Monte-Carlo Simulation on Gold Nanoshells Enhanced Laser Interstitial Thermal Therapy on Target Tumor

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The laser-induced interstitial thermal therapy (LITT) is emerging as a very promising way for minimally invasive treatment on tumor. To realize a highly efficient heating, the gold nanoshells were recently identified as most useful materials to enhance thermal energy deposition of laser in target tissues. However, there is currently a strong lack of understanding the laser energy distribution and the transient temperature field in the tissues due to addition of nanoshells which would seriously impede successful operation of a LITT surgery. This paper is dedicated to present a theoretical modeling on the optical and temperature fields during gold nanoshells enhanced hyperthermia through combining the Monte-Carlo simulation strategy and the Pennes bioheat transfer equation. Effects of size, concentration of the nanoshells to the heating behaviors were evaluated through parametric studies and important conclusions were obtained. The method as developed in the paper would serve well for future treatment planning for the nanoshells enhanced LITT on target tumor tissues.

Keywords: Nano Hyperthermia, Laser-Induced Thermal Therapy, Nanoshell, Gold Particle, Monte-Carlo Simulation, Bioheat Transfer.

1. INTRODUCTION

The laser-induced thermal therapy (LITT) is a method of destroying solid tumors by inserting flexible bare fibers into the tumor domain to induce ablation via laser radiation.¹ Its promising merit lies in the minimally invasive hyperthermia feature which has the advantages of fast recovery, fewer complications, and shorter hospital stays. In order to reach tumors in the deep body and reduce thermal damage to the surrounding healthy tissues, the wavelength of the laser beam adopted in the LITT is usually within the near-infrared (NIR) region, which could provide a maximal penetration of light through tissues.²,³ However, the clinically used LITT in clinics still has evident limitation due to slow thermal diffusion in tissues and difficulty in discriminating tumor from the surroundings. Therefore, an effective way in energy delivery is urgently needed for the targeted ablation of tumor.

Accompanying with the development of nanotechnology and its applications in biomedical engineering field, nanoparticles are being gradually tried in drug delivery, cancer cell diagnostics, and various therapeutics.⁴,⁵ This opens an innovative possibility for the nanoparticle-enhanced laser-induced thermal therapy. Among the many efforts ever made, the nanoshells have been identified as the most efficient materials to absorb energy from the laser. Such nano material belongs to a novel class of nanoparticles consisting of a dielectric silica core coated with a thin metallic gold shell. Through adjusting the relative dimensions of the core and the shell, nanoshells can be manufactured to absorb light at a specific wavelength across NIR region.⁶ In addition, the absorption cross section of nanoshells are six orders larger than that of indocyanine green.⁷ As a result, the nanoshells generally have the ability to transduce light energy into heat efficiently. This would act as the intense heat absorbers and thus improve the ability to destroy cancerous tissue with a lower thermal dose when the nanoshells are injected into tumors. Therefore introducing gold nanoshells into tumor tissue as photothermal agents is a rather promising approach to enhance the energy delivery efficacy and the contrast between tumor and normal tissue during LITT. Recently, the photo thermal therapy using the absorption properties of gold nanoshells has been demonstrated to selectively kill cancer cells.²,⁷
Although the empirical study of the nanoshells enhanced laser-induced thermal therapy has been tried by several authors, few theoretical studies are available on characterizing the optical properties of the living tissues loaded with nanoshells. There is currently a strong lack of quantitative understanding of the heating behavior of the nanoshells enabled LITT. Numerical simulation on laser energy distribution and heat transfer in the tissue is urgently needed when nanoshell are injected into tumors. The aim of this paper is dedicated to perform a theoretical investigation on this important issue.

2. THEORETICAL METHOD

In this paper, taking nanoparticle into consideration, the laser energy distribution was simulated by the Monte Carlo method. After the energy distribution was obtained and substituted into the classic heat transfer models, the temperature distribution in living tissues can be predicted.

