SIMPLIFIED APPROACHES TO RADIATIVE TRANSFER SIMULATIONS IN LASER-INDUCED HYPERTHERMIA OF SUPERFICIAL TUMORS

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ABSTRACT. A promising approach to the treatment of superficial human cancer is laser induced hyperthermia. A correct choice of the parameters used for the treatment planning should be based on modeling of both radiative transfer and transient heating of human tissues which will allow to predict the thermal conversions in the tumor. In this paper, we focus on the radiative transfer modeling which should be as simple as possible to be implemented in the combined heat transfer model. In general, the well-known \( P_1 \) approximation is known to be sufficiently accurate in calculations of the absorbed radiation power distribution. At the same time, the error of this approximation may increase in the case of external irradiation, and thus needs to be examined by the comparison with the direct Monte Carlo simulation. The computational study with realistic geometrical and optical parameters of the problem undertaken in this work showed that the \( P_1 \) approximation considerably underestimates the intense absorption near the body surface in comparison with the direct Monte Carlo solution. At the same time, it has been shown that a 1-D solution for radiative transfer can be used as a valid approach due to intense scattering of radiation by tissues. As a result, the modified two-flux approximation is recommended as a component of the multidimensional combined heat transfer model for soft thermal treatment of superficial tumors.

NOMENCLATURE

\begin{align*}
\text{Greek symbols} & \\
\alpha & \text{ absorption coefficient} \\
\beta & \text{ extinction coefficient} \\
\gamma & \text{ coefficient in boundary condition} \\
\sigma & \text{ scattering coefficient} \\
\kappa & \text{ index of absorption} \\
\mu & \text{ direction cosine} \\
\overline{\mu} & \text{ scattering asymmetry factor} \\
\omega & \text{ scattering albedo} \\
\hat{\Omega} & \text{ unit vector of direction} \\
\end{align*}

\begin{align*}
\text{Subscripts and superscripts} & \\
\text{a} & \text{ absorbed} \\
\text{ray} & \text{ traced rays} \\
\text{s} & \text{ scattered} \\
\text{t} & \text{ human tissue} \\
\text{tr} & \text{ transport} \\
\lambda & \text{ wavelength} \\
\end{align*}

\begin{align*}
a & \text{ particle radius} \\
D & \text{ radiation diffusion coefficient} \\
f_v & \text{ volume fraction of gold nanoshells} \\
G & \text{ irradiation} \\
J & \text{ diffuse component of radiation intensity} \\
m & \text{ complex index of refraction, } n - ik \\
n & \text{ index of refraction} \\
N & \text{ ray number} \\
Q & \text{ efficiency factor of absorption or scattering} \\
r & \text{ radial coordinate} \\
\tilde{r} & \text{ radius-vector} \\
R & \text{ Fresnel’s reflectivity, random numbers} \\
V & \text{ volume} \\
W & \text{ absorbed radiation power} \\
z & \text{ axial coordinate} \\
\end{align*}
INTRODUCTION

The use of laser light directly or via minimally invasive fiber optics for induced thermal treatment (hyperthermia) of tumors, in which the temperature increases in the range of 41–45°C, is one of the present-day tools to treat cancer [1, 2]. The normal human tissues are highly scattering but weakly absorbing media in the wavelength range from about 0.6 to even 1.4 μm which provides a “therapeutic window”. The absorption of laser light leading to a targeted heating of the tumor cells can be greatly increased by embedding silver or gold nanoparticles in the tumor. These nano-sized noble metal particles are characterized by strong resonance absorption and relatively weak scattering in the therapeutic window. Particularly, silica-core gold nanoshells with specific geometrical parameters are very good absorbers for the laser light at a wavelength of 0.6328 μm [3–5].

