A calibration-free, one-step method for quantitative photoacoustic tomography

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Purpose: Recently reported quantitative photoacoustic tomography (PAT) has significantly expanded the utilities of PAT because it allows for recovery of tissue optical absorption coefficient which directly correlates with tissue physiological information. However, the recovery of optical absorption coefficient by the existing quantitative PAT approaches strongly depends on the accuracy of absorbed energy density distribution, and on the knowledge of accurate strength and distribution of incident light source. The purpose of this study is to develop a new algorithm for the reconstruction of optical absorption coefficient that does not depend on these initial parameters.

Methods: Here the authors propose a novel one-step reconstruction approach that can directly recover optical absorption coefficient from photoacoustic measurements along boundary domain. The authors validate the method using simulation and phantom experiments.

Results: The authors have demonstrated experimental evidence that it is possible to directly recover optical absorption coefficient maps using boundary photoacoustic measurements coupled with the photon diffusion equation in just one step. The authors found that the method described is able to quantitatively reconstruct absorbing objects with different sizes and optical contrast levels.

Conclusions: Compared to the authors' previous two-step methods, the reconstruction results obtained here show that the one-step scheme can significantly improve the accuracy of absorption coefficient recovery. © 2012 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4760981>]

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Biomedical photoacoustic tomography (PAT), as a future imaging modality, can visualize the internal structure and function of soft tissues in multiscale (from millimeters to centimeters) with high spatial resolution and excellent optical contrast.^{1–3} While conventional PAT can image tissues with high spatial resolution, it recovers only the distribution of absorbed light energy density that is the product of tissue optical absorption coefficient and local optical fluence. Recently reported quantitative PAT (qPAT) (Refs. 4–14) has significantly expanded the utilities of PAT as it allows for recovery of tissue absorption coefficient which directly correlates with tissue physiological information. All these methods for qPAT require a model-based reconstruction algorithm or model-free method to first capture the map of absorbed energy density or initial pressure. Then under various assumptions, the absorption coefficient is deduced from the obtained absorbed energy density/initial pressure through the photon diffusion equation or a measurement technique that can provide the distribution of exciting fluence.

However, there are several fundamental limitations associated with the existing qPAT techniques. First, one has to know the exact boundary reflection coefficients as well as the exact strength and distribution of a specified incident light source associated with the photon diffusion/transport model. It requires careful experimental calibration procedures in order to

obtain these initial parameters. Second, the recovered optical absorption coefficient also strongly depends on the accuracy of the distribution of absorbed energy density. Generally, it is a challenging task to obtain an exact distribution of absorbed energy density due to several reasons: the limited bandwidth of ultrasound transducers for ultrawideband photoacoustic frequency response, dependency on the orientation, size, and shape of the targets with respect to the ultrasound receiving aperture, and effect of the optical scattering. Finally, an optical measurement method for measuring the optical fluence will increase the complexity and cost of hardware systems.¹²

To overcome the limitations mentioned above, here we propose a novel one-step reconstruction approach that can directly recover optical absorption coefficient from photoacoustic measurements along boundary domain. We validate the method using simulations as well as phantom experiments.

The photoacoustic wave equation in frequency domain for an acoustically homogeneous medium is written as (note that the method described here can be easily extended to time domain or acoustically heterogeneous cases),

$$\begin{aligned}\nabla^2 p(r, \omega) + k_0^2 p(r, \omega) &= ik_0 \frac{c_0 \beta \mu_a \Phi}{C_p} \text{ or} \\ \nabla^2 p(r, \omega) + k_0^2 p(r, \omega) &= ik_0 \frac{c_0 \beta E}{C_p}\end{aligned}\quad (1)$$

where p is the pressure wave; $k_0 = \omega/c_0$ is the wave number described by the angular frequency, ω and the speed of acoustic wave in the medium, c_0 ; β is the thermal expansion coefficient; C_p is the specific heat; E is the absorbed light energy density, which is the product of absorption coefficient μ_a and optical fluence Φ ($E = \mu_a \Phi$). Based on the finite element solution to Eq. (1),⁹ we use Marquardt–Tikhonov regularization based Newton method to directly recover/update absorption coefficient from an initial guess of $\mu_{a,0}$ by minimizing an objective function composed of a sum of the squared difference between computed and measured acoustic pressure around the boundary areas given by

$$\text{Min: } F = \sum_{j=1}^L \sum_{i=1}^M (p_i^o(j) - p_i^c(j))^2. \quad (2)$$