Figure 1 is a schematic diagram demonstrating a patient undergoing laser-induced interstitial thermal therapy on a malignant liver tumor. Here the laser needle is inserted into the liver tumor to induce irreversible tissue thermal damage.

2.1. Monte Carlo Model

The radiative transfer theory which focuses on the photon migration in biological tissue has become an important tool for analyzing the interaction between laser and tissues. A generalized form for the radiation transfer equation can be expressed as follows:

\[ s \cdot \nabla I(\mathbf{r}, \mathbf{s}) + \mu_s I(\mathbf{r}, \mathbf{s}) = \frac{\mu_t}{4\pi} \int_{4\pi} p(\mathbf{s}', \mathbf{s}) I(\mathbf{r}, \mathbf{s}') d\omega' \]  

(1)

where \( \mathbf{r} \) is the position vector; \( \mathbf{s} \) and \( \mathbf{s}' \) are direction vectors; \( I(\mathbf{r}, \mathbf{s}) \) is the intensity of laser light at position \( \mathbf{r} \) in the \( \mathbf{s} \) direction; \( \omega' \) is the solid angle; \( \mu_t \) is the total attenuation coefficient defined as the sum of the absorption coefficient \( \mu_a \) and the scattering coefficient \( \mu_s; \) \( p(\mathbf{s}', \mathbf{s}) \) is the phase function.

Clearly, exactly solving the transport equation is rather difficult. As an alternative, the Monte Carlo simulation is widely adopted for an approximation of the exact transport equation, which is useful for simulating random walk of photons through turbid media and investigating light propagation in tissues. Considering the different physical properties between tumor and normal tissue, a two-layer model with tumor domain and surrounding normal tissues (Fig. 2) can be used to simulate the energy transport during thermotherapy. The Monte Carlo simulation is employed for the present prediction of the effect of nanoshells on tissue reflectance.

The present model is capable of capturing the changes in optical properties due to nanoshell inclusion and tissue property variation during laser surgery. To quantify the effects of the nanoshell with Monte Carlo simulation, we consider the following three quantities of interest as usual: the absorption coefficient, the scattering coefficient, and the anisotropic factor.

According to the well established light scattering theory, when one adds nano particles to a medium, the change in the optical coefficient \( \Delta u(p) \) is given as:\[16\]

\[ \Delta u(p) = N \times C \]  

(2)

where, \( N \) is the number of particles per unit volume and \( C \) is the scattering or absorption cross section.

This equation can then be correlated with the volume fraction \( (V_f) \) of nanoparticles added to the models, and also the scattering \( (C_{sc} \) or absorption cross section \( (C_{abs}) \) normalized by the volume of the particle used \( (V_p) \), i.e., Ref. [16]

\[ \Delta u_{sc,abs}(p) = \frac{C_{sc,abs} V_f}{V_p} \]  

(3)

According to the existing experiments, the concentration of nanoparticles added to the cell culture medium is about \( 5 \times 10^3/ml \), taking R50/60 nanoshell as

![Image 1](https://example.com/image1.png)

**Fig. 1.** A schematic diagram demonstrating a patient undergoing laser-induced interstitial thermal therapy.

![Image 2](https://example.com/image2.png)

**Fig. 2.** Two-layer model for LITT.
an example, the volume fraction of the gold nanoshell is given as \( V_t = n (4/3) \pi R^3 \approx 4.5 \times 10^{-4} \). So in the present study, \( V_t = 4.5 \times 10^{-5} \) was adopted during the Monte Carlo simulation without losing any generality.

Table I(a) lists the optical properties calculated from Mie solutions for various gold particles at an 830 nm excitation wavelength such as volume-normalized scattering (Sca/Vol), absorption cross sections (Abs/Vol) and scattering-to-absorption efficiency ratio (Sca/Abs Ratio). Here, R40/50 represents a nanoshell with a 40 nm core radius with a 5 nm thick gold shell. Table I(b) gives the change in the optical coefficient due to addition of particles in a medium according to the foregoing analysis.