Nanoscale thermal therapy of targeted cancer cells is a promising new weapon in the battle against cancer. A combination of hyperthermia with radiotherapy and chemotherapy has been shown to be effective in prolonging the survival of cancer patients. Many studies have been published on different aspects of the complicated and multi-faceted problem of photothermal therapy. Theoretical studies have focused particularly on resonance optical properties of various gold nanoparticles, modeling of propagation of laser radiation in human tissues, and development of specific heat transfer models taking into account heat conduction, blood perfusion, metabolic heat generation, and radiative power absorbed in the processed tissues [6–8].

A radical change in the ordinary heating strategy proposed recently by Dombrovsky et al. [9] is the use of indirect heating when the tumor is not subject to collimated laser irradiation. It was suggested to embed gold nanoshells in a circular region around the tumor instead of in the tumor itself. Laser heating of these particles leads to formation of a hot ring in the healthy tissues surrounding the tumor followed by conduction of the accumulated heat from outside region into the tumor. As it may be difficult to supply gold nanoshells to the circular region and control their concentration the same indirect strategy but without gold nanoshells was also considered. Since simplified 1-D heat transfer models of laser induced hyperthermia [3–5] were not appropriate for simulating indirect heating of tumors, a 2-D model was developed in [9]. It was shown that indirect heating offers some advantages as compared to direct irradiation of the tumor. The analysis for a periodic laser irradiation showed that the required uniform heating of the tumor can be achieved for some superficial tumors even without gold nanoshells or other invasive procedures.

The radiative transfer analysis performed in [9] was based on the $P_1$ approximation. Accuracy of this simple approach is anticipated to be insufficient for modeling the laser-induced hyperthermia. The objective of the present study is to examine the error of the $P_1$ approximation for the indirect hyperthermia of tumors. The general Monte Carlo ray tracing method is used to obtain a reference exact solution to the problem.

RADIATIVE PROPERTIES OF HUMAN TISSUES WITH EMBEDDED GOLD NANOPARTICLES

Spectral absorption and scattering coefficients of a heterogeneous medium consisting of a host component with dispersed small particles of low to moderate volume fraction $f_v$ and uniform radius $a$ can be calculated using the following relations [10]:

\[
\begin{align*}
\alpha_\lambda &= \alpha_{\lambda,0} + 0.75 f_v \frac{Q_a}{a} \\
\sigma_\lambda &= \sigma_{\lambda,0} + 0.75 f_v \frac{Q_s}{a} \\
\sigma_{\lambda}^\text{tr} &= \sigma_{\lambda,0}^\text{tr} + 0.75 f_v \frac{Q_s^\text{tr}}{a}
\end{align*}
\]  

(1)
where $\alpha_\lambda$ is the absorption coefficient, $\sigma_\lambda$ is the ordinary scattering coefficient, and $\sigma^w_\lambda = (1 - \mu_s)\sigma_\lambda$ is the transport scattering coefficient ($\mu_s$ is the asymmetry factor of scattering). $Q_\alpha$ and $Q_\sigma$ are the efficiency factors of absorption and scattering, $Q^w_\sigma$ is the transport efficiency factor of scattering for single particles. The transport scattering properties have been introduced because of their key significance for modeling radiative transfer in scattering media [10, 11]. Note that the transport extinction coefficients $\beta^w_\lambda = \alpha_\lambda + \sigma^w_\lambda$ and the transport scattering albedo $\omega^w_\lambda = \sigma^w_\lambda / \beta^w_\lambda$ are often used to model radiative transfer in scattering human tissues, which are complex disperse systems even without any presence of embedded gold nanoparticles. Fortunately, in the therapeutic window, most of soft tissues can be assumed as optically soft media with optical constants satisfying the following conditions:

$$\kappa << 1 \quad |n - 1| << 1$$

where $\kappa$ and $n$ are the spectral indices of absorption and refraction, respectively. In this case, the absorption and scattering properties are practically independent of each other. The absorption coefficient of a tissue is determined by the local value of spectral absorption index of the substance and totally insensitive to the tissue morphology. On the contrary, the scattering properties are practically independent of absorption and mainly determined by the tissue morphology and the resulting spatial variation of the refraction index [12].

