Region-based diffuse optical tomography with registered atlas: *in vivo* acquisition of mouse optical properties

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**Abstract:** The reconstruction quality in the model-based optical tomography modalities can greatly benefit from *a priori* information of accurate tissue optical properties, which are difficult to be obtained *in vivo* with a conventional diffuse optical tomography (DOT) system alone. One of the solutions is to apply *a priori* anatomical structures obtained with anatomical imaging systems such as X-ray computed tomography (XCT) to constrain the reconstruction process of DOT. However, since X-ray offers low soft-tissue contrast, segmentation of abdominal organs from sole XCT images can be problematic. In order to overcome the challenges, the current study proposes a novel method of recovering *a priori* organ-oriented tissue optical properties, where anatomical structures of an *in vivo* mouse are approximately obtained by registering a standard anatomical atlas, *i.e.*, the Digimouse, to the target XCT volume with the non-rigid image registration, and, in turn, employed to guide DOT for extracting the optical properties of inner organs. Simulative investigations have validated the methodological availability of such atlas-registration-based DOT strategy in revealing both *a priori* anatomical structures and optical properties. Further experiments have demonstrated the feasibility of the proposed method for acquiring the organ-oriented tissue optical properties of *in vivo* mice, making it as an efficient way of the reconstruction enhancement.

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**OCIS codes:** (110.2960) Image analysis; (170.3010) Image reconstruction techniques; (170.6960) Tomography; (170.3880) Medical and biological imaging.

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1. Introduction

In the model-based optical tomography regime, such as functional diffuse optical tomography (DOT) and small-animal fluorescence molecular tomography (FMT), the fidelity and sensitivity of image reconstruction highly depend on the knowledge of tissue optical heterogeneities for correct modeling of light propagation [1–3]. The common approach that assumes a homogenous optical background definitely exerts adverse effects on the reconstruction sensitivity and accuracy. One of the solutions is to use region- or shape-based DOT to in vivo estimate the optical properties with the support from a priori anatomical structures, and then incorporate them into the forward calculation to enhance the underlying reconstruction [3–6]. Although this method can effectively overcome the limitations of conventional voxel-based DOT in spatial-resolution and quantification [7], its successful application is critically influenced by the reasonability and accuracy of a priori target anatomical structures adopted in the computation.

In principle, in vivo acquisition of a priori target anatomical structures can be performed with commonly used anatomical imaging modalities, such as X-ray computed tomography (XCT) or magnetic resonance imaging (MRI), within the framework of multi-modality imaging mechanisms [8–11]. Although it has been extensively reported that a priori anatomical structures obtained from XCT or MRI are effective in constraining the reconstruction of DOT/FMT through structured regularizations, e.g., hard-priori, Laplacian/Helmholtz-type, or weighted segment scheme, etc [6, 8, 12–15], they are less applicable to in vivo acquisition task of the optical properties in a whole body, since the requested accurate and complete anatomical structures are unavailable due to XCT inefficiency in soft-tissue contrasting [16] or MRI incapability in skeleton differentiation [17].

On the other hand, substantial efforts have been made on accurate acquisition of standard (generic) mouse anatomical atlases, i.e., the Digital Mouse. Segars et al have developed the MOBY atlas, a realistic and flexible four dimensional digital mouse phantom created from magnetic resonance microscopy and MRI data sets [18]. Dhenain et al have presented the archetypal digital atlas of mouse embryo based on micro-MRI [19]. The accurate anatomical structure can also be obtained by a combination of XCT with other imaging modalities. Dogdas et al have provided the Digimouse atlas, a three-dimensional (3-D) organ-labeled whole body tetrahedron-tessellated mesh constructed from co-registered XCT, positron emission tomography (PET) and cryosection images [20].

Despite of being able to accurately obtain a realistic anatomical atlas, direct incorporation of the aforementioned methodologies into the DOT/FMT workflow greatly increases both the experimental complexity and the system cost. Nevertheless, the published atlases hold great promise of helping researchers reasonably localize organs in a target mouse through an image
registration strategy, as having been similarly demonstrated in brain functional near-infrared spectroscopy and MRI [21, 22], as well as in radiation therapy [23].