As a consequence, for each of the L frequencies, the complex matrix equation for the forward problem in Eq. (1) is stated as

$$\mathbf{A}_{N \times N} \mathbf{P}_N = \mathbf{B}_N. \quad (3)$$

And the following matrix equation capable of inverse solution of μ_a , is obtained for the inverse calculation:⁹

$$(\mathfrak{J}^T \mathfrak{J} + \lambda \mathbf{I}) \Delta \chi = \mathfrak{J}^T (\mathbf{p}^o - \mathbf{p}^c), \quad \mu_a = \mu_{a,0} + \zeta \Delta \chi \quad (4)$$

where $\mathbf{p}^o = \sum_{j=1}^L (p_1^o(j), p_2^o(j), \dots, p_M^o(j))^T$ and $\mathbf{p}^c = \sum_{j=1}^L (p_1^c(j), p_2^c(j), \dots, p_M^c(j))^T$ in which complex $p_i^o(j)$ and $p_i^c(j)$ are observed and computed normalized acoustic measurements for $i = 1, 2, \dots, M$ boundary locations with frequency j ,⁹ and N is the nodal number of the finite element mesh in the entire problem domain; $\Delta \chi$ (dimension: N) is the update vector for μ_a ; $\mathfrak{J}$ (dimension: $(L \times 2M) \times N$) is the Jacobian matrix formed by $\partial p / \partial \mu_a$ at the boundary measurement sites; λ is a scalar; ζ is calculated from common backtracking line search¹⁵ and $\mathbf{I}$ is the identity matrix. In consideration of $E = \mu_a \Phi$, the sensitivity of pressure to absorption coefficient ($\partial p / \partial \mu_a$) equals the product of the sensitivity of pressure to energy density ($\partial p / \partial E$) in full field and the sensitivity of energy density to absorption coefficient ($\partial E / \partial \mu_a$) in local field. Specifically, the elements in Jacobian matrix $\mathfrak{J}$ are determined by

$$\begin{aligned} & \frac{\partial p_i}{\partial \mu_{a,j}} \\ &= \sum_{k=1}^N \left(\frac{\partial p_i}{\partial E_k} \frac{\partial E_k}{\partial \mu_{a,j}} \right) \quad (i = 1, 2, \dots, M; j, k = 1, 2, \dots, N) \end{aligned} \quad (5)$$

in which the sensitivities of $\partial p / \partial E$ in each iteration can be calculated from Eq. (3) based on the adjoint method:⁹

$$[\mathbf{A}] \left\{ \frac{\partial p}{\partial E} \right\} = \left\{ \frac{\partial B}{\partial E} \right\} - \left[\frac{\partial A}{\partial E} \right] \{P\}. \quad (6)$$

Noted here $[\partial A / \partial E] = 0$ and the derivatives $\partial E / \partial \mu_a$ in Eq. (5) are further written as

$$\frac{\partial E_k}{\partial \mu_{a,j}} = \begin{cases} \Phi_k + \mu_{a,k} (\partial \Phi_k / \partial \mu_{a,j}) & \text{if } (k = j) \\ \mu_{a,k} (\partial \Phi_k / \partial \mu_{a,j}) & \text{if } (k \neq j) \end{cases}. \quad (7)$$

