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Estimating nanoparticle optical absorption with magnetic resonance temperature imaging and bioheat transfer simulation

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Abstract

Purpose—Optically activated nanoparticle-mediated heating for thermal therapy applications is an area of intense research. The ability to characterize the spatiotemporal heating potential of these particles for use in modeling under various exposure conditions can aid in the exploration of new approaches for therapy as well as more quantitative prospective approaches to treatment planning. The purpose of this research was to investigate an inverse solution to the heat equation, using magnetic resonance temperature imaging (MRTI) feedback, for providing optical characterization of two types of nanoparticles (gold-silica nanoshells and gold nanorods).

Methods—The optical absorption of homogeneous nanoparticle-agar mixtures was measured during exposure to an 808nm laser using real-time MRTI. A coupled finite element solution of heat transfer was registered with the data and used to solve the inverse problem. The L_2 norm of the difference between the temperature increase in the model and MRTI was minimized using a pattern search algorithm by varying the absorption coefficient of the mixture.

Results—Absorption fractions were within 10% of literature values for similar nanoparticles. Comparison of temporal and spatial profiles demonstrated good qualitative agreement between the model and the MRTI. The weighted root mean square error was $<1.5 \sigma_{\text{MRTI}}$ and the average Dice similarity coefficient for $T = 5^\circ\text{C}$ isotherms was > 0.9 over the measured time interval.

Conclusion—This research demonstrates the feasibility of using an indirect method for making minimally invasive estimates of nanoparticle absorption that might be expanded to analyze a variety of geometries and particles of interest.

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Declaration of Interest

The authors report no declarations of interest.

Keywords

gold nanorod; gold nanoshell; nanoparticle mediated LITT; magnetic resonance temperature imaging

I. Introduction

Among the rapidly developing minimally invasive interventions being investigated for the treatment of solid tumors, magnetic resonance-guided laser interstitial therapy (LITT) procedures have received a considerable amount of interest because they can be guided and monitored effectively using magnetic resonance imaging (MRI). [1,2] Currently, there are at least two FDA cleared systems (Visualase, Visualase, Houston, TX; NeuroBlate, Monteris Medical, Plymouth MN) on the market that incorporate this synergy with MRI, enhancing the safety and efficacy of these procedures and facilitating their execution in extremely sensitive areas, such as the brain. [3] Another unique advantage of LITT is its compatibility with optically activated nanotechnology, which is emerging as a potential approach toward enhancing the conformality of LITT therapies. [4] Nanoparticles such as nanorods (NR), nanoshells (NS), and carbon nanotubes can be engineered to exhibit absorption resonances in the near infrared ‘water window,’ where optical penetration in normal tissue is highest, facilitating therapeutically relevant heating of the nanoparticles at powers below those resulting in heating of normal tissue. Integrated with existing interstitial LITT technology, localization of nanoparticles to tumor tissue may provide a means for better conforming heat delivery to the target tissue. [4,5]

While the enhanced absorption resonances of nanoparticles provide the potential for enhanced heating, their variable optical properties and concentration in tissue inevitably make it difficult to estimate the temperature increase before therapy. This makes the planning of nanoparticle-mediated LITT procedures to optimize fiber number and placement subject to safety constraints before therapy a priority. A technique capable of measuring optical properties in phantoms and preclinical models is needed to aid in the development and validation of predictive models for these procedures. To be successful, such a technique must make measurements with high spatial resolution, be minimally invasive, and cannot be limited by tissue depth. These requirements preclude the use of many direct optical methods such as diffuse optical tomography. [6–8]

In this work we propose a novel inverse problem technique for non-invasively estimating optical absorption that is uniquely suited for investigating nanotechnology-mediated thermal therapy procedures. This approach uses finite element method (FEM)-based solutions of LITT bioheat transfer as the nonlinear mapping from model parameters to temperature predictions. Magnetic resonance temperature imaging (MRTI) provides the temperature estimates to guide the inverse problem. Iterative, constrained adjustment of the FEM model parameters until they best match the measured MRTI distribution facilitates estimation of optical absorption. A similar approach using MRTI has been utilized in the field of focused ultrasound for estimating thermal properties of tissue. [9–11] This approach has several advantages. MRTI and heat transfer modeling are both well characterized for LITT therapies and has no depth limitations while providing a large number of independent temperature

measurements for the inverse problem. [12,13] Additionally, it does not require additional invasive probes that could perturb the material being measured. Making measurements on these materials first in phantoms and later in tissue will provide valuable information for developing models thermal therapy procedures and could eventually aid in developing predictive models. In this paper, we investigate the feasibility of this technique in estimating the optical absorption of phantoms made from gold NS and gold NR, which were chosen because they have been identified as promising for LITT.