### 2.2. Bioheat Transfer Model

To avoid carbonization of tissue surrounding the heating part of laser fiber during treating tumor by laser-induced interstitial thermotherapy, cold fluid (water) was ventilated for cooling laser fiber and tissue in the vicinity of laser fiber in this study.

Figure 3 depicts the computational domain with specific dimension indicated. It is assumed that the physical properties of tissue are homogeneous along the circumferential direction and the outer layer range of normal tissue is large enough. The radius and length for the normal tissue and tumor tissue are 25 mm, 100 mm, and 2.5 mm, 5 mm, respectively. The radius of the fluid cooling area is 0.5 mm.

Unlike previous studies where the Pennes bioheat equation was used to calculate heat transfer in whole region, different models were used to solve the heat transfer in tissues and water cooling regions respectively, instead.

In the tissue area, the classical Pennes bioheat equation was adopted to characterize the temperature distribution. Its typical expression is:\(^{19}\)

\[
\rho_t C_t \frac{\partial T}{\partial t} = \nabla (K_t \nabla T) + \rho_t w_p C_s (T_a - T) + q_s (r, z, t) \tag{4}
\]

where, \( \rho_t, C_t, K_t, \) are density, specific heat and thermal conductivity of tissue, respectively; \( \rho_s, C_s \) are the density and specific heat of blood respectively; \( w_p \) is Blood perfusion; \( T_a \) is the arterial temperature; \( q_s \) is the spatial heating in tissue, which represents the volumetric laser energy distribution and can be obtained in advance as explained in Section 2.

In the fluid cooling area, the transient heat transfer model is set up as follows, due to the convective heat transfer of the cooling water:

\[
\rho_b C_b \left( \frac{\partial T}{\partial t} + u \frac{\partial T}{\partial z} \right) = \nabla (K_b \nabla T) + q_b (r, z, t) \tag{5}
\]

where, \( u \) is the flow rate of the cooling water, \( \rho_b, C_b, K_b \) are density, specific heat and thermal conductivity of water, respectively; \( q_b \) is the spatial heating in cooling area, which represents the volumetric laser energy distribution and can also be obtained in advance as explained in Section 2. Equations (4) and (5) were numerically solved using the finite difference method in cylindrical coordinates.

During LITT surgery, the tissues at external boundary region will almost not be affected and maintain at a constant temperature 37 ˚C; the axis of the cylinder is defined as insulated boundary \( \hat{n} \cdot \nabla T = 0 \) due to symmetried property and the initial condition for the whole tissue region can be approximated as \( T_0 = 37 \) ˚C. The boundary and initial conditions can then be expressed as:

\[
-k \frac{\partial T}{\partial r} = 0, \quad r = 0, \quad r = R \tag{6}
\]

\[
-k \frac{\partial T}{\partial z} = 0, \quad z = 0, \quad z = L \tag{7}
\]

\[
T = T_{in}, \quad 0 \leq r \leq r_p \tag{8}
\]

\[
T = T_f, \quad t = 0 \tag{9}
\]

**Table Ia.** Optical properties of various nanoshells at an 830 nm wavelength.

<table>
<thead>
<tr>
<th>R40/45</th>
<th>R50/60</th>
<th>R50/55</th>
<th>R55/80</th>
<th>R40/80</th>
<th>R75/115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scat/Vol</td>
<td>1.50 x 10^{-5}</td>
<td>1.39 x 10^{-5}</td>
<td>1.47 x 10^{-5}</td>
<td>3.15 x 10^{-5}</td>
<td>3.02 x 10^{-5}</td>
</tr>
<tr>
<td>Abs/Vol</td>
<td>2.54 x 10^{-3}</td>
<td>3.67 x 10^{-3}</td>
<td>2.10 x 10^{-3}</td>
<td>9.85 x 10^{-3}</td>
<td>4.82 x 10^{-3}</td>
</tr>
<tr>
<td>Sca/Abs</td>
<td>0.059</td>
<td>0.306</td>
<td>0.701</td>
<td>3.199</td>
<td>6.270</td>
</tr>
</tbody>
</table>

