Laser-induced photo-thermal magnetic imaging

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Due to the strong scattering nature of biological tissue, optical imaging beyond the diffusion limit suffers from low spatial resolution. In this letter, we present an imaging technique, laser-induced photo-thermal magnetic imaging (PMI), which uses laser illumination to induce temperature increase in a medium and magnetic resonance imaging to map the spatially varying temperature, which is proportional to absorbed energy. This technique can provide high-resolution images of optical absorption and can potentially be used for small animal as well as breast cancer and lymph node imaging. First, we describe the theory of PMI, including the modeling of light propagation and heat transfer in tissue. We also present experimental data with corresponding predictions from theoretical models, which show excellent agreement. © 2012 American Institute of Physics.

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Diffuse optical imaging (DOI) aims to recover spatially resolved optical properties of thick tissue using boundary measurements. The region of interest is illuminated from multiple sites using light in the near-infrared (NIR) range of the spectrum, 600-1000 nm, which maximizes the probing depth due to the weak absorption of biological tissues in this range. Multiple sources and detectors are placed on the boundary of the object being imaged and an inverse problem is solved to reconstruct absorption and scattering images from the measurements. Unfortunately, the spatial resolution of DOI beyond the diffusion limit is poor due to the strong scattering of biological tissue in the NIR range.¹⁻⁸ Recently, an intriguing combination of optical and ultrasound techniques has led to the development of photo-acoustic tomography (PAT). In PAT, acoustic waves are generated by the absorption of pulsed light within an illuminated object and these waves measured at the object boundary. These measurements are then back-propagated to obtain an image proportional to the initial pressure distribution from the absorption of the pulsed light, resulting in an absorbed energy map.⁹⁻¹¹ This map reveals physiologically specific optical absorption contrast. Because acoustic waves are scattered in tissue much less than light, the resulting absorbed energy map can be reconstructed with much higher resolution than traditional DOI. However, PAT has its own challenges: structures such as bone and air cause significant ultrasound image distortion and shadowing due to the strong sound wave scattering and reflection they induce.¹² Additionally, shallow objects with strong optoacoustic signals can mask smaller signals from deeper sources. Hence, the resolution of PAT also depends on the probing depth.¹³ Finally, PAT, in general, requires tissue-transducer contact, which may be undesirable in certain applications.

In this letter, we introduce a different approach termed laser-induced photo-thermal magnetic imaging (PMI). In this approach, the medium under investigation is irradiated with near-infrared light and the laser-induced heating is measured

using a magnetic resonance imaging (MRI) thermometry technique. The MRI temperature map is proportional to the optical energy absorbed at each point and thereby provides optical absorption contrast. There are several advantages of this PMI. First, it provides images at MRI resolution, limited to some extent by blurring due to heat diffusion. The faster the MRI images are acquired, the less heat diffusion blurs the images. Acquiring measurements during heating also mitigates diffusion blurring. Second, the use of RF-waves in MR imaging alleviates the problem of scattering at tissue boundaries, which is problematic when imaging with acoustic waves, such as in PAT. Third, in PMI, no scattering occurs after the interaction of light with tissue. In DOI, light is only measured after it has travelled through tissue and scattered multiple times as it diffuses to the boundary, causing resulting in ill-posedness in the inverse problem. In PMI, the MR measurement is directly localizable to the point of absorption, within the object being imaged. This is the fundamental reason why PMI is expected to mitigate or eliminate the ill-posedness problem of DOI. Finally, PMI is a non-contact technique, which can be a major advantage for some imaging applications. MRI can thus be used to measure optical absorption contrast at MR resolution, without scattering at tissue boundaries, with measurements not affected by photon diffusion, while requiring no tissue contact.

The first step in PMI is the modeling of light propagation and heat transfer, using the finite element method. Light propagation can be modeled with the diffusion approximation:¹⁴

$$\nabla[D(\vec{r})\nabla\Phi(\vec{r})] - \mu_a(\vec{r})\Phi(\vec{r}) = -S(\vec{r}), \quad (1)$$

where $\Phi(\vec{r})$ is the optical light fluence rate (W/mm²), $S(\vec{r})$ is the optical source term (W/mm²), $D(\vec{r})$ is the photon diffusion coefficient, and μ_a is the photon absorption coefficient.

