A methodology for determining optimal thermal damage in magnetic nanoparticle hyperthermia cancer treatment

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SUMMARY

Hyperthermia treatment of tumors uses localized heating to damage cancer cells and can also be utilized to increase the efficacy of other treatment methods such as chemotherapy. Magnetic nanoparticle hyperthermia is one of the least invasive techniques of delivering heat. It is based on injecting magnetic nanoparticles into the tumor and subjecting them to an alternating magnetic field. The technique is aimed at damaging the tumor without affecting the surrounding healthy tissue. In this preliminary study, we consider a simplified model (two concentric spheres that represent the tumor and its surrounding tissues) that employs a numerical solution of the Pennes bioheat equation. The model assumes a Gaussian distribution for the spatial variation of the applied thermal energy and an exponential decay function for the time variation. The objective of the study is to optimize the parameters that control the spatial and the time variation of the thermal energy. The optimization process is performed by formulating a fitness function that rewards damage in the region representing the tumor but penalizes damage in the surrounding tissues. Because of the flatness of this fitness function near the optimum, a genetic algorithm is used as the optimization method for its robust non-gradient-based approach. The overall aim of this work is to propose a methodology that can be used for hyperthermia treatment in a clinical scenario. Copyright © 2011 John Wiley & Sons, Ltd.

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KEY WORDS: hyperthermia; thermal dose; magnetic heating; breast cancer

1. INTRODUCTION

Heat transfer has been used in both diagnosing and treating diseases. The earliest known use of thermal diagnostic via skin temperature measurement dates back to the work of Hippocrates in 480 BC [1]. Mud slurry was spread over the skin of patients and was allowed to dry. The areas of the skin which were found to dry faster than others were thought to show the presence of a disease. The history of hyperthermia dates back to 5000 BC when Egyptian doctors tried to burn superficial tumors [2]. Although the principle of thermal ablation was known, the means to properly direct the flow of thermal energy into the tumor have only become available in modern times. Some of these include microwave [3, 4], ultrasound [5–7], radiofrequency [8–12], and laser [13, 14] thermal ablation. Since the early 1990s, several techniques have been investigated that utilize nanoparticles for delivering appropriately distributed thermal energy localized within the tumor [15]. Magnetic fluid hyperthermia is one such technique, where magnetic nanoparticles (such as iron oxide) are delivered to the site of the tumor through the blood stream or by direct injection into the tumor. The latter is usually more effective, as nanoparticles delivered through the blood stream penetrate only a limited depth through the tumor surface, particularly in poorly perfused tumors. The particles are then heated by application of an alternating magnetic field. The process of thermal energy...
generation can be explained by a combination of Néel (rotation of the magnetic moment within a nanoparticle) and Brownian (rotation of entire nanoparticle) relaxation mechanisms [16, 17]. For a given value of particle size and magnetic field (strength and frequency), the spatial distribution of thermal energy generation rate (W/m$^3$) can be expected to follow the concentration distribution of nanoparticles in the tumor. A recent study [18] investigated the concentration distribution of magnetic nanoparticles in agarose gel (with porous structures similar to biological tissue) and proposed a Gaussian distribution about the injection site as a reasonable model for future theoretical studies.

The current study presents a simplified model that utilizes a numerical solution of Pennes bioheat equation to calculate the time–temperature history in a spherical heated region (representing the tumor) and the surrounding domain (representing healthy tissue). The time–temperature history is then used for calculating the thermal damage accumulated over the duration of the hyperthermia treatment [19]. For a given treatment time, the goal is to maximize the damage in the region representing the tumor and minimize the damage in the surrounding region. This goal can be achieved by solving for an optimal spatiotemporal heating profile for the region representing the tumor. Although in general such solutions will be non-unique, realistic assumptions (described later) can be made regarding the shape of the spatiotemporal profile. A suitable method can then be used for estimating the optimal values of the parameters governing this profile. Different estimation methods were considered; however, because of the flatness of the fitness function near the optimum, a genetic algorithm (GA) was selected because of its robust non-gradient-based optimization approach. More information regarding the theory of GAs can be found in [20, 21].

Several authors have used the bioheat equation to propose analytical solutions that could be utilized in optimizing thermal damage during the treatment (e.g., [22, 23]). Although these analytical solutions are computationally less expensive than the current numerical approach, they cannot be extended to more complex three-dimensional simulation domains obtained from MRI or computed tomography (CT).