II. Materials and Methods

II. A. Phantom fabrication

Gold-silica NS and gold NR (Nanospectra Biosciences, Inc.; Houston, TX) were mounted into homogeneous agarose phantoms. NS had approximately 120/150-nm core/shell diameters, while NR were approximately 46 nm $\times$ 12 nm, as observed on transmission electron microscopy images. NS and NR had absorption peaks centered at 812 nm and 779 nm, respectively, as measured via a spectrophotometer (Genesys 5; Thermo Spectronic, Rochester, NY) (Fig. 1). All particles used were conjugated with polyethylene glycol (500 MW, Laysan Bio, Huntsville, AL) for biocompatibility. We mixed 35 mL of 1.5% agar solution with the appropriate amount of stock nanoparticle solution needed to obtain a phantom with an approximate optical density of 0.695 at 810 nm which was allowed to solidify in MR-compatible plastic vials (2.75 cm diameter). This resulted in estimated nanoparticle concentrations of 1.39×10^{11} NR/mL and 1.92×10^9 NS/mL ($\pm 20\%$) which is consistent with the concentrations observed in mouse xenografts after intravenous administration. [14,15] After allowing the agar nanoparticle mixtures to set, we poured an additional 2.2-cm (13-ml) layer of normal agar gel to reduce air-gel susceptibility errors in MRTI at the interface for more accurate measurements (Fig. 2).

II. B. Nanoparticle heating under MRTI monitoring

At room temperature, phantoms were exposed to an 808-nm medical laser (15 Plus CW, (American Biomedical Corporation, Westminister, MA) connected to an external laser fiber directed down the cylinder axis with real-time MRTI monitoring. Exposures were made with a power output of 1.06 W (for nondestructive, reproducible heating) focused on a 5-mm-diameter spot on the phantom surface. Power output and spot size were verified using an optical power meter (model 840; Newport Corp., Irvine, CA) and infrared card (VC-1550, Thorlabs Inc., Newton, NJ), respectively. All MRTI estimates of the temperature change from baseline during heating were made using a custom 7.6 cm inch spiral receive coil connected to a 1.5 T clinical MRI scanner (Signa Excite HDxt, GE Healthcare, Waukesha, WI) using a single-slice radiofrequency spoiled gradient-recalled echo acquisition (256×128 acquisition matrix, 10-cm $\times$ 10-cm field of view, slice thickness of 3 mm, receiver bandwidth of 7.8 Hz/pixel, and TE/TR/ α of 7.84 ms/72.88 ms/30°). MRTI data were acquired at 5-s intervals for 5 minutes with a 180-s laser exposure. We used a fluoroptic temperature probe (m3300, Luxtron, Santa Clara, CA) to make independent temperature measurements to account for any unanticipated background field errors. Temperature changes from baseline were estimated using the temperature-dependent water proton resonance frequency shift estimated from complex phase difference imaging [16] using in-

house designed processing (MATLAB 7.9.0; MathWorks, Natick, MA). A schematic of the setup is shown in Fig. 2.