Heat transfer is also modeled when data acquisition times extend beyond a thermal confinement period, several milliseconds, during which heat diffusion and convection are not negligible. A commonly used model for thermal transfer is the bioheat transfer equation.¹⁵

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$$\rho c \frac{\partial T(\vec{r}, t)}{\partial t} = \nabla[k \nabla T(\vec{r}, t)] + Q_R + Q_M + \omega_b c_b (T_a(\vec{r}, t) - T(\vec{r}, t)), \quad (2)$$

where ρ , c , and k denote mass density, specific heat, and thermal conductivity, respectively; c_b is the specific heat of blood; ω_b is the blood perfusion rate; Q_R and Q_M represent radiative and metabolic heating, respectively; T_a is the arterial blood temperature; and T is the local tissue temperature. For phantom experiments presented in this letter, the metabolic heating and blood perfusion terms are neglected. The diffusion and bioheat transfer equations, when both used, are coupled by using the $\mu_a \Phi(\vec{r})$ term from the diffusion equation as the radiative heating source in the bioheat transfer equation. For the heat transfer equation boundary conditions, we consider only heat convection, which is: $-k \partial T(r)/\partial n = h(T_f - T(r))$, where h is the heat transfer coefficient (W/(mm² °C)) between the surface of the medium and the surrounding medium at temperature T_f (°C).

With a model in place, the process of PMI data acquisition can be explained. During laser-induced heating of a medium, the temperature increase in the medium is imaged with MRI thermometry. MRI thermometry has found significant use in MR-guided thermal therapy: both in low-temperature hyperthermia as well as high-temperature thermal ablation.^{16,17} It is used to both minimize the dose received by uninvolved tissues as well as ensure adequate dosing of targeted areas. Proton resonance frequency (PRF)-based methods are the most frequently used MR thermometry techniques due to their sensitivity, invariance in different tissue types and speed (e.g., up to 10 frames per second).^{18,19} The proton resonance frequency is affected by the increase in nuclear shielding caused by decreased hydrogen bonding with increasing temperature. As a result, the proton resonance frequency decreases as temperature increases. Using a phase sensitive MRI sequence such as gradient echo, asymmetric spin echo, or EPI, the measured phase change between successive frames is directly related to the temperature change between frames and corresponding temperature change maps can be obtained.¹⁶

During PMI measurements, a laser is used to illuminate and heat the medium inside the MRI. Dynamic MR phase maps are obtained before, during and after heating to monitor spatially and temporally varying temperature. This temperature change is directly proportional to the local optical photon density and the local absorption coefficient, as shown in the following equation:

$$\Delta T \propto \mu_a(\vec{r}) \Phi(\vec{r}, t, \mu_a(\vec{r}), \mu_s(\vec{r})). \quad (3)$$

In this equation, ΔT is the measured temperature change, μ_a is the absorption coefficient, μ_s is the reduced scattering coefficient, and Φ is the photon density, which is a function of position, time, absorption, and scattering.

The baseline MRI frame is then subtracted from the subsequent frames to obtain phase shift maps. This phase shift is linearly related to the temperature change through the following relation:

$$\Delta T = \frac{\phi(t) - \phi(t_0)}{\gamma \alpha B_0 T_E}, \quad (4)$$

where ΔT is the change in temperature; $\phi(t)$ is the measured phase at some time, t ; $\phi(t_0)$ is the baseline phase; γ is the gyromagnetic ratio (42.58 MHz/T for hydrogen); α is the coefficient relating phase change to temperature (typically -0.1 ppm/°C for tissue); B_0 is the local magnetic field; and T_E is the MR echo time, or the time between excitation and data acquisition.