2. NUMERICAL MODEL

The model used in this study employs a finite element numerical solution of the Pennes bioheat equation

$$k \nabla^2 T + \rho_b c_b \omega_b (T_a - T) + Q_{met} + Q_{ext} = \rho c \frac{\partial T}{\partial t}$$

On the left-hand side of the equation, $T$ is the unknown tissue temperature (K), $k$ is the tissue thermal conductivity (W/m K), $\rho_b$ is the density of blood (kg/m$^3$), $\omega_b$ is a term that represents blood perfusion (m$^3$/m$^3$ s), $c_b$ is the specific heat of blood (J/kg K), $T_a$ is the arterial blood temperature (K), $Q_{met}$ is the volumetric metabolic heat generation rate (W/m$^3$), and $Q_{ext}$ is externally applied heat source (W/m$^3$), such as heating caused by an electromagnetic field. On the right-hand side of the equation, $\rho$ is the tissue density (kg/m$^3$), $c$ is specific heat of the tissue (J/kg K), and $\partial T/\partial t$ is the time rate of temperature change (K/s).

In the current study, two concentric spheres (with 0.02- and 0.04-m diameters) are used to represent the tumor and its surrounding healthy tissues. Because of symmetry, the geometry becomes one dimensional if a spherical coordinate system is used. The model has the outer boundary condition set at an arterial blood temperature of 37°C. Continuity of temperature and heat flux is assumed at the inner boundary. The initial temperature is set at 37°C in both domains. The inner sphere has different thermal properties (required for solving the bioheat equation) from the surrounding. These properties are estimates from literature and are summarized in Table I [9]. The thermal conductivity ($k$), specific heat ($c$), and density ($\rho$) of the region representing the tumor are assumed to be the same as that for the region representing the healthy tissue. It is known that for a tumor in its vascular stage, the metabolic heat generation rate $Q_{met}$ is significantly higher because of higher metabolic activity (which is the basis for medical infrared thermography) [24]. The tumor also has higher blood perfusion $\omega_b$ because of a growing network of capillaries and blood vessels that it develops. As there are significant uncertainties associated with $Q_{met}$ and $\omega_b$, a sensitivity study (described
Table I. Values of biothermal properties used in the model [9].

<table>
<thead>
<tr>
<th>Property</th>
<th>Tissue</th>
<th>Blood</th>
<th>Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermal conductivity (W/m K)</td>
<td>0.512</td>
<td>–</td>
<td>0.512</td>
</tr>
<tr>
<td>Specific heat (J/kg K)</td>
<td>3600</td>
<td>4180</td>
<td>3600</td>
</tr>
<tr>
<td>Density (kg/m$^3$)</td>
<td>1060</td>
<td>1000</td>
<td>1060</td>
</tr>
<tr>
<td>Metabolic heat generation (W/m$^3$)</td>
<td>700</td>
<td>–</td>
<td>3500</td>
</tr>
<tr>
<td>Blood perfusion (m$^3$/m$^3$ s)</td>
<td>0.0064</td>
<td>–</td>
<td>0.032</td>
</tr>
</tbody>
</table>

Later) is performed to gauge their effects on the optimal thermal damage. Although constant properties are used in this study, the model can easily be extended to include spatial and temperature variations in properties.

Equation 1 splits the heat source term into metabolic and externally applied heat source components. In the current study, the governing equation for the externally applied heat source is given by

$$Q_{\text{ext}} = B e^{-(r/r_0)^2} e^{-\left(t/\tau\right)}$$

Equation 2 assumes decoupled spatial and temporal profiles, which is a reasonable assumption if the concentration distribution of nanoparticles remains unchanged during the course of the treatment, after the initial injection. The spatial profile of the heat source is based on a Gaussian distribution, as discussed previously. Here, $B$ represents the maximum strength of the heat source (W/m$^3$) at the injection site, $r$ is radial distance from the injection site, and $r_0$ (dependent on rate of nanoparticle gel injection and concentration) is related to the diffusion distance [18]. The value of $B$ is assumed to be $2 \times 10^{-6}$ W/m$^3$ on the basis of maximum level of power that can be expected from the present level of magnetic nanoparticle technology. The temporal profile in Equation 2 is an exponential decay function, where $\tau$ is the time constant. Although other functions (linear, polynomial, etc.) were also considered, it was found that exponential function was most suitable, in agreement with previous studies [23, 25].

The numerical solution to Equation 1 can be used to obtain a time temperature history of the treatment, which can then be used in calculating the accumulated thermal damage in the domains of interest. The finite element numerical solution was implemented using the scripting capabilities of COMSOL® software package (Burlington, MA, USA). A script was written to create the geometries, discretize the domains, and define and solve the governing equations with the above boundary conditions. Approximately 2000 finite elements were used and found to be adequate (increasing the number of elements did not lead to any changes in the results) for obtaining simulation results with negligible numerical error. The COMSOL’s transient solver uses a fifth-order backward differentiation formula as the time-stepping method with a time-step of 5 s. At time step, the code solves a nonlinear system of equations by using the damped Newton method. A tolerance (residual error) of 1e−5 was specified for the output temperatures.