II. C. Heat transfer modeling

Appropriate models for photon fluence and heat transfer were identified to simulate the spatiotemporal heat distribution in the experiment. Photon fluence, $\phi(r, t)$, is described by the Boltzmann radiation transport equation [17]. Generally, this integro-differential equation must be solved numerically and a variety of techniques are available. Although Monte Carlo methods can achieve high accuracy in arbitrary 3D geometries they can require millions of particle simulations to simulate photon transport over several centimeters of tissue. [18] Deterministic approaches, such as the discrete ordinates methods, permit faster computation times at the expense of losing the statistical information provided by Monte Carlo. Harmonic expansion methods enable even faster computation by approximating the radiance as a sum of orthogonal polynomials, thus eliminating the need to discretize the angular dependence of the radiance. [17] Of the harmonic expansion methods we chose the delta-P1 (δ -P1) approximation because it is more accurate for higher-absorbing media compared to the most basic harmonic expansion method, the standard diffusion approximation, and has been previously demonstrated to work well for the NS at these concentrations. [19,20] Under the (δ -P1) approximation the photon fluence is parameterized by three values: the absorption and scattering coefficients, μ_a and μ_s , which represent the probability of a photon being absorbed or scattering over an infinitely small distance and the anisotropy factor, g , which is the average cosine of the scattering angle of the photons. Thus, an anisotropy factor of 0 represents isotropic scattering while an anisotropy factor of 1 represents pure forward scattering. It is common to refer to a fourth quantity, the reduced scattering coefficient (μ_s'), which is defined by the relation $\mu_s' = \mu_s(1-g)$, that represents the scattering coefficient of a medium assuming all scatterers are effectively isotropic. We refer to the reduced scattering coefficient throughout the remainder of the study.

The governing equations and boundary conditions that describe the photon fluence, $\phi(r, t)$, for a Gaussian source term can completely describe the fluence and, when multiplied by the absorption coefficient, define the source term of the inhomogeneous heat conduction equation,

$$\rho c \frac{\partial T(r, t)}{\partial t} = \nabla \cdot k \nabla T(r, t) + \mu_a \phi(r, t), \quad \text{Eq. 1}$$

yielding a system of coupled equations describing fluence and heating. Convection effects are ignored because the powers used in this experiment are not sufficient to melt the gel. The coupled set of equations was solved numerically using FEM. Meshes were generated with 39,666 hexahedral elements to achieve a resolution on the order of the imaging data (.75 elements/mm³ vs. 2.18 voxels/mm³) with two simulation regions defined by the presence or absence of nanoparticles. A Crank-Nicolson time-stepping scheme was used to advance the temperature distribution with no flux boundary conditions applied at the agar boundaries. This coupled system resulted in 79,332 degrees of freedom. Details of the δ -P1 approximation solved using FEM are provided in the appendix.

II. D. Parameter selection

Given that we are simulating a physical system, the solution search space, and hence the range of the optimized parameters, has to be appropriately restricted to realistic values. For these reasons, we used as much *a priori* information as possible to minimize the number of optimized variables, and restricted those to the physically realizable bounds. Each simulation region for our coupled δ -P1 bioheat transfer model is uniquely defined by three optical parameters—anisotropy factor, g ; absorption coefficient, μ_a ; and reduced scattering coefficient, $\mu'_s = \mu_s(1-g)$ —and three thermal/physical parameters—thermal conductivity, k ; specific heat, c ; and density, ρ . For the two regions in our phantom simulations, this represents 12 total parameters. The thermal conductivity, specific heat, physical density, and anisotropy factors are assumed to remain unperturbed in the presence of nanoparticles, [20,21] reducing the number of parameters needed to eight. The absorption coefficient of agar was assumed to be the same as that of water [22,23], and the reduced scattering coefficient was estimated by measuring the extinction coefficient, μ_{tr} , with the spectrophotometer and by assuming the relation $\mu_{tr} = \mu'_s + \mu_a$. The values used for thermal conductivity, specific heat, physical density, and agar optical properties are shown in Table 1.

The effective extinction coefficient of the nanoparticle-agar regions were estimated using MRTI because the increased scattering the cross-section reduces the accuracy of the spectrophotometer reading. According to Roemer et al., [24] in the early stages of heating the spatial gradient of temperature is small, causing the source term from equation 2 to dominate the heat transfer process. We make this assumption at the location of maximal absorption immediately after the laser is turned on so that the time derivative of the temperature will be equal to a constant,

$$\rho c \frac{\partial T(r)}{\partial t} \cong \mu_a \varphi(r). \quad \text{Eq. 2}$$

Using the pixels where this relation holds and assuming that the fluence along the central axis approximately follows Beer's law allowed an exponential fit to the time derivative of temperature to provide an estimate of the extinction coefficient. This estimation reduced the number of variables for the inverse problem to one, since any value of μ_a necessarily determines the value of μ'_s . This also provided physical limits on the upper bound of the value of μ_a , ensuring that the solutions are physically realizable.