Both scattering and absorption properties of gold nanoparticles depend on optical constants of the ambient medium. In the region of the tissue semi-transparency, where $\kappa << n$, the effect of absorption index is negligible and it is sufficient to know the index of refraction of the tissue [10].

**Optical Properties of Human Tissues** It is well known that soft human tissues are semi-transparent for long-wave visible light and for spectrally adjacent near-infrared radiation. Of course, various tissues have specific optical properties but the most wide therapeutic window considered in literature is a wavelength range from 0.6 to 1.4 µm [13]. One can find also a lot of particular data for optical properties of healthy tissues of various human and animal organs in the literature [14–17]. The data for the absorption and scattering coefficients, asymmetry factor of scattering, and index of refraction are usually given. In cellular media, the important scatterers are the subcellular organelles. The characteristic size range of these organelles includes the wavelength of the therapeutic window, as their dimensions vary from less than 100 nm to 6 µm. The size parameter of most of these structures belongs to the Mie regime [11, 18], exhibiting highly-anisotropic scattering.

**Optical Properties of Gold Nanoparticles** The optical properties of various gold nanoparticles in the therapeutic window were studied in some detail in [7, 8]. These particles are characterized by a resonance absorption and scattering, but scattering is usually much less than absorption. So, the use of embedded gold nanoparticles leads to considerable increase in absorption of human tissues whereas their effect on the radiation scattering by the tissues is relatively small. Note that the optical properties of spherical gold nanoshells with a silica core can be easily calculated using the Mie theory [5].

**RADIATIVE TRANSFER MODELING BASED ON $P_1$ APPROXIMATION**

In our study, we employ a continuum approach to model the radiative transfer in an absorbing and scattering human tissue. The radiative transfer equation (RTE) for randomly polarized radiation can be written as follows [10, 19, 20]:

$$\tilde{\Omega}V I_\lambda(\tilde{r}, \tilde{\Omega}) + \beta_\lambda I_\lambda(\tilde{r}, \tilde{\Omega}) = \frac{\sigma_\lambda}{4\pi} \int I_\lambda(\tilde{r}, \tilde{\Omega}') \Phi_\lambda(\tilde{\Omega} | \tilde{\Omega}') d\tilde{\Omega}'$$  

(3)
The absorption coefficient \( \alpha_\lambda \), the scattering coefficient \( \sigma_\lambda \), and scattering phase function \( \Phi_\lambda \) depend on the spatial coordinate \( \vec{r} \). Equation (3) is written for the case of an isotropic medium when the coefficients do not depend on direction. Possible anisotropy of some tissues is not important for radiative transfer in highly scattering tissues [10, 12].

An accurate solution to the RTE in scattering media is a challenging task because of the integral term on the right-hand side of Eq. (3). Accuracy of solutions to Eq. (3) has steadily improved due to development of numerous numerical methods of increasing fidelity. Several variants of the discrete ordinates method (DOM) and the Monte Carlo ray-tracing (MC) methods are most commonly employed. For the problem under consideration, one can refer to papers [21, 22], in which the MC method is used in biomedical applications. Further information can be found in paper [23], in which a mesh free collocation method for complete RTE is presented.

To avoid mathematical complexity, one can use the well-known transport approximation [10, 11], for which the RTE takes the same form as for isotropically scattering media, i.e. with \( \Phi_\lambda \equiv 1 \), but it uses modified scattering and extinction coefficients:

\[
\bar{\Omega} I(\vec{r} \cdot \bar{\Omega}) + \beta_\mu I(\vec{r} \cdot \bar{\Omega}) = \frac{\sigma_\mu}{4\pi} \int I(\vec{r} \cdot \bar{\Omega}) d\bar{\Omega}
\]

Hereafter, the subscript \( \lambda \) is omitted for brevity.