And photon fluence Φ in Eq. (7) can be computed by the finite element solution to the following photon diffusion equation:

$$\nabla \cdot D(r) \nabla \Phi(r) - \mu_a(r) \Phi(r) = -S(r) \quad (8)$$

in which $S(r)$ is the normalized light source term, $D(r)$ is the diffusion coefficient and is considered a constant here. The finite element discretized form of Eq. (8) is written as,

$$[\mathbf{K}]_{N \times N} \{\Phi\}_N = \{b\}_N. \quad (9)$$

Based on Eq. (9), the sensitivity $\partial \Phi / \partial \mu_a$ in Eq. (7) is obtained from the following equation in the whole problem domain using adjoint method:

$$[\mathbf{K}] \left\{ \frac{\partial \Phi}{\partial \mu_a} \right\} = - \left[\frac{\partial \mathbf{K}}{\partial \mu_a} \right] \{\Phi\}. \quad (10)$$

Thus the absorption coefficient distribution can be reconstructed through a Newton iterative solution procedure described by Eq. (3) (forward solution) and Eq. (4) (inverse solution) to minimize the objective function in Eq. (2). Equations (5)–(10) are employed to calculate the Jacobian matrix in Eq. (4), and Eqs. (2)–(4) are solved separately for each iteration. The regularization parameter is determined by combined Marquardt and Tikhonov regularization schemes.⁹ We have found that when $\lambda = (\mathbf{p}^o - \mathbf{p}^c) \times \text{trace}(\mathbf{J}^T \mathbf{J})$, the reconstruction algorithm generates the best results for PAT image reconstruction.

The image formation process described above is first tested using simulated data. The test geometry is shown in Fig. 1(a) where a two-dimensional circular background region (50.8 mm in diameter) contained four circular targets (5 mm in diameter each). The optical properties for the background were absorption coefficient $\mu_a = 0.01 \text{ mm}^{-1}$ and reduced scattering coefficient $\mu'_s = 1.0 \text{ mm}^{-1}$, while the optical properties were $\mu_a = 0.2 \text{ mm}^{-1}$ and $\mu'_s = 1.0 \text{ mm}^{-1}$ for the top left and bottom right targets, and $\mu_a = 0.1 \text{ mm}^{-1}$ and $\mu'_s = 1.0 \text{ mm}^{-1}$ for the top right and bottom left targets. In the simulation, a homogeneously distributed area source was utilized to illuminate the whole imaging domain, the same as in our experiments. A total of 120 ultrasound receivers were equally distributed along the boundary of background region.

For the phantom experiments, a pulsed light from a Nd:YAG laser (wavelength: 532 nm, pulse duration: 3–6 ns; Altos, Bozeman, MT) was sent to the top surface of the cylindrical phantom via an optical subsystem and consequently generated acoustic signals.⁹ A transducer (1 MHz central frequency; GE Panametrics, Waltham, MA) and the phantom were immersed in a water tank. A rotary stage rotated the transducer relative to the center of the tank. The incident optical fluence was controlled below 10 mJ/cm^2 and the incident laser beam diameter was 5 cm. The complex wavefield signal was first amplified by a preamplifier (gain: 17 dB, 5 kHz to 25 MHz; Onda, Corporation, Sunnyvale, CA), and then amplified further by a Pulser/Receiver (GE Panametrics, Waltham, MA). In the experimental tests, we embedded one or two objects with a size ranging from 0.5 to 3 mm in the 5-cm-diameter solid cylindrical phantom. The phantom materials used consisted of Intralipid as scatterer and India ink as

FIG. 1. Exact distribution of optical absorption coefficient μ_a (a) exact distribution of energy density (b), the recovered μ_a image using the new method (c), and recovered optical absorption profile plotted along $y = 7.5$ mm from the image shown in Fig. 1(c) (d). The axes (left and bottom) illustrate the spatial scale, in mm, whereas the gray scale (right) records the normalized absorbed energy density in arbitrary units, or μ_a in mm^{-1} .

