (20) are the following [10], [20], [21]

$$B_e(\xi_1,\xi_2,\xi_3)\varphi_e(\xi_1,\xi_2,\xi_3) + \sum_{l=0}^{\infty}\iint_\Gamma q_e(x,y,z)V_{le}^*(\xi_1,\xi_2,\xi_3,x,y,z)d\Gamma = \sum_{l=0}^{\infty}\iint_\Gamma T_e(x,y,z)Z_{le}^*(\xi_1,\xi_2,\xi_3,x,y,z)d\Gamma - \frac{Q_e(x,y,z)}{\lambda_e}\sum_{l=0}^{\infty}\iint_\Gamma Z_{le}^*(\xi_1,\xi_2,\xi_3,x,y,z)d\Gamma. \quad (22)$$

The above boundary-integral equation is solved using the method described in [16], [19], [21]–[23].

3. Results

The real shape of human hand has been approximated by irregular three dimensional shape of dimensions $H_x = 0.08$, $H_y = 0.1$, $H_z = 0.1$ [m] as shown in Fig. 1, while the tumor has been approximated by 3D shape which is described by six parameters: maximum lengths in each axis $R_x = 0.02$, $R_y = 0.02$, $R_z = 0.03$ [m] and center position ($x = 0.02$, $y = 0.5$, $z = 0$ [m]). The voltage of opposite heating area is 15V and –15V.

At first, the temperature distribution in the tissue with a tumor subjected to electric field action in the case of "natural" situation (the particles are not intro-

duced) has been considered. For healthy tissue the following parameters have been assumed: thermal conductivity $\lambda_1 = 0.5$ [W/(mK)], metabolic heat source $Q_{met1} = 4200$ [W/m^3], perfusion heat source $Q_{perf1} = -2000$ [W/m^3]. It has been revealed that existence of malignant tumor often leads to very different blood perfusion and abnormally high capacity of metabolic heat source in the tumor region [4], [9]. The following parameters are thus given for a highly vascularized tumor situated in the tissue: $Q_{met2} = 42000$ [W/m^3], $Q_{perf2} = -8000$ [W/m^3], $\lambda_2 = 0.75$ [W/(mK)] [10]. The parameters collected above can be treated as the mean values. Recently appeared the papers in which the properties of tissue are treated as the interval numbers (e.g., [24]). On the skin surface the Robin boundary condition (equation (11): $\alpha_w = 45$ [W/(m^2 K)], $T_w = 20$ °C) has been accepted.

Additionally, it is assumed that the frequency of electromagnetic field is equal to $f = 1$ [MHz] and the radius R of magnetic induction loop is equal to 0.01 [m]. The following values of parameters have been used [9]: electric conductivity of healthy tissue $\sigma_1 = 0.4$ [S/m], electric conductivity of tumor region $\sigma_2 = 1.2 \cdot \sigma_1$ [S/m], dielectric permittivities $\varepsilon_1 = 100 \cdot \varepsilon_0$ and $\varepsilon_2 = 1.2 \cdot \varepsilon_1$ ($\varepsilon_0 = 8.85 \cdot 10^{-12}$ [C^2/(Nm^2)]), respectively.

The nanoparticles are made from iron oxides maghemite γ-Fe_2O_3 which electric conductivity equals to $\varepsilon_3 = 25000$ [S/m], thermal conductivity: $\lambda_3 = 40$ [W/(mK)] and $\chi'' = 18$ [9].

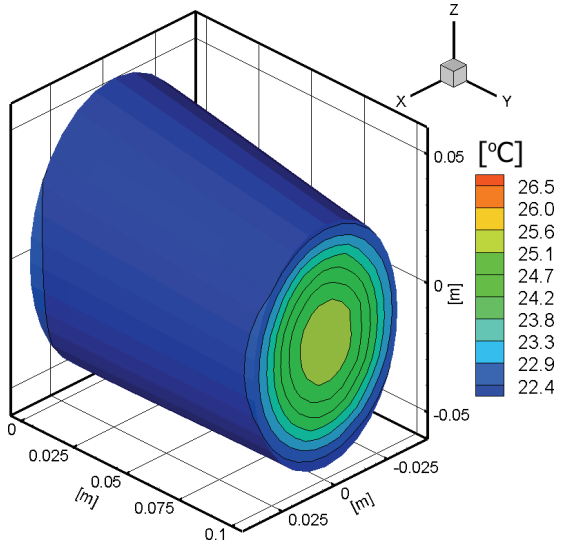

Fig. 4. Temperature distribution in healthy tissue

In Figs. 4 and 5, the temperature distributions in domain of healthy tissue and tissue with tumor without electric field and nanoparticles are shown. Figure 6 presents the electric field distribution for $U = 15$ [V], while Fig. 7 illustrates the temperature field in the tissue subjected to the electric field.