An axisymmetric problem for laser induced hyperthermia of a superficial tumor is considered in the present paper. The problem statement is based on the following assumptions:
- The axis of the computational region coincides with the normal to a flat surface of a human body. The laser beam is directed along the axis of the computational region.
- The body surface is optically smooth. This assumption may seem to be not realistic but this is compensated by a significant volumetric scattering of the radiation by human tissues.
- The tissue index of refraction is uniform in the computational region. Strictly speaking, there is a spatial variation of the refractive index in the real multi-layer tissue. Nevertheless, we will use this assumption to simplify the computational procedures.

A solution for the directional component of the radiation intensity can be obtained using the local 1-D solution for the directional radiation component. As to the diffuse radiation component, it can be determined using the simplest \( P_1 \) approximation. Note that the error of \( P_1 \) increases significantly in the case of a nonuniform spatial distribution of the medium properties and near the interfaces [10]. In our case, the computational region is optically thick and the boundary conditions for Eq. (4) are:

\[
I(\vec{r} \cdot \bar{Q}_n) = R(\bar{Q}_n)I(\vec{r} \cdot \bar{Q}_n) + (1 - R_n) q_e \delta(1 - \mu); \quad \text{At other surfaces:} \quad I(\vec{r} \cdot \bar{Q}_n) = 0 \quad (5)
\]

where \( \bar{Q}_n > 0 \), \( q_e \) is the incident radiative flux, \( R(\mu) \) is the Fresnel’s reflectivity [24]. Note that one can use simplified relations for \( R(\mu) \) because the index of absorption is relatively small: \( k << n \). It is important that \( R(\mu) < 1 \) when \( \mu > \mu_c \) and there is a total internal reflection (\( R = 1 \)) when \( \mu \leq \mu_c = \sqrt{1 - 1/n^2} \). Note that \( R_n = R(1) = (n - 1)^2/(n + 1)^2 \).

Following the usual technique, we present the radiation intensity \( I \) as a sum of the diffuse component \( J \) and the term, which corresponds to the transmitted and reflected directional external radiation:

\[
I = J + (1 - R_n) q_e E \delta(1 - \mu) \quad E = \exp(-\tau_u) \quad \tau_u = \int_0^z \beta_\mu dz \quad (6)
\]

The mathematical problem statement for the diffuse component of radiation intensity is as follows:
\[ \dot{\Omega} \nabla J + \beta_{\alpha} J = \frac{\sigma_n}{4\pi} (G + F) \quad G = \int J d\dot{\Omega} \quad F = (1 - R_\alpha) q_r E \] (7a)

At the body surface: \( J(\tilde{r}, \tilde{\Omega}) = R(\tilde{\Omega}) J(\tilde{r}, -\tilde{\Omega}) \) At other surfaces: \( J(\tilde{r}, \tilde{\Omega}) = 0 \) (7b)

The spectral radiation power absorbed in the medium, \( W \), is expressed as

\[ W = -\nabla q = - \int \dot{\Omega} J d\dot{\Omega} = \alpha (G + F) \] (8)

The problem for the diffuse component of the radiation intensity is still very complex. Therefore, the \( P_1 \) approximation is often considered [10, 11]. This approach is known to lead to the boundary-value problem for the modified Helmholtz equation—a problem much simpler than the problem (6)–(8). Here, a variational formulation of this problem is preferred because the 2-D finite-element method (FEM) can be readily employed to solve it [9–11].

Note that \( P_1 \) has been characterized in recent review paper [25] as a good approach for modeling laser-induced thermal therapy. This agrees with the conclusions of paper [26], where this method was recommended to identify optical properties of biological tissues. One should recall here a computer code LATIS for laser-tissue interaction modeling [27]. This code mainly uses the MC method, but there is an ability to invoke the \( P_1 \) approximation to shorten computational time. Note that the general discrete ordinates method is also used in some studies to accurately simulate radiative transfer in human tissues [28].