absorber with Agar powder (1%–2%) for solidifying the Intralipid and India ink solution. We then immersed the object-bearing solid phantom into the water tank. The absorption of the background phantom was 0.01 mm^{-1} , while the absorption coefficient of the target(s) was 0.03 mm^{-1} . The reduced scattering coefficients of the background medium and target(s) were 1.0 and 3.0 mm^{-1} , respectively. As a final test, we placed human hair-containing phantom (four hairs) into the water tank to show the high resolution imaging capability of the developed scheme. The initial guess for the μ_a is 0.005 mm^{-1} for the experimental tests. It is noted that constant Gruneisen function $\Gamma = c_0^2 \beta / C_p$, acoustic velocity ($c_0 = 1495 \text{ m/s}$), and reduced scattering coefficient (1.0 mm^{-1}) were employed for all the reconstructions using both simulated and phantom data.

The results from simulated data are shown in Fig. 1, where Figs. 1(a) and 1(b) provide the exact distribution of μ_a and absorbed energy density, respectively, while Fig. 1(c) presents the reconstructed μ_a image using the one-step qPAT algorithm. We can see from Fig. 1(c) that the targets are clearly identified in terms of the target position, size, and absorption coefficient value. The target size was estimated to be 4.6 mm in diameter using the full width at half-maximum (FWHM) of the recovered μ_a profile in Fig. 1(d).

It is also observed from Fig. 1(b) that the influence of the inhomogeneous distribution of optical fluence on the energy density map is apparent, where low values of energy density appear in the center area of the four targets and results in hollow phenomena for the solid targets. However, the absorption coefficient map shown in Fig. 1(c) indicates that the new method has the capability to completely remove effect of the heterogeneous distribution of local fluence.

The results from the first experiment are shown in Fig. 2, where Figs. 2(a) and 2(b) show the recovered μ_a maps using the previous⁹ and present qPAT methods, respectively. By estimating the FWHM of the specific profiles for the images shown in Fig. 2(b), we found the recovered object sizes were 1.9 and 3.1 mm , which are in good agreement with the actual object sizes of 2.0 and 3.0 mm . Figure 3 plots the reconstructed absorption coefficient images for experimental test 2 using both the previous⁹ and present qPAT schemes. The recovered target size using the present and previous schemes, as shown in Fig. 3(c), was found to be 0.55 and 0.8 mm , respectively, compared to the actual target size of 0.5 mm . Obviously the previous method overestimated the target size in most cases. We also found from Figs. 2 and 3 that the current qPAT method is able to considerably reduce the effect of local optical fluence and boundary noise. Further, it is

FIG. 2. Reconstructed μ_a image using the previous scheme (a), the new scheme (b), and recovered optical absorption profile plotted along $y = -7.0$ mm from the images shown in Figs. 2(a) and 2(b) (c). The axes (left and bottom) illustrate the spatial scale, in mm, whereas the gray scale (right) records μ_a in mm^{-1} .

FIG. 3. Reconstructed μ_a images using (a) the previous, (b) new scheme, and (c) recovered optical absorption profile plotted along $y = 1.0$ mm from the images in (a) and (b).

observed from Fig. 4 that based on the developed scheme, the human hairs embedded in phantom are clearly identified with submillimeter resolution and quantitative absorption coefficient.

In summary, we have demonstrated experimental evidence that it is possible to directly recover the absolute μ_a image using boundary photoacoustic measurements coupled with the photon diffusion equation in just one step. The method described is able to quantitatively reconstruct absorbing objects with different sizes and optical contrast levels. In particular, it is noted that this method does not depend on any calibration procedure because it allows for the use of relative incident laser source strength and normalized boundary measurements of acoustic pressure. The source intensity and boundary condition coefficient can be optimized and localized based on the photon diffuse equation by minimizing f with the normalized acoustic measurements $\bar{p}$: $f = \sum_{i=1}^M ((\mu_a \Phi)_i - \bar{p}_i)^2$. As such, the reconstruction of absorption coefficient with the new algorithm does not depend on the absolute val-

ues of absorbed energy density and optical fluence whereas the previous methods are all dependent on these values. Additionally, we note that different transducer sensitivity may lead to a different scaling factor of the reconstructed absorption coefficient images. Routine calibrations on the transducer response had to be done in our previous study.⁹ However, in the new scheme presented here, we use normalized acoustic data in arbitrary units (i.e., the largest value of pressure is 1.0) to recover the absorption coefficient, reducing the impact of transducer sensitivity significantly. It should be pointed out, however, that the choice of the initial guess of μ_a does have some effect on the recovered results. Finally, further investigation is warranted to consider optical scattering, inhomogeneous acoustic properties, inhomogeneous light illumination field, and multispectral photoacoustic measurements within the framework of this new method.