Thermal damage is the destruction of the tissue resulting from elevated temperatures. Sapareto and Dewey [19] have proposed a mathematical model for thermal damage as

$$D(x, y) = \int_0^{t_f} R^{(43-T(x,y,t))} dt$$

where $T(x, y, t)$ is the temperature in °C, and the value of $R$ (empirically obtained from hyperthermia experiments with living tissues) is 0.5 when the temperature $T(x, y, t)$ is above 43°C and 0.25 when the temperature is below 43°C. As the tissue will continue to experience elevated temperatures for some time even after the heat source is switched off, the integration is carried out over a period of $t_f$ (seconds), which includes both heating and cooling. The cooling time for any given case is chosen such that temperature at all locations falls below 38°C. Using Equation 3, we considered a thermal damage of 3600 as the desired value in the region representing the tumor, as maintaining the
tissue at a constant temperature of 43°C for 1 h (3600 s) is known to be lethal. The fitness function to be maximized is formulated based on Equation 3, as described in the next section.

3. ESTIMATION METHODOLOGY AND PROCEDURE

The estimation methodology involves using a numerical simulation to the bioheat equation and a GA as depicted in Figure 1. The GA is used to solve for the optimal values of the unknown parameters by maximizing the fitness function

\[ F = \alpha_1 D_1 - \alpha_2 D_2 \]

\( D_1 \) and \( D_2 \) are the average values of thermal damage in the tumor and the surrounding healthy domain, respectively, calculated using Equation 3. Both \( D_1 \) and \( D_2 \) are evaluated using estimates for the unknown parameters \( r_0 \) and \( \tau \). The coefficients \( \alpha_1 \) and \( \alpha_2 \) are the weight factors (both assumed unity in the present work) that can be adjusted to control the relative importance of destroying tumor tissue versus preserving the healthy tissue. A zero value is assigned to the fitness function if the parameter estimates produce a temperature rise above 80°C (a limit used in clinical settings to avoid the risk of over-heating or boiling).

The GA is programmed in COMSOL scripting language and based on the algorithm by Goldberg [20]. In the implementation of the GA, the potential solution (chromosome) contains the diffusion parameter \( r_0 \) and time constant \( \tau \) as the 2 genes, and 15 bits are used to represent the value of each gene in binary format. Therefore, each chromosome has 30 bits. The population size has been chosen to be 20. The initial population pool is generated using a random number generator. The code is currently written to perform a set number of iterations.

The parameters contained in each chromosome are changed from their binary representation to floating point representation using (for the \( i \)th parameter)

\[ P_i = a + \frac{b - a}{2^{nb} - 1}(m) \]

where \( P_i \) is the decimal value of \( i \)th parameter, \( a \) and \( b \) are the lower and upper limits of the search interval, respectively, \( nb \) is the number of bits used to represent the parameter (15 in this case), and \( m \) is the decimal value of the parameter in binary form. The lower limit \( a \) and the upper limit \( b \) for the diffusion parameter \( r_0 \) are taken to be 0.001 and 0.1, respectively. The lower limit corresponds to a sharp peak at the center of the tumor region, whereas the upper limit produces an almost spatially
uniform heat generation. Similarly, the lower and upper bounds for the time constant $\tau$ are taken to be $1 \times 10^3$ (a fast-decaying sharp peak centered at $t = 0$) and $50 \times 10^3$ (almost uniform heat generation during the treatment time), respectively.

The value of the objective function was used as the fitness of each chromosome. A chromosome of higher fitness is more likely to be selected to reproduce and contribute its genetic material to the next generation. A probability of mutation (random changing of a chromosome) of 0.20 and a probability of crossover (formation of children) equal to 0.90 are used to determine how members of the population will reproduce to bring forth the next generation. A flowchart of the solution method is presented in Figure 2. Several cases (with different treatment times) were simulated to predict the optimal damage parameters. Treatment times between 30 and 90 min were investigated to determine their impact on the level of fitness of the final result.