Oriented toward in vivo acquisition of a priori organ-oriented tissue optical properties of a whole-body mouse, we propose herein an atlas-registration-based DOT strategy in the combination of the registration-based anatomy acquisition and the previously developed region-based optical properties extraction [4]. The whole process includes two phases, namely, a non-rigid image registration procedure for a priori anatomical structures creation and an organ-constrained reconstruction for recovering the a priori optical properties. The validity and applicability of the proposed method are firstly demonstrated using simulated scenarios, and then a pilot experiment is performed on living mouse models that, to the best of our knowledge, presents the first in vivo measurement of the optical properties of the major organs.

2. Methodology

Figure 1 depicts two phases of the proposed atlas-registration-based DOT strategy:

In phase I, the whole-body XCT slices of the target mouse are firstly obtained through a micro-CT system, and assembled into the target volume, with its voxel positions denoted as a $3 \times N$ matrix, $V^{(t)} = [v_1^{(t)}, v_2^{(t)}, ..., v_N^{(t)}]$, where $v_n^{(t)}$ ($n = 1, 2, ..., N$) is the coordinate vector of the n-th voxel. Then the standard volume, i.e., the three dimensional XCT data set collected for generating the Digimouse atlas [20], with its voxel positions similarly defined as $V^{(s)} = [v_1^{(s)}, v_2^{(s)}, ..., v_N^{(s)}]$, are registered to the target volume by the 3-D non-rigid registration method described in subsection 2.1. In the method, the displacement field is generated by a two-step process of the pre-registration based on point-matching and the post-registration based on block-matching. Finally, the displacement field is applied to the standard atlas to approximately construct the target atlas, i.e., a priori anatomical structures of the target mouse.

In phase II, a three-dimensional time-domain (TD)-DOT measurement is further conducted on the same target mouse, from which its organ optical properties are reconstructed by a region-based featured-data scheme for TD-DOT, which is developed within the framework of the modified generalized pulse spectrum technique (GPST) [24]. In this algorithm, the TD-DOT inversion is Laplace-transformed to complex-frequency domain and the registered standard atlas is then incorporated to regularize the original voxel-based reconstruction in the hard-prior scheme [25].

2.1 Non-rigid image registration for target atlas creation

This phase is accomplished with two successive steps, referred to as the pre-registration based on point-matching and the post-registration based on block-matching, as illustrated in Fig. 2.
Step 1: pre-registration based on point-matching

Prior to the pre-registration, the Cartesian coordinate systems are established for the standard mouse and the target mouse, separately, with the coordinate origin set at the center of the XCT slice where the top of the mouse head locates on, and the x-, y- and z-axes pointing to the back, the right side and the tail of the mouse, respectively. With the coordinate systems, both the bone landmarks and surface landmarks of the standard and target mice are determined from their respective XCT volumes, separately. The process include a thresholding for the skeleton and tissue region segmentation, a seed-filling for hole remedy, a contour detecting for skeleton and mouse surface extraction, and finally a random sampling for bone and surface landmark selection. Then, the bone landmarks of the standard mouse \( \mathbf{B}^{(s)} = [\mathbf{b}_{s}^{(s)}, \mathbf{b}_{s}^{(s)}, \ldots, \mathbf{b}_{N_{s}}^{(s)}] \), with \( \mathbf{b}_{i}^{(s)} = [x_{i}^{bs}, y_{i}^{bs}, z_{i}^{bs}]^{T} \) being the \( i \)-th landmark coordinates, are registered to those of the target mouse \( \mathbf{B}^{(t)} = [\mathbf{b}_{t}^{(t)}, \mathbf{b}_{t}^{(t)}, \ldots, \mathbf{b}_{N_{t}}^{(t)}] \), with \( \mathbf{b}_{j}^{(t)} = [x_{j}^{bt}, y_{j}^{bt}, z_{j}^{bt}]^{T} \) being the \( j \)-th landmark coordinates, using the Thin Plate Spline-Robust Point Matching (TPS-RPM) algorithm [26]. The algorithm aims at minimizing the fuzzy-assignment least-squares energy function as follows