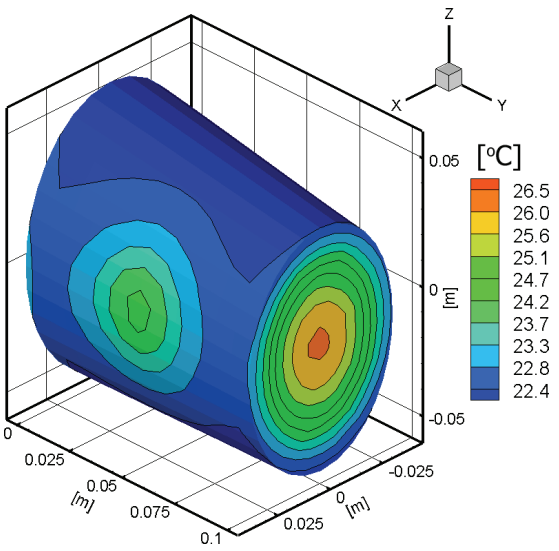

Fig. 5. Temperature distribution in tissue with tumor

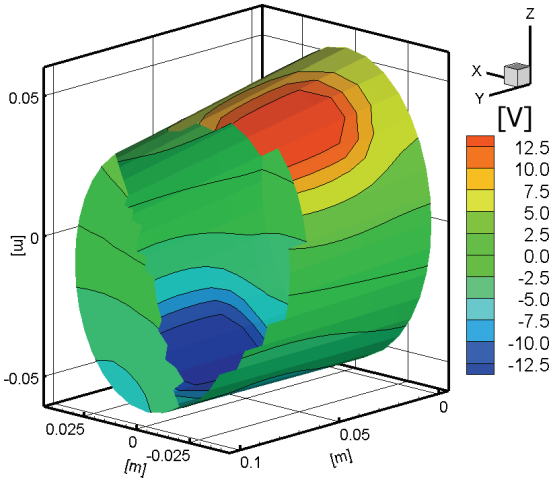

Fig. 6. Electric field distribution ($U = 15$ [V])

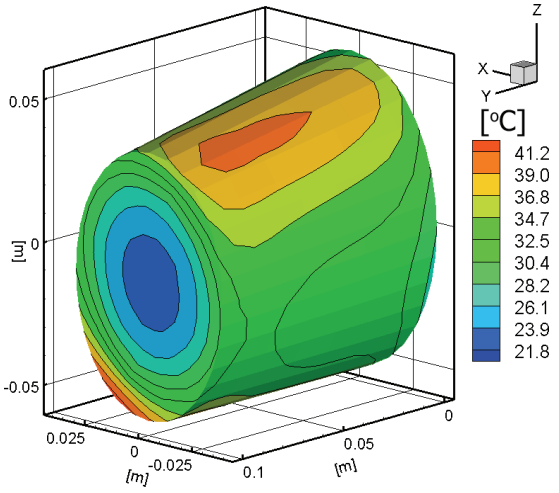

Fig. 7. Temperature distribution in the domain subjected to the electric field ($U = 15$ [V])

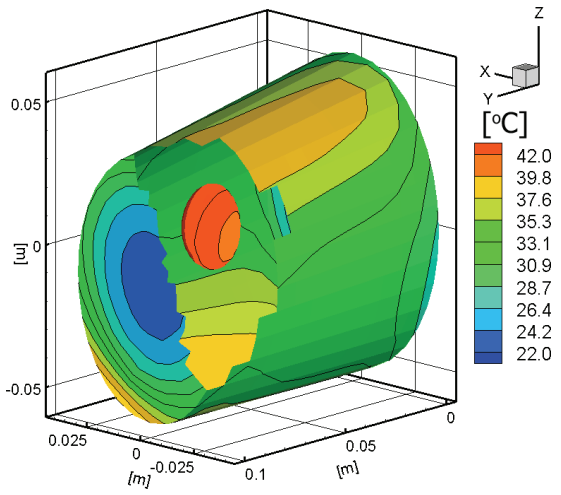

Fig. 8. Temperature distribution ($U = 12.5$ V, $n = 9.2 \times 10^{12}$)