4. SENSITIVITY ANALYSIS

Sensitivity and uncertainty analysis is used to study how the uncertainty in the value of inputs in the numerical model affects the output of the model. The first step in this analysis is to identify the critical input parameters. Then, for each critical output parameter $\eta_j(\beta)$ that depends on the input parameters $\beta$, the first order derivative of $\eta_j(\beta)$ with respect to $\beta_i$ is called the sensitivity coefficient for $\beta_i$ and written as

$$X_{ij} = \frac{\partial \eta_j}{\partial \beta_i}$$

(6)

Sensitivity coefficients are important as they indicate the magnitude of the change in response $\eta_j$ due to perturbations in the values of input parameters [26]. These sensitivity coefficients can also be
written in dimensionless form given by

\[ x_{ij}^+ = \frac{\partial \eta_j/\eta_{j0}}{\partial \beta_i/\beta_{i0}} \]  

(7)

where \( \eta_{j0} \) and \( \beta_{i0} \) are nominal values of output and input parameters. In the present study, we look at the dimensionless sensitivity of the optimal fitness function (given by Equation 4) to the various thermal properties (summarized in Table I) by introducing a 5% variation in the properties.

5. RESULTS AND DISCUSSIONS

The maximized fitness (Equation 4) values for different treatment times are shown in Figure 3, along with the corresponding values of the parameters \( r_0 \) and \( \tau \). As the treatment time is increased from 30 to 90 min, the fitness is maximized by a combination of a smaller diffusion constant and a larger time constant. This corresponds to a slower decaying and spatially more concentrated power deposition profile. The relatively high values of time constants (for all the treatment times that were investigated) can be attributed to the fact that the maximum available power is restricted to \( 2 \times 10^{-6} \) W/m^3. As the magnetic nanoparticle technology evolves, an increase in this power limit can be expected to produce faster decaying solution with better fitness.

The maximized fitness values in Figure 3 increase with treatment time until 60 min and then decrease slightly. This can be attributed to the fact that heating longer than necessary does not increase the damage to the tumor (because of an upper limit of 3600) but would cause damage in the surrounding region (because of diffusion of heat). The treatment time of 60 min on the basis of our simplified model is typical in current clinical hyperthermia treatments.

A contour of the fitness (Equation 4) in the parameter solution space (for 60-min treatment time) is shown in Figure 4. The figure also shows the location \( (r_0 = 0.0165 \text{ m}, \tau = 41,139 \text{ s}) \) of the maximum fitness value (3482.8). The contour plot shows that the function is badly scaled and has multiple local maxima in the neighborhood of the global maximum. Therefore, gradient-based calculus methods would likely converge to a local peak, unless the starting point (initial guess) for search is sufficiently close to the true maximum. GA was found to be well suited for this problem because of its robust non-gradient-based optimization approach.

The result of the sensitivity analysis is shown in Figure 5. The most important input parameters affecting the accuracy of the numerical model are the volumetric heat capacity of blood
(c_b \times \rho_b), perfusion in the domain representing the tumor (\omega_{b,tumor}), thermal conductivity (same for both domains), and perfusion in the healthy domain (\omega_{b,tissue}). As expected, the most important input parameters are those governing the conduction and convection heat transfer. The impact of metabolic heat generation rate in this simplified model was found to be negligible.

Figure 6 shows the maximum temperature and input power during the 60-min treatment time and the cool-down period. As expected, the temperature profile follows the profile of the applied input

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power. The time temperature history observed in Figure 6 is typical for current clinical hyperthermia treatments, which gives confidence in our results. However, on the basis of the sensitivity analysis of our model, more accurate representation is needed to account for the blood flow heterogeneities in tumors. The current methodology can incorporate more realistic conditions in the future and can be used for designing hyperthermia treatment in a clinical scenario.

6. CONCLUSIONS AND FUTURE DIRECTIONS

A methodology was presented for designing optimal hyperthermia treatment using magnetic nanoparticle technology, which is less invasive than other hyperthermia techniques, and hence is more desirable. Considering the maximum power dissipation available from current state of magnetic nanoparticles technology, the optimal power deposition profile was found to be a slow decaying spatially concentrated pulse of thermal energy. The optimal treatment time was found to be 1 h.

The current approach utilizing GAs can be extended to more realistic scenarios, such as creating three-dimensional models from MRI or CT scan data for modeling the tumor and surrounding tissue. Although the biothermal properties were considered spatially uniform in the current study, they show considerable spatial variation depending on the stage of tumor vascularization and growth and can be investigated in more realistic models.

In the present study, the temporal profile of the power deposition function is chosen to be an exponential decay, but other profiles (such as polynomials, power functions, Bezier curves, splines) can be investigated to improve the treatment. The choice of appropriate profile would likely be affected by the maximum power dissipation that can be achieved from magnetic nanoparticles. This maximum power dissipation is expected to rise with advancing technology, and it would be worthwhile to investigate its impact on both the optimal treatment time and the optimal spatiotemporal profile. If the increased power dissipation can alleviate the bad scaling of the fitness function in the parameter space, the methodology can revert back to using computationally less expensive (in comparison with GA) traditional gradient-based methods.

REFERENCES