\[
E(C, f) = \sum_{i=1}^{N_{s}} \sum_{j=1}^{N_{t}} c_{ij} || \mathbf{b}_{i}^{(s)} - f(\mathbf{b}_{j}^{(t)}) ||^{2} + \lambda T || Lf ||^{2} + T \sum_{i=1}^{N_{s}} \sum_{j=1}^{N_{t}} c_{ij} \log c_{ij} + T_{0} \sum_{i=1}^{N_{s}} c_{iN_{t}+1} \log c_{iN_{t}+1} + T_{0} \sum_{i=1}^{N_{t}} c_{N_{s}+1, i} \log c_{N_{s}+1, i} + T_{0} \sum_{i=1}^{N_{s}} c_{iN_{t}+1} \log c_{iN_{t}+1}
\]

where \( C \) is a \((N_{s}+1) \times (N_{t}+1)\) fuzzy correspondence matrix, with its entries \( c_{ij} \in [0, 1] \); the inner \( N_{s} \times N_{t} \) matrix of \( C \) indicates the correspondence between \( \mathbf{b}_{i}^{(s)} \) and \( \mathbf{b}_{j}^{(t)} \), and the \((N_{s} + 1)\)-th row and the \((N_{t} + 1)\)-th column of \( C \) are used to handle the outliers, i.e., the points which cannot be matched, in both landmarks; \( T \) is the temperature parameter with \( T_{0} \) being its initial value; \( f \) is the thin plate spline (TPS) transformation function; \( L \) is a second derivative operator that places appropriate constraints with the smooth measure || Lf ||^2; \( \lambda \) is a weight parameter for controlling the non-rigidity of the TPS transformation. Normally, minimization of Eq. (1) is solved with a deterministic annealing technique that alternately updates the correspondence matrix \( C \) and transformation function \( f \) while gradually reducing the temperature parameter \( T \). In the process, the fuzzy correspondence matrix \( C \) is updated by...
\[
\begin{align*}
\mu_{ij} & = \frac{1}{T} \exp\left(-\frac{\|b_i(j) - f(j)^{(s)}\|^2}{2T}\right) \quad \text{for } i=1,2,\ldots,N_b \text{ and } j=1,2,\ldots,N_s \\
\mu_{ij} & = \frac{1}{T_0} \exp\left(-\frac{\|b_{N_b+1}(j) - f(j)^{(s)}\|^2}{2T_0}\right) \quad \text{for } i=1,2,\ldots,N_b \text{ and } j=N_b+1 \\
\mu_{ij} & = \frac{1}{T_0} \exp\left(-\frac{\|b_i(j) - f(j)^{(s)}\|^2}{2T_0}\right) \quad \text{for } i=N_b+1 \text{ and } j=1,2,\ldots,N_s
\end{align*}
\]

where \(b_i(j)^{(s)}\) and \(b_{N_b+1}(j)^{(s)}\) are the centroid of \(B^{(s)}\) and \(B^{(s)}\) separately. Normalization is performed to \(C\) for satisfying the constraints \(\sum_{j=1}^{N_s} \mu_{ij} = 1 \) for \(j=1,2,\ldots,N_b\) and \(\sum_{i=1}^{N_b} \mu_{ij} = 1 \) for \(i=1,2,\ldots,N_s\). On updating \(f\), an estimated point set \(B^{(s)} = [b_1(j)^{(s)}, b_2(j)^{(s)}, \ldots, b_{N_b}(j)^{(s)}]\) corresponding to the standard bone landmarks \(B^{(s)}\) is calculated by the \(C\)-weighted sum of the target bone landmarks \(B^{(s)}\)

\[
b_i(j)^{(s)} = \sum_{j=1}^{N_b} \mu_{ij} b_j(j)^{(s)}
\]

and \(f\) is updated by minimizing the TPS bending energy function [26], to achieve the final TPS transformation from \(B^{(s)}\) to \(B^{(s)}\). When \(T\) is lower than the limit, the final estimated point set \(B^{(s)}\) can be regarded as the pre-registered bone landmarks. Analogously, the pre-registered surface landmarks \(S^{(s)}\) can be established by registering the \(N_s\) surface landmarks of the standard mouse \(S^{(s)}\) to those of the target mouse \(S^{(s)}\).