**Table Ib.** The change in optical coefficient of the tissue due to addition of particles.

<table>
<thead>
<tr>
<th>R40/45</th>
<th>R50/60</th>
<th>R50/55</th>
<th>R55/80</th>
<th>R40/80</th>
<th>R75/115</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta \beta_{\text{Sca}} )</td>
<td>2.86</td>
<td>37.73</td>
<td>57.22</td>
<td>333.78</td>
<td>323.84</td>
</tr>
<tr>
<td>( \Delta \beta_{\text{Abs}} )</td>
<td>48.48</td>
<td>99.62</td>
<td>73.18</td>
<td>105.62</td>
<td>51.69</td>
</tr>
</tbody>
</table>

Table II. Thermal properties of tissue and nanoshell.

<table>
<thead>
<tr>
<th></th>
<th>( \rho ) (kg m(^{-3}))</th>
<th>( c_p ) (kJ kg(^{-1}) K(^{-1}))</th>
<th>( \lambda ) (W m(^{-1}) K(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue</td>
<td>1200</td>
<td>3.20</td>
<td>0.550</td>
</tr>
<tr>
<td>Nanoshell</td>
<td>19320</td>
<td>0.128</td>
<td>317</td>
</tr>
</tbody>
</table>

where, \( T_{in} \) is the temperature of the entrance of the cooling area which is defined as 0 °C in this study.

We substitute the thermal properties of Au nanoshells by those of the Au block (Table II) due to the data scarcity of the thermal properties of Au nanoshells and the typical values for tissue thermal properties are applied as given in Ref. [20].

The corresponding data for the composite consisting of cancerous tissue and injected Au nanoshell depends on the particle concentration and the amount of simultaneously injected fluid (e.g., physiologic saline).\(^{21}\) In this study, for simplicity, the mean value of specific heat, density, and thermal conductivity for cancerous tissue embedded with Au nanoshell can be approximated by the respective volume proportions of the two materials.

\[
\rho_2 = (1 - \eta)\rho_1 + \eta \rho_3 \quad (10) \\
C_2 = (1 - \eta)C_1 + \eta C_3 \quad (11) \\
\frac{1}{K_2} = \frac{(1 - \eta)}{K_1} + \frac{\eta}{K_3} \quad (12)
\]

where \( \eta = n/(4/3)\pi R^3 \) stands for the volume concentration of particles inside the sphere. \( n \) is the number of particles, \( V \) is the volume of the sphere, \( R \) is the radius of the sphere.

But these parameter differences between normal tissue and micro/nanoparticles are not evidently large because the volume concentration of particles is too small. In order to achieve a higher accuracy, determination of these parameters may be experimentally performed in the near future.

3. RESULT AND DISCUSSION

3.1. Nanoshells Enhanced Optical and Thermal Deposition

To assess the influence of nanoshells upon thermal effects, we simulated the temperature field of human liver tissue with and without Au nanoshell as a comparison and the result was shown in Figure 4 and Figure 5.

During the simulation, the optical properties for the normal and metastatic human liver tissue as used are collected and listed in Table III.\(^{22}\) The power used in Monte Carlo simulation is 3 W and kept constant for all simulations.

Depicted in Figure 4 was typical temperature distribution of tissues during LITT, either with or without Au nanoshells, respectively. It indicated that, the highest temperature for the case of injecting nanoshells can reach 71.4 °C, which is about 16 °C higher than that of no nanoshell case (55.3 °C). Obviously this was caused by the addition of Au nanoshells into tissues which enhanced the heat absorption and conduction in tissue.