II. E. Inverse solution algorithm

After selecting simulation parameters, we registered the FEM and MRTI datasets by aligning the interfaces of the agar and agar-nanoparticle regions (Paraview 3.8.1, Kitware, Clifton Park, NY). The modeling and inverse problem solutions used the Common Optimization Library Interface (COLINY) pattern search algorithm [26] implemented within the Design Analysis Kit for Optimization and Terascale Applications (DAKOTA) version 5.1 (Sandia National Laboratory, Albuquerque, NM). [27] This pattern search algorithm is a derivative-free optimizer that minimizes an arbitrarily specified objective function of n

variables by searching parameter space using “patterns” of 2n trial points centered on an initial guess. Although derivative based optimizers theoretically offer more efficient convergence properties, gradient information is not currently available for the model used in this work. We optimized on three 16-processor nodes (Ranger cluster, Texas Advanced Computer Center (TACC), Austin, TX) over one variable using the L_2 norm of the FEM and the MRTI in a region of interest (ROI) encompassing the region where significant heating was observed, with each node dedicated to a trial point.

II. F. Data analysis

The first method used to evaluate the agreement between MRTI and FEM data was the comparison of spatial and temporal profiles. While it provides a simple and intuitive comparison, this method is sensitive to registration errors and only utilizes a small fraction of the available data. For these reasons agreement was quantified using the Dice similarity coefficient (DSC)[28] defined by:

$$DSC = \frac{2 * (A_{Model} \cap A_{MRTI})}{A_{Model} + A_{MRTI}}, \quad \text{Eq. 3}$$

where A_{MRTI} is the area enclosed by an isotherm on the MRTI and A_{Model} is the area enclosed by the same isotherm on the FEM model. The value of the DSC represents the degree of overlap between isotherms with values of one and zero representing perfect and no overlap, respectively. This metric is less sensitive to small registration errors and incorporates more spatial data than a comparison of profiles. A drawback of the DSC is that it still does not utilize all of the available data because it can only be calculated for particular isotherms.

A global metric that can make use of all of the available data is the RMS error between the MRTI and FEM model. To more accurately reflect the agreement between the datasets the uncertainty in temperature at the i^{th} pixel was calculated according to:

$$\sigma_{T,i} = \frac{\sigma_{air} \cdot \sqrt{2}}{2\pi \cdot \left(\sqrt{\frac{4-\pi}{2}} \right) \cdot S_i \cdot \alpha \cdot \gamma \cdot B_0 \cdot TE}, \quad \text{Eq. 4}$$

where S_i is the signal measured in a pixel, α is the temperature sensitivity coefficient of -0.0097 ppm/ $^{\circ}\text{C}$, γ is the proton gyromagnetic ratio, B_0 is the main magnetic field strength, TE is the echo time, and σ_{air} is the standard deviation of an ROI containing no signal. The square of the uncertainties is used as a weighting factor in the RMS calculation giving rise to the weighted RMS error (wRMSE):

$$wRMSE = \sqrt{\frac{\sum_{i=1}^n \frac{1}{\sigma_{T,i}^2} (MRTI_i - FEM_i)^2}{\sum_{i=1}^n \frac{1}{\sigma_{T,i}^2}}}, \quad \text{Eq. 5}$$

where $MRTI_i$ and FEM_i are the temperatures in the i^{th} pixel measured by MRTI and heat transfer simulation, respectively. This weighting effectively reduces the contribution of

pixels according to the uncertainty in temperature so that the spatially varying SNR in the MRTI data does not bias the results. To further prevent imaging from biasing the measurement of wRMSE the calculation was restricted to an ROI away from boundaries and known artifacts, such as those caused by the fluoro probe. Thus, the wRMSE represents the average difference between the MRTI measurements and model predictions in a given ROI. This metric is reported in an absolute sense (units of temperature) and relative to the average noise observed in the MRTI (unitless). Representing the wRMSE relative to the MRTI noise provides a lower limit for the metric and allows agreement to be judged in the context of the average noise observed in the MRTI measurements.