These temperature difference maps reveal the optical energy absorbed at each point between time t_0 and t . Hence, PMI directly provides spatially resolved optical absorption contrast maps similar to PAT. To show the feasibility of PMI, phantom experiments were performed. Simulations were also undertaken and compared to these phantom results. The picture and schematic diagram of the PMI system are shown in Fig. 1. A 90 cm bore, 4T MRI, along with an 82 mm diameter birdcage RF coil, and a SMIS console were used for data acquisition. An 808 nm laser diode (LD) (Jenoptik) was used with a VueMetrix HCT diode driver for laser illumination which was coupled to a single 430 μ m fiber. The laser, laser driver, and the computer were kept in the MR control room and an optical fiber connected to the laser was routed to the MR scanning room and mounted on the RF coil for illuminating the phantom, as shown in Fig. 2. An aspheric condenser lens was placed in front of the fiber to provide uniform illumination. The spot size on the sample was 1.3 cm in diameter and the laser power delivered to the phantom surface was approximately 1.2 W resulting in power density levels on the surface of 900 mW/cm², nearly 2.7 times of the maximum skin exposure limits defined by the American National Standards Institute (ANSI).

MR thermometry measurements were performed with a gradient echo sequence with $T_R = 80$ ms, $T_E = 48$ ms, FOV

FIG. 1. Diagram of the PMI system. Shows the sample placed in an MR RF coil and a long optical fiber used to deliver light from the LD located at a semi-distant location away from the magnet. The fiber optic probe is attached to the RF coil above the imaging sample to illuminate it from the top.

FIG. 2. The home-built PMI interface is placed in the 4T MRI. The phantom is placed at the center of the birdcage RF-coil using a custom holder and illuminated from the top using a fiber probe. The phantom is pulled back and illuminated with a red laser close to its edge for illustration purposes.

of 80 mm, acquisition matrix 256 (phase encoding) $\times$ 256 (frequency encoding), and a flip angle of 90° . Temporal resolution was 8 s per frame. A series of dynamic MR images were acquired with the first image being acquired before heating and used as a baseline. The laser was then turned on for nearly 24 s (triggered by the MRI RF pulse) to illuminate and heat the object being imaged. The sequence is illustrated in Fig. 3. The acquisition of images continues through the cooling of the phantom.

Two 5 mm inclusions were embedded 4.5 mm below the surface (edge-to-center) of a cylindrical, 40 mm diameter agarose phantom, with optical properties chosen to match tissue optical properties using Intralipid and India ink as scattering and absorbing agents, respectively. The inclusions were positioned 8.5 mm apart as shown in Fig. 4. The inclusions had only optical contrast and were not visible in MR images. The background absorption and scattering coefficients were set to 0.01 mm^{-1} and 1.0 mm^{-1} , respectively, while the absorption coefficient of the inclusion was set to 0.04 mm^{-1} , resulting in a target-to-background contrast to four. The cylindrical phantom was illuminated broadside with laser light as shown in Fig. 4. Numerical modeling was performed to estimate the spatial and temporal temperature distribution given this illumination pattern, while consider-

FIG. 3. PMI timing diagram. The red line (top) indicates the laser on/off status, the green line (middle) is the temperature rise from baseline at some representative point in the phantom, and blue (bottom) shows the MRI data acquisition window and number of frames.

FIG. 4. Gradient echo anatomic image showing location of the inclusions (indicated by the red circles) and laser illumination pattern. The inclusion has optical absorption contrast of four-to-one and is not visible in the MR image.

ing light diffusion and heat transfer within the phantom. Fig. 5 shows four time-lapse temperature images of the phantom. The first two images were acquired during the heating phase with the laser on, while the other two were acquired during the cooling phase. The simulated temperature maps, obtained via numerical modeling, are presented side by side with the experimental data. The temporal resolution of MRI acquisition was 8 s, while the time step for solving the heat transfer equation was one second. MRI measures the mean temperature for the duration of a single, 8 s frame. For this reason, the simulated temperature maps presented in Figure 5 are averages of the temperature for the 8 s MR acquisition frame. During the cooling phase, the phantom temperature declines slowly, as illustrated in Fig. 3. Hence, the temperature distribution measured in frames #3 and #4 is similar, except that the objects are less identifiable in #4 due to the blurring effect of diffusion.