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FIG. 4. The recovered μ_a image for the human hair phantom.

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¹L. V. Wang and H. Wu, *Biomedical Optics: Principles and Imaging* (Wiley, New York, 2007).

²G. Paltauf and H. Schmidt-Kloiber, "Pulsed optoacoustic characterization of layered media," *J. Appl. Phys.* **88**, 1624–1631 (2000).

³A. A. Oraevsky, S. L. Jacques, and F. K. Tittel, "Measurement of tissue optical properties by time-resolved detection of laser-induced transient stress," *Appl. Opt.* **36**, 402–415 (1997).

⁴R. Zemp, "Quantitative photoacoustic tomography with multiple optical sources," *Appl. Opt.* **49**, 3566–3572 (2010).

⁵Y. Yuan, S. Yang, and D. Xing, "Optical-resolution photoacoustic microscopy based on two-dimensional scanning galvanometer," *Appl. Phys. Lett.* **100**, 023702 (2012).

⁶B. Cox, S. Arridge, K. Kostli, and P. Beard, "2D quantitative photoacoustic image reconstruction of absorption distributions in scattering medium using a simple iterative method," *Appl. Opt.* **45**, 1866–1875 (2006).

- ⁷C. Xu, P. Kumavor, A. Aguirre, and Q. Zhu, "Quantitative recovery of absorption coefficient using DOT-assisted photoacoustic tomography for breast imaging," in *BsuD in OSA Biomedical Optics Topical Meeting*, Miami, FL, 2010.
- ⁸B. Banerjee, S. Bagchi, R. M. Vasu, and D. Roy, "Quantitative photoacoustic tomography from boundary pressure measurements: Non iterative recovery of optical absorption coefficient from the reconstructed absorbed energy map," *J. Opt. Soc. Am. A* **25**, 2347–2356 (2008).
- ⁹Z. Yuan and H. Jiang, "Quantitative photoacoustic tomography: Recovery of optical absorption coefficient map of heterogeneous medium," *Appl. Phys. Lett.* **88**, 231101 (2006).
- ¹⁰Z. Yuan, Q. Wang, and H. Jiang, "Reconstruction of optical absorption coefficient map of heterogeneous media by photoacoustic tomography coupled diffusion equation based regularized Newton method," *Opt. Express* **15**, 18076–18081 (2007).
- ¹¹B. T. Cox, J. G. Laufer, and P. C. Beard, "Quantitative photoacoustic image reconstruction using fluence dependent absorbers," *Biomed. Opt. Express* **1**, 201–208 (2010).
- ¹²L. Yin, Q. Wang, Q. Zhang, and H. Jiang, "Tomographic imaging of absolute optical absorption coefficient in turbid medium using combining photoacoustic and diffusing light measurements," *Opt. Lett.* **32**, 2556–2558 (2007).
- ¹³G. Bal and G. Uhlmann, "Inverse diffusion theory of photoacoustics," *Inverse Probl.* **26**, 085010 (2010).
- ¹⁴H. Gao, H. Zhao, and S. Osher, "Quantitative photoacoustic tomography," University of California Los Angeles (UCLA) Computational and Applied Mathematics Reports (UCLA, 2011), Vols. 11–28.
- ¹⁵Z. Yuan and H. B. Jiang, "An image reconstruction scheme that combines modified Newton method and efficient initial guess estimation for optical tomography of finger joints," *Appl. Opt.* **46**, 2757–2768 (2007).