III. Results

To illustrate the correlation between model and measurement, we plotted the longitudinal, radial, and temporal heating profiles for a single common point in space and time for NS and NR (Fig. 3). Generally, good agreement is observed across the profiles. However, the temporal profiles show visibly slightly larger disagreement near $t = 30$ s, corresponding to the start of laser irradiation. Examination of the profile residuals reveal similar but more subtle errors that occurred once irradiation ceased. These errors could have resulted from a slight misregistration between the timing of the MRTI and the simulation due to the coarseness of temporal MRTI sampling or temporal averaging of a rapid change in temperature over 5 s by the MRTI. To avoid including these errors in our quantitative techniques, all spatial profiles in figures 3 and 4 were taken 5s before maximum temperature was achieved

Agreement is observed to be better in the NS profiles than in the NR profiles, with the NR solution slightly over-predicting temperature during heating and under-predicting temperature during cooling. This disparity between the model and MRTI is also observed for the NR in the radial profile, where a consistent under-prediction of temperature is observed.

The NR phantom reached a higher maximum temperature (13.8°C MRTI/13.6°C model) than the NS phantom (11.1°C MRTI/10.5°C model) for the same incident fluence and approximately same OD. Additionally, the NR phantom exhibited a more narrowly peaked temperature distribution than the NS phantom in the radial and axial profiles.

The DSC values were calculated for both phantoms at the $T = 5^{\circ}\text{C}$ isotherm and are plotted as a function of time in Fig. 4. This isotherm was chosen because both phantoms reached temperatures well above 5°C , thus providing a reasonably large area of measurement for comparison, and because the usefulness of agreement measurements at significantly lower or higher temperatures was clearly impacted by noise or lack of data, rendering those data unsuitable for quantitative comparison in this investigation. Using an interval between $t = 60$ s and $t = 190$ s, a region at which the value of the DSC is no longer transient because of the sustained laser exposure, the measured DSC $_{T=5^{\circ}\text{C}}$ was 0.91 ± 0.02 and 0.91 ± 0.03 for NR versus NS, respectively. An overlay of representative isotherms ($t = 170$ s) is also shown in Fig. 4, with the 95% confidence interval defined by $+2\sigma_{\text{MRTI}}$ in each voxel, for reference. The predicted heating from the NS and NR models fall almost entirely within confidence

interval of the measurements with the NR model consistently closer to the lower confidence interval in the radial and axial directions proximal to the laser source.

The wRMSE was measured in an ROI chosen to encompass the heating while excluding regions of measurement artifact, such as the susceptibility artifacts caused by the presence of the fluoroptic probe, and was plotted as a function of time (Fig. 5). The wRMSE is plotted both in an absolute sense and relative to the average uncertainty in temperature, $\sigma_{T,i}$, observed throughout the ROI which was approximately .4°C for both shells and rods. As previously described, larger changes in wRMSE were observed in both phantoms at the points of laser activation and de-activation. Despite the deviation at power on/off timepoints, the wRMSE remained $1.5\sigma_{\text{MRTI}}$ for the duration of the experiment. The wRMSE was relatively constant during heating (30 s – 210 s), with values of $0.45 \pm 0.04^\circ\text{C}$ and $0.44 \pm 0.02^\circ\text{C}$ for the NR and NS phantoms, respectively. There was a slight increase in the wRMSE value over time in the NR phantom, consistent with the observations of slightly underestimating heating. The peak measured errors not attributed to the high temporal gradients were 0.50°C ($1.17 \sigma_{\text{MRTI}}$) and 0.56°C ($1.40 \sigma_{\text{MRTI}}$) for NS and NR, respectively. Both errors were less than a degree.