Figure 5 gives the comparison of the transient maximum temperature during the NIR irradiation. Clearly,
3.2. Effect of Nanoshell Size

We then choose different nanoshells with varying relative dimensions of the core and shell to evaluate the effect of loading nanoshells in tissue, in order to provide a basis to planning the surgery when doing thermotherapy.

Figure 6 reflects the influence of various kinds of nanoshells on the thermal therapy. It can be easily seen that various kinds of nanoshells result in different temperature distribution and the maximum temperatures in Figure 6(a), (b), 6(c), and 6(d) are 59.4 °C, 60.0 °C, 70.7 °C, and 71.4 °C, respectively. The reason is that the optical response of gold nanoshells depends dramatically on the relative size of the nanoshell core and the thickness of the gold shell. Therefore those various kinds of nanoshells lead to different optical properties and thermal conductivities of particle-tissue mixtures which enabled different thermal dynamics. From Figure 5, one can find that the R55/80 and R40/80 nanoshells which has the thicker Au shell produces much more influence on LITT process than that by R40/55 and R50/60 nanoshells, which indicates that the relative dimensions of the core and shell of the nanoshell is an important parameter for LITT. This suggests that a careful planning for a practical surgery is strongly needed.

3.3. Effects of Nanoshell Concentration

As mentioned above, the variation in the optical coefficient \( \Delta \mu_p \) is related to the volume fraction \( \langle V_t \rangle \) of nanoparticles as added to the models. Therefore the concentration of the nanoshell injected into the tumor tissue plays a rather important role during the LITT process. We simulated the highest temperature during the LITT process of different nanoshell (R50/60 nanoshell) concentration from \( 10^9 \) to \( 10^{11} \). The result is shown in Figure 7. Clearly when the concentration of the nanoshell was increased, the maximum temperature first increased then decreased and the maximum value is at a nanoshell concentration of \( 10^{10} \).

However, it should be mentioned that, *in vivo* experiments about the effects of the nanoshell concentration on the temperature responses should be performed in the near future to justify the simulation result.

3.4. Effects on Heating Area

The energy affected zone along radial direction in Figure 8(a) is within 5 mm, while another case in Figure 8(b) is almost within 2.5 mm. Figure 9 also shows that the region below 38 °C in Figure 9(a) is smaller than that in Figure 9(b). Therefore the heating region is almost within the tumor tissue when nanoshells were injected, which can minimize the thermal damage to the healthy surrounding the tumor.

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**Table III.** The optical properties for normal and metastatic human liver tissue.

<table>
<thead>
<tr>
<th>Property</th>
<th>Normal liver tissue</th>
<th>Liver metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption coefficient (mm(^{-1}))</td>
<td>0.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Scattering coefficient (mm(^{-1}))</td>
<td>20.4</td>
<td>10.8</td>
</tr>
<tr>
<td>Anisotropy</td>
<td>0.955</td>
<td>0.902</td>
</tr>
</tbody>
</table>
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Fig. 7. Effects of the nanoshell concentration.

What’s more, one can find that the downstream temperature is increased, evidently caused by the coming water flow, and the highest temperature is not at the center of the tumor. Therefore, in a LITT, the laser irradiation spot should be positioned in the upstream of the cancer region in order to achieve a better treatment effect over the whole diseased domain.

4. CONCLUSION

In this study, the principles of photon transportation and heat transfer in biological tissues loaded with nanoshells were simulated based on the physical and mathematical models for LITT. A two-layer model with nanoshells injected into the tumor tissue was developed for characterizing the cooling effect of the blood flow during LITT. The Monte Carlo method as well as the Pennes equation were introduced to numerically calculate the temperature distribution and predict the effect of the nanoshells. The results show that the relative dimensions of the core and...
Acknowledgments: This work is partially supported by NSFC Grant 50776097 and Tsinghua-Yue-Yuen Medical Sciences Fund.

References