With the aforementioned point-matching procedures, a \(3 \times (N_b + N_s)\) matrix representing the displacement of the bone and the surface landmarks,

\[
L^{(pre)} = [B^{(s)} - B^{(s)}, S^{(s)} - S^{(s)}]
\]

is formulated for the standard volume to calculate the pre-registration displacement field \(D^{(pre)} = [d_1^{(pre)}, d_2^{(pre)}, \ldots, d_N^{(pre)}]\), i.e., a \(3 \times N\) matrix assembling the displacement vectors, \(d_n^{(pre)}\) \((n=1,2,\ldots,N)\), of all the \(N\) voxels in the standard volume. The approach is realized by Free-form Deformation (FFD) method [27] where the displacement vector of the \(n\)-th voxel \(d_n^{(pre)}\) is calculated by a multi-level B-spline interpolation function which is formed by the summation of a sequence of tri-cubic functions generated by a coarse-to-fine hierarchy of control lattices [28].

The pre-registered standard atlas, \(A^{(pre)} = [a_1^{(pre)}, a_2^{(pre)}, \ldots, a_{N_a}^{(pre)}]\), is thereby obtained by moving the \(N_a\) nodes of the standard atlas, \(A^{(s)} = [a_1^{(s)}, a_2^{(s)}, \ldots, a_{N_a}^{(s)}]\), in terms of its corresponding displacement \(d_j^{(pre)}\)

\[
a_i^{(pre)} = a_i^{(s)} + d_j^{(pre)}
\]

where \(d_j^{(pre)}\) is the displacement vector of the \(j\)-th voxel in the standard volume, whose coordinate \(v_j^{(s)}\) is nearest to \(a_j^{(s)}\), i.e., \(j\) is indexed by a minimum norm criterion

\[
\min_j \|a_j^{(s)} - v_j^{(s)}\|.
\]
Step 2: post-registration based on block-matching

In this step, the post-registration is applied based on the block-matching method to refine the pre-registered standard atlas, where the voxel intensities are utilized as additional information:

Firstly, the pre-registered standard volume is built by transforming the standard volume according to $D^{(pre)}$ with the forward mapping method [29], where voxels in the standard volume are moved to new positions, i.e., $V' = V^{(i)} + D^{(pre)}$, and interpolated onto the voxel positions $V^{(t)}$ of the target volume to obtain the pre-registered standard volume. Analogously, surface and skeleton of the mouse in the pre-registered standard volume are extracted with thresholding, seed-filling and contour extraction.

Then the pre-registered standard volume is evenly divided into blocks with each being a $N_x \times N_y \times N_z$ sub-volume. $N_f$ blocks whose center points $P^{(pre)}_1, P^{(pre)}_2, \ldots, P^{(pre)}_{N_f}$ locates on the extracted skeleton and surface in the pre-registered standard volume are selected as the feature blocks. The feature blocks are registered to the most similar blocks in the target volume by the block-matching method which is widely used in motion estimation [30]. The 3-D correlation coefficient is chosen as the similarity metric. The most similar target block of a feature block centered at $P^{(pre)}_{i}$ is found by Exhaustive Search (ES) method [30], where similarities between the feature block and all the possible blocks in the search region, i.e., a larger sub-volume centered at $P^{(pre)}_{i}$ in the target volume, are calculated in the process. The size of search region is chosen as $2N_x \times 2N_y \times 2N_z$ voxels for guaranteeing the preservation of topology through limiting the center of the most similar block $P^{(post)}_{i}$ locates within the $P^{(pre)}$ centered feature block.

Thereafter, a $3 \times N_f$ matrix representing the displacement of the feature blocks is calculated

$$L^{(post)} = P^{(pre)} - P^{(post)}$$

where $P^{(post)}=[P^{(post)}_1, P^{(post)}_2, \ldots, P^{(post)}_{N_f}]$. Analogously, the post-registration displacement field $D^{(post)}=[d^{(post)}_1, d^{(post)}_2, \ldots, d^{(post)}_{N_f}]$ can be calculated through interpolating $L^{(post)}$ onto the coordinates of pre-registered standard voxels, $V^{(pre)}$. The registered standard atlas, i.e. the target atlas, $A^{(t)}=[a^{(t)}_1, a^{(t)}_2, \ldots, a^{(t)}_{N_t}]$ is finally obtained by moving the $N_t$ nodes of the pre-registered standard atlas $A^{(pre)}$ in terms of its corresponding displacement $d^{(post)}_j$

$$a^{(t)}_i = a^{(pre)}_i + d^{(post)}_j$$

where $d^{(post)}_j$ is the displacement vector of the $j$-th voxel in the pre-registered volume, whose coordinate $V^{(pre)}_j$ is nearest to $a^{(pre)}_i$, i.e., $j$ is indexed by the minimum norm criterion: $\min_j \|a^{(pre)}_i - V^{(pre)}_j\|$.

2.2 Organ-constrained reconstruction for a priori optical properties recovery

Although, the effective separation of the absorption and scattering effects can be in principle achieved by both TD and frequency-domain (FD) modes, the FD one generally requires a high modulation frequency of $>300$ MHz for small-animal applications, which would lead to low stability and high expense in instrumentation, as well as difficulties in measurement and
theory due to the exponential decay of the alternating-current amplitude with the frequency.

On overall consideration, we adopt the TD-DOT for the task.

As aforementioned, the reconstruction of the optical properties is developed within the GPST framework for TD-DOT, where Laplace-transforms is used to convert the TD signals into the complex-frequency domain, or, for computational simplicity, into the imaginary frequency (real-number) domain, and inverts the transformed diffusion-equation (DE) for at least two frequencies to effectively separate the absorption and scattering [24]. In comparison to the full time-resolved scheme that may generate improved image quality [34], this featured-data scheme performs more robustly owing to its insensitivity to the time-origin uncertainty and its exception from the reference measurements [35].

In the GPST-based reconstruction, the ratio between the Laplace transformed measurements at two distinct real-domain frequencies \( p_1 \) and \( p_2 \) is used as the data-type \( R(\xi_1, \zeta_1) = \Gamma(\xi_1, \zeta_1, p_1) / \Gamma(\xi_2, \zeta_2, p_2) \), where \( \Gamma(\xi_1, \zeta_1, p) = \int_0^\infty \Gamma(\xi_1, \zeta_1, t) e^{-pt} dt \); \( \Gamma(\xi_1, \zeta_1, t) \) is the TD-measurement; \( \zeta_1 \) (s = 1,2,...,S) and \( \xi_2 \) (d = 1,2,...,D) index the S source positions and D detector positions on the imaging domain, respectively. The imaging equation is expressed in the following iterative format

\[
R - F(\mu^{(k)}) = \mathbf{J}^{(k)} \Delta \mu^{(k)}, \quad \mu^{(k+1)} = \mu^{(k)} + \Delta \mu^{(k)}
\]  

(8)

where \( R \) being a column vector that presents \( R(\xi_1, \zeta_1) \) for all the \( M \) source-detector pairs; \( F(\mu^{(k)}) \) denotes the forward operator which is the ratio between the Laplace transformed DE solution at \( p_1 \) and \( p_2 \); \( \mu^{(k)} \) denote optical properties in the \( N_a \) nodes at the k-th iteration stage with \( \Delta \mu^{(k)} \) denoting their perturbations; \( \mathbf{J}^{(k)} = [J_a^{(k)}, J_s^{(k)}] \) is the Jacobian matrices for the \( N_a \) nodes with respect to data type \( R \) at the k-th iteration [24].

In the reconstruction, the target atlas acts as an anatomy-labeled discrete mesh to achieve the inversion with the hard-priori guidance [4, 25], where the imaging domain is divided into \( N_o \) optically homogenous