The absorption and reduced scattering coefficients returned by the pattern search optimization were 93.6m^{-1} and 70.2m^{-1} respectively for NS and 148.1m^{-1} and 28.2m^{-1} for NR, which is consistent with the range at which the δ -P1 approximation is demonstrated to deviate from the standard diffusion approximation [29] These values correspond to 57% and 84% of the interacting photons being absorbed versus scattered in the NS and NR models, respectively. The objective function was plotted for each of the values of μ_a used by the algorithm (Fig. 6). Convergence to a solution took approximately 22 min for both cases. For both phantoms, the objective function appeared to be convex indicating the algorithm converged to a unique solution within the bounds of the physically realizable values.

IV. Discussion

We expected the inverse problem approach to estimating the optical absorption to meet two conditions. First, the FEM model should predict a temperature distribution that matches experimental data when using the optimized absorption values. This agreement is shown qualitatively by the overlaid MRTI and FEM temperatures in figure 3 and with respect to MRTI noise using 5°C isotherms in figure 4. The Dice coefficient of 5°C isotherms (figure 4) and the wRMSE (figure 5) demonstrate that the differences are stable and on the order of the MRTI error throughout both experiments. In all of these comparisons the inverse approach consistently provided a better fit in the shell model compared to the rod model and the coarseness of MRTI temporal sampling contributes to transient increase in the observed error.

The second condition is agreement between the optimized parameters and either theoretical values or independent measurement. From reported literature, we expected the absorption-to-reduced-scatter ratio to be approximately 60% for NS and 93% for NR, which corresponds to a difference of -3% for NS and -9% for NR against published theoretical results of particles with approximately the same size and shape. [30–32] These differences

are shown visually in figure 6 where the circles represent the value of the objective function at each iteration of the optimization algorithm and the vertical dotted lines represent the literature values. Part of the difference in error observed between the two particles may be explained by the source of the quoted literature values. Optical properties computed from Mie theory electromagnetic calculations of NS optical properties are fairly reliable within the distribution of the mean size of our particles, because they can be calculated analytically and reflect the precise geometry of the particles used in our experiment. Due to their lack of spherical symmetry, the optical properties of NR cannot be well described analytically, and the literature values were taken from particles with the approximate properties of those used in this study. As stated previously, we used a wavelength that was slightly off resonance (808nm vs. 779nm) so we expect to obtain a smaller percent absorption compared to that tabulated by Jain et al. who refers to the ratio at the peak resonance wavelength. [30] Additionally, the accuracy of the δ -P1 approximation, while better than the standard diffusion approximation, still degrades as the scatter-to-absorption ratio decreases and therefore may contribute more error to the NR model. This suggests that the applicability of this method may be limited by the scatter-to-absorption ratio of the particle sample being considered and is consistent with the lower agreement between the MRTI and the model in the case of the NR.

Other limitations, common to both particles, help explain the deviation from the theoretically calculated values. Theoretical values do not accurately reflect a distribution in particle size or the associated geometrical defects that have been shown to affect optical properties. [33–35] The small, but nonzero, optical properties of agar, which have also been shown to alter optical properties of absorbing and scattering particles at other wavelengths, could have also had an impact on the results of the inverse problem solution. [36] This points at the future challenge of measurements made in *ex vivo* or *in vivo* environments and the need to characterize the particles as well as possible prior to moving to these turbid tissue environments. Experimental uncertainties such as those in the imaging plane and laser position, combined with the limited accuracy of the MRTI, also likely contributed to the error observed between measured and literature values.

We consider this study as being successful in confirming the feasibility of applying an inverse problem that relies on using MRTI data and heat transfer modeling for estimating the absorption coefficient of photothermal absorbers. Specifically, we observed that the technical limitations of MRI imaging and finite computing resources do not prevent the execution of this study with reasonable accuracy and speed. Although some special consideration was made for coarse temporal sampling, the spatial sampling and noise properties of the MRTI were sufficient for comparison with the finite element model. The delta-P1 approximation, which was chosen for its relative computational simplicity, is capable of modeling the particles used in this study and is expected to perform even better if used in a turbid media such as tissue.

Despite the success of this study there are several areas where this approach could be improved. One of the primary limitations is that this preliminary investigation was performed on a single concentration of nanoparticles. A study over a range of concentrations would provide a more complete idea of the range of situations where this approach would be

valid. We also observed laser activation and deactivation errors that could be accounted for by being discarding or appropriately weighing their contribution to the objective function as a way of improving accuracy in future studies. This study was also conservative with regards to the number of optimized parameters because of the potential impact on the convergence of the optimization algorithm.