**PARAMETERS OF THE MODEL PROBLEM**

The schematic of the example problem for indirect heating strategy and FEM grid with 60x60 intervals and 7200 triangular elements are presented in Fig. 1. We used a nonzero internal radius of the computational region equal to the radial discretization step to avoid a singularity specific to the in-house developed FEM code. It should be noted that the annular region can be irradiated by rapidly moving a relatively narrow laser beam along its surface. Sensitivity analysis was performed by varying the spatial resolution of the computational mesh to achieve acceptable accuracy of the numerical results. The nonuniform finite-element mesh shown in Fig. 1 was found to be sufficiently refined to obtain reliable results In addition, because of the linear and steady-state character of the presented computational problem, the suitability of the selected computational mesh is corroborated by the smooth profiles of the computed absorbed radiative power.

A realistic variant of \( r_1 = 5 \text{mm} \) and \( r_2 = 10 \text{mm} \) was considered. The dimensions of tissue layers and the spectral optical properties of tissues at the wavelength of 0.6328 \( \mu \text{m} \) are given in Table 1. The thickness of the computational region, \( d = 10 \text{mm} \), is chosen to justify the use of the simplified boundary condition at \( z = d \) given by Eq. (6b). The radial size of the computational region is equal to \( R = 15 \text{mm} \). The radiative properties provided in Table 1 are the same as those in [9]. The values of \( \mu_r \) for epidermis and dermis are taken from [13]. Following the studies [5, 9], the index of refraction is assumed to be uniform over the computational region and equal to \( n = 1.45 \). No reliable data for \( \mu_r \) for fat and muscle tissues were found in the literature. Fortunately, their uncertainties are not critical to accurately solve the problem under consideration. Therefore, we assume typical values \( \mu = 0.9 \) for both fat and muscle layers. For the variant with embedded gold nanoshells, the parameters from paper [9] are used: \( f_v = 10^{-6}, \ Q_a = 7.828, \ Q_a^u = 1.144 \). The calculated value of \( \mu = 4.3 \times 10^{-4} \) indicates that these particles are very close to the Rayleigh region where \( \mu = 0 \). In an example problem considered in this paper, the particle cloud is positioned between radii 5 and 10 \( \text{mm} \) (just opposite the laser beam) from the body surface to the plane \( z = 4 \text{mm} \) [9].
Figure 1. Schematic of an axisymmetric computational region; 
1, 2, 3, 4 – the numbers of tissues listed in Table 1.

Table 1. Properties of tissues in the computational region

<table>
<thead>
<tr>
<th>Layer number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue name</td>
<td>Epidermis</td>
<td>Papillary and reticular dermis</td>
<td>Fat</td>
<td>Muscle</td>
</tr>
<tr>
<td>Layer thickness, mm</td>
<td>0.1</td>
<td>1.4</td>
<td>2.0</td>
<td>6.5</td>
</tr>
<tr>
<td>$\alpha$, 1/mm</td>
<td>0.3</td>
<td>0.27</td>
<td>0.19</td>
<td>0.12</td>
</tr>
<tr>
<td>$\sigma_{\alpha}$, 1/mm</td>
<td>2.5</td>
<td>3.75</td>
<td>2.7</td>
<td>0.9</td>
</tr>
<tr>
<td>$\bar{\mu}$</td>
<td>0.8</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
</tr>
</tbody>
</table>

RESULTS OF CALCULATIONS

The ratio of the volumetric radiation power absorbed in the tissue to the incident radiation flux calculated using $P_1$ approximation at conditions of the model problem is plotted in Fig. 2. One can see that numerical solution in the central part of the irradiated region is very close to the 1-D solution. This result agrees with recent calculations reported in [30]. Note that additional calculations for narrow laser beam of thickness $r_2 - r_1 = 2$ mm showed similar results. It is explained by very high transport scattering coefficient of the weakly absorbing human tissues. This result is qualitatively correct. While there is no need in using more accurate methods to estimate small 2-D effects near the boundaries of the laser beam, the accuracy of $P_1$ approximation in the problem under consideration needs to be examined.
Figure 2. Radial profiles of the radiation power absorbed in human tissues of Fig. 1 for several radial grid lines (1 – body surface, 4 – boundary between epidermis and dermis, 8–16 – inside the dermis layer): a – without gold nanoshells, b – with gold nanoshells.