The profile plots, taken along the horizontal axis through the inclusions, are also shown for both experimental and estimated images for each time point. As seen in the figure, the theoretical calculations agree well with experimental results. The correlation coefficient between the two curves were also calculated for four frames: 0.9873, 0.9933, 0.9978, 0.9924, respectively.

To evaluate the linearity of the system with respect to variations in absorption, different phantoms with various target-to-background absorption contrast ratios were used. A single 5 mm inclusion was embedded 5 mm below the surface of a 40 mm diameter agar phantom. The background absorption and scattering coefficients were set to 0.01 mm^{-1} and 1.0 mm^{-1} . The scattering coefficient of the inclusion was set to be the same as the background, resulting in no scattering contrast. The absorption contrast of the inclusion

FIG. 5. Four time-lapse temperature images of the phantom (inclusion absorption is 0.04 mm^{-1} , making the target-to-background contrast four). The first column is the map of the temperature increase due to laser illumination predicted by numerical modeling, while the second column is the actual temperature change measured by MR thermometry. Frame #1 and #2 are acquired during the heating phase, while frames #3 and #4 were acquired during the cooling phase. The profile plots along the horizontal axis and across the inclusions (indicated by dashed line) for both theoretically predicted and experimental data at each time step are shown in the third column.

varied over a broad range: 0.5, 1, 2, 4, and 6. Data were acquired for each phantom with the same imaging parameters. A region-of-interest (ROI) was drawn around the inclusion for each case and the mean phase shift in the ROI was calculated. As shown in Fig. 6, the measured phase shift (blue dots) is linear with respect to the target-to-background absorption contrast ratio. The correlation coefficient is 0.998 for the fitted curves (red line). This linear result shows that the measured phase change can potentially be used to determine the absorption properties of the phantom.

In summary, we have used PMI to measure relative optical absorption at MR resolution. The temperature change measured in PMI is directly proportional to absorption for a single-inclusion phantom, and this phenomenon can be accurately modeled using a finite element approach. One particular application of DOI is cancer imaging. Imaging modalities

FIG. 6. Experimental verification: Measured phase shift versus target-to-background absorption contrast (x-axis: Absorption Contrast Ratio). The blue dots represent the phase shift values, measured with MR thermometry. The red line represents the linear least-squares fit. These results show that the measured phase change can potentially be used to determine the absorption properties of the phantom.

currently in use, such as MRI, CT, and ultrasound mainly image structural properties with little functional correlation, resulting in potentially high sensitivity, as in breast cancer MRI, but low specificity. The result is a high false-positive rate using these modalities and many unnecessary biopsies for nonmalignant cancers. PMI has the potential to contribute functional imaging to improve the specificity of cancer imaging and eliminate unnecessary and invasive tissue biopsy. Using multiple wavelength measurements, total hemoglobin and oxygen saturation maps can be obtained due to the distinct absorption spectra of oxy- and deoxy-hemoglobin. Tumors typically have higher total hemoglobin and lower oxygen saturation owing to angiogenesis and hypermetabolism. Using sequential, multiple wavelength illumination, PMI can provide the same functional information as DOI or PAT, but at MRI resolution ($\sim 1 \text{ mm}$) and can make an impact on the clinical management of cancer by minimizing unnecessary biopsy. Although PAT can currently provide higher resolution than PMI at superficial depths, its performance degrades with depth.¹³ PMI, on the other hand, has no fundamental degradation of resolution with imaging depth. Primary applications may be breast, prostate, and lymph node imaging. Additionally, using exogenous contrast agents such as gold nanoparticles or FDA approved indocyanine green (ICG), the contrast between malignant and benign tissue can be enhanced such as in fluorescence optical imaging and multi-spectral photoacoustic imaging.^{20–24}

The laser illumination pattern and MRI data acquisition scheme can be further improved for better imaging quality and temporal resolution. Results shown thus far have only been qualitative, however, an algorithm is being developed that applies the model of light transport and heat transfer iteratively and converges on a quantitative estimate of the

optical absorption. Most importantly, PMI measurements obtained throughout the whole volume may alleviate the under-determinedness and ill-posedness of the conventional optical inverse problem, which has hampered the use of DOI clinically. Hence, PMI is expected to provide high resolution images with quantitative accuracy.

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