Ideally, the inverse problem would be used on an expanded parameter space to simultaneously make measurements of thermal and optical properties, while taking care to properly evaluate the physical model at different points during the exposure and cooling cycle.

We hope to further improve our approach with differing concentrations in a mixed heterogeneous environment to assess the ability to translate this work into tissue environments. Heterogeneity is expected to introduce significant challenges as the fixed parameters in this study are known with less certainty and may bias the solution if kept fixed. This expansion of free variables would likely require the implementation of a gradient based optimization algorithms which become increasingly advantageous as the number of free parameters is expanded. Perhaps the greatest challenge to modifying this technique to be used *in vivo* is the potential to have significant spatial variation in the optical properties. This would likely require some sort of regularization be included in the optimization to allow convergence. This study is a first step in investigating if this approach can eventually be adapted for application in tissue.

V. Conclusions

This work demonstrates that an inverse problem that uses MRTI in conjunction with a heat transfer model can successfully estimate nanoparticle optical absorption in homogeneous media. The heat distributions predicted by the model compared favorably with the MRTI measurements, both qualitatively and quantitatively. However, the NS model estimates slightly outperformed the NR model estimates. The best representation of agreement, the wRMSE, stayed within $1.5\sigma_{\text{MRTI}}$ throughout the duration of the experiment for both nanoparticles. The estimated ratio of optical absorption to reduced scattering agreed within 5% and 10% of values found in literature for particles with similar composition and geometry as our NS and NR, respectively. Despite the benefits of having a non-invasive method for evaluating the relative effectiveness of nanoparticle batches for photothermal therapies in phantom, the success in a homogeneous environment are just the first step toward useful translation. Additional research must be performed in optimizing the fluence model, developing a minimization algorithm, and implementing *a priori* information to extend this approach to heterogeneous media.

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Appendix. Delta-P1 approximation to the radiative transport equation

The δ -P1 approximation to the radiative transport equation may be concisely expressed as an elliptic partial differential equation, [37]

$$\nabla \cdot \left(\frac{1}{3\mu_{tr}} \nabla \varphi_d(\mathbf{r}) \right) - \mu_a \varphi_d(\mathbf{r}) = -\mu_s^* E(\mathbf{r}) + \nabla \cdot \left(\frac{g^* \mu_s^*}{\mu_{tr}} E(\mathbf{r}) \hat{s}_0 \right),$$

where $g^* = \frac{g}{(g+1)}$, $\mu_s^* = \mu_s(1-g^2)$, and the direction of the photon propagation of the external collimated Gaussian beam is denoted $\hat{s}_0$. The coefficients of the source term are obtained by

fitting the assumed form of the phase function to the Henyey-Greenstein function.

Cylindrical symmetry is assumed with the radius given by $r = \sqrt{x^2 + y^2}$ and the axial length denoted z . The Gaussian beam width is denoted by r_0 and E_0 denotes the initial fluence. At the point of entry into the agar-nanoparticle mixture, the external fluence is assumed to have attenuated over the length of the agar without nanoparticles, z_0 in proportion to the total attenuation coefficient of the agar μ_{t0} ,

$$\varphi_c(\mathbf{x}) = E(r, z) = \begin{cases} E_0(1-R_s) \exp(-\mu_t^* z) \exp\left(-\frac{2r^2}{r_0^2}\right) \\ E_0(1-R_s) \exp(-\mu_{t0}^* \Delta z_0) \exp(-\mu_t^*(z - \Delta z_0)) \exp\left(-\frac{2r^2}{r_0^2}\right) \end{cases}$$

where the effective attenuation coefficient (μ_t^*) is defined by $\mu_t^* = \mu_a + \mu_s^*$. Cauchy boundary conditions are assumed at the collimated laser and agar interface with refractive index, n . The diffusive fluence is assumed to decay to zero at the far boundary,

$$\begin{aligned} -\nabla \varphi_d \cdot \mathbf{n}|_{z=0} &= \frac{1}{Ah} (\varphi_d + 3Ahg^* \mu_s^* E(r, z)|_{z=0}) \\ \varphi_d(\mathbf{x})|_{\mathbf{x} \rightarrow \infty} &= 0 \end{aligned}$$

where

$$\begin{aligned} A(n) &= 520.13755n^3 + 4.3390n^2 - 4.90366n + 1.6896 \\ h &= \frac{2}{3}\mu_{tr} \end{aligned}$$