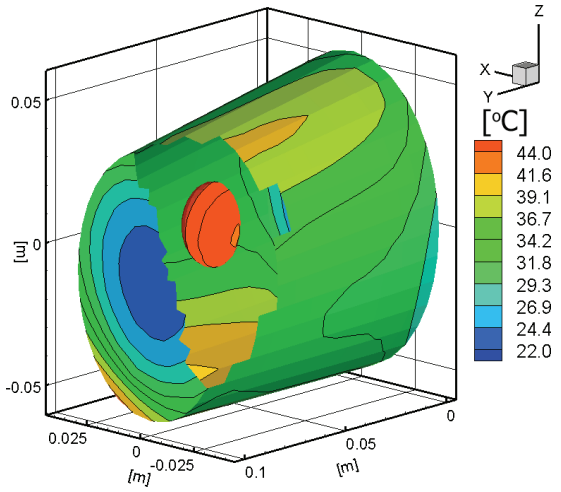

Fig. 9. Temperature distribution ($U = 15.3$ V, $n = 6.8 \times 10^{12}$)

The aim of inverse problem computations is to determine the electric potential of electrodes and number of nanoparticles assuring the minimum value of functional (13) for $T_h = 42$ °C or 44 °C. In other words, the temperature in domain of tumor should be close to the postulated value of T_h. The results of computations obtained by evolutionary algorithm are shown in Figs. 8 and 9, and collected in Table 2. The following intervals (c.f. (15)) to generate a starting population have been accepted $1 \le U \le 20$, $1 \cdot 10^9 \le n \le 1 \cdot 10^{14}$.

4. Discussion

Coupled problem resulting from a combination of fields, electrical and thermal, is solved by the boundary element method with multiple reciprocity principle. Mathematical model for three-dimensional problem consists of two equations, namely the Laplace equation for electric field and the Pennes equation for thermal field. The coupling was performed based on the heat source function generated by the electric field.

The coupled problem discussed in this paper concerns, as pointed above, the 3D task and the shape of domain considered is close to the real geometry of the forearm. The solutions of the direct and inverse problems analyzed correspond to 3D problem, of course, and from the numerical point of view a such approach is more complex in comparison with 1D or 2D models.

The changes of the voltage of external electrodes cause the changes of temperature in the entire domain considered, but the possibilities of temperature field control (e.g., a concentration of maximum temperature at the central point of tumor region) are rather unrealizable, because the maximum temperature we could observe in the neighbourhood of the electrodes. So, the idea consisting in the introduction of nanoparticles to the tumor region (for the concentrated energy deposition at the target tissue) is very effective. We obtain the maximum temperature exactly in the tumor domain.

Causing the phenomenon of hyperthermia using electric field requires the proper selection of the potential on the electrodes. The maximum temperature occurs in the vicinity of the electrodes. The higher the potential, the higher the temperature. Application of the nanoparticles allows targeting of the source function resulting from the electric field intensity in the sub-domain of tumor. The inverse problem was to determine the values of electric potential and the number of nanoparticles in the tumor sub-domain in order to receive the appropriate temperature for the phenomenon of hyperthermia, or 42 °C or 44 °C, depending on the case. Receiving the assumed temperature across the sub-domain of tumor is not possible, hence the fitness function (13) does not reach a value equal to zero, of course. Therefore, the presented so-

Table 2. Solution of inverse problem using EA

Design variable	found value		fitness function (13)	found value		fitness function (13)
	$T_h = 42$°C			$T_h = 44$°C		
Electric potential U [V]	12.5	13.2	9.781462	15.3	14.5	5.993136
Number of nanoparticles n	$9.2 \cdot 10^{12}$	$8.1 \cdot 10^{12}$	9.781209	$6.8 \cdot 10^{12}$	$7.7 \cdot 10^{12}$	5.997954

lution is not the only one possible. Although it should be taking into account that a large value of electric potential will cause too much temperature increase, while too small will not induce the phenomenon of hyperthermia. In the case of nanoparticles, too small number of nanoparticles does not focus the heat pulse to a tumor region.

The results obtained as a solution of inverse problem using evolutionary algorithm seems to be quite satisfactory.

As previously mentioned, the problem of numerical modelling of temperature field in domain of tumor with embedded nanoparticles and surrounding healthy tissue subjected to the electric field has been discussed in several publications e.g., [4], [9], [25]. In this paper the method of estimation of the nanoparticles number and electrodes potential ensuring the destruction of the tumor based is proposed. A similar approach is presented in the work [4] but it relates to a 2D problem and a simplified geometry of cancer (square) and surrounding tissue (rectangle).

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