To examine the quality of $P_1$ approximation in this specific problem 1-D modeling for the irradiated region was undertaken. The collision-based MC simulation [31] was employed as the reference method. In this method, radiation from the source is simulated by independently tracing a large number of stochastic rays $N_{ray}$. The current physical quantity of interest, the absorbed radiation power, is determined based on the number of rays terminated at a given location due to absorption. The scattering processes by tissue and gold nanoshells are treated independently. Note that scattering by nanoshells has been assumed to be isotropic [5]. The absorbed radiation power distribution is obtained as the average of results from ten different runs. Each run consists of $10^7$ rays and uses a unique seed for the random number generator. The error of the MC calculations is estimated as the standard deviation based on the results of the ten different runs and is found to be less than 1 %.

A comparison of $P_1$ and MC results for the 1-D model problem is presented in Fig. 3. The results obtained using the modified two-flux approximation (MDP$_0$, [32, 33]) employed by the authors in [5] are additionally shown in this figure. In contrast to the $P_1$, this approach takes into account the effect of total internal reflection at the boundary of a refracting medium and gives more accurate results for the radiation field near the boundaries of the computational region [10, 32, 33].

Figure 3. Axial profiles of the absorbed radiation power:

a – without gold nanoshells, b – with gold nanoshells.
One can see that $P_1$ profiles are qualitatively correct but underestimate the local peak of absorption near the irradiated surface due to significant contribution by the diffuse radiative intensity component. These errors, about 45% for the case without gold nanoshells and 30% with gold nanoshells, are too high to be ignored. At the same time, the transport approximation is found not to lead to considerable errors. As expected, the $MDP_0$ approximation taking into account discontinuous angular dependence of the radiation intensity near the interface is much more accurate. This advantage of a model based on the two-flux approximation as compared to the $P_1$ approximation in the case of multi-layered skin has been utilized in the recent paper by Yudovsky and Durkin [34] to develop a hybrid diffusion ($P_1$) and two-flux approximation model for radiative transfer in multi-layered human tissues.

Note that the thermal treatment procedure suggested in [9] includes water cooling of the irradiated body surface. In this case, underestimated absorbed radiation power in a thin surface layer of thickness about 0.5 mm does not lead to considerable error in transient temperature field in the body. The latter effect is illustrated by the computational results for the case of a periodic laser heating (see Fig. 4).

![Figure 4. A fragment of time dependence of the incident radiative flux in periodic heating.](image)

![Figure 5. Typical temperature fields in the human tissue at the end of soft thermal treatment of a superficial tumor ($t = 60$ min) obtained using (a) $P_1$ and (b) 2-D extension of the $MDP_0$ (for radiative transfer. The red+orange region corresponds approximately to the tumor region.](image)
The calculated temperature fields in the body without gold nanoshells are presented in Fig. 5. The formulation of heat transfer problem and details of the computational procedure can be found in paper [9]. The difference between temperature fields shown in Figs. 5a and 5b is very small which means that $P_1$-based results reported in [9] were correct. At the same time, it is interesting to note that $P_1$ approximation results in slightly greater estimates of the tumor temperature. This can be explained by a slightly increased internal absorption of the radiation achieved in the case of $P_1$.

To our mind, one can recommend the use of 1-D solution based on $MDP_0$ for simplified and sufficiently accurate computational analysis of indirect laser-induced hyperthermia of superficial tumors.

**CONCLUSION**

The numerical study for realistic values of the main parameters of the indirect laser-induced hyperthermia of superficial tumors showed that the $P_1$ approximation considerably underestimates the absorbed radiation power in the local region of the highest absorption near the irradiated surface of the body. Fortunately, it was found that this result is not important for the indirect thermal treatment procedure with water cooling of the irradiated body surface. Our analysis showed that 1-D solution for radiative transfer is a valid approach due to intense scattering of radiation by human tissues and therefore the modified two-flux approximation can be recommended for radiative transfer simulations as a component of the multidimensional combined heat transfer model for soft thermal treatment of superficial tumors.

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