Fig. 1. Extinction of nanoshells and nanorods

The extinction of the nanoshells and nanorods used in the study are shown. A broad plasmon resonance is observed for nanoshells, while a narrower resonance is observed for nanorods.

Fig. 2. Experimental setup

A schematic of the experimental setup is shown. The FEM mesh is shown with T2-weighted and MRTI imaging overlaid. The arrow at the top depicts the laser direction relative to the phantom. The fluoroptic temperature probe can be seen in the T2-weighted image.

Fig. 3. Temporal and spatial heating profiles

Temporal (left), axial (middle), and radial (profiles) of MRTI (blue $\circ$) and heat transfer simulation (red line) for nanoshells (top) and nanorods (bottom). All plots of the same phantom share a common time point (black $\diamond$) at the position of maximum heating at $t = 205$ s to avoid the error caused by high temperature gradients that result from the laser's being turned off. Distance measurements are zeroed to this common point, and the increased absorption efficiency of the nanorods is apparent as they reach a higher maximum temperature difference (13.8°C MRTI/ 13.6°C model) than the nanoshells (11.1°C MRTI/ 10.5°C model).

Fig. 4. Dice coefficient of $T = 5^{\circ}\text{C}$ isotherms

The Dice similarity coefficients were calculated for $T = 5^{\circ}\text{C}$ isotherms as a function of time (Left) for nanoshells (top) and nanorods (bottom). Isotherms (Right) are plotted for the model (green) and MRTI (blue) and the edges of the 95% confidence interval (thin blue) at 205 s for both nanoshells (top) and nanorods (bottom). The model falls within the 95% confidence interval for both particles except in the case of the rod plot, in which the model tends to predict temperatures consistent with the lower end of the confidence interval.

Fig. 5. Weighted RMS differences

The wRMSE difference is shown as a function of time for nanoshells (blue solid) and nanorods (red solid) on an absolute scale and relative to the average uncertainty (σ) in MRTI measurements (dotted) at the same region of interest. The grey-shaded area represents times when the laser was turned on. In both cases, the RMS difference stayed within $1.5\sigma_{\text{MRTI}}$ for the duration of the experiment. Large increases are seen at $t = 30$ s and $t = 210$ s because of the high temporal gradients associated with turning the laser on and off. Magnitude images are shown for each type of particle with the center of heating, ROI, and position of fluoroptic probe (cyan) overlaid.

Fig. 6. Minima of Inverse Problem Solution

The objective function is plotted as a function of the value of the absorption coefficient used at each trial point in the inverse solution algorithm for nanorods (red) and nanoshells (blue). The objective function was taken from a region of interest centered on heating, did not receive any weighting to account for uncertainty in the MRTI, and was normalized to the minimum value observed. Over the range of physically realizable bounds, the change in the objective function appears to be convex, with the algorithm finding an absolute minimum in each case. Vertical lines are plotted to give the expected values of absorption, assuming literature values for the absorption-to-scattering ratio.

TABLE I

Optical and thermal parameters

Parameter	Variable	Material		
		Agar	Nanoshell-Agar	Nanorod-Agar
Absorption coefficient, [m^{-1}]	μ_a	2[22,23]	-	-
Reduced scattering coefficient, [m^{-1}]	μ_s'	22.2	-	-
Extinction coefficient, [m^{-1}]	μ_{tr}	24.2	163.8	176.3
Anisotropy factor	g		0.9[20,21]	
Thermal conductivity, [$\text{Wm}^{-1} \text{K}^{-1}$]	k		0.60[25]	
Specific heat, [$\text{J kg}^{-1} \text{K}^{-1}$]	c		3900 [25]	
Physical density, [kg/L]	ρ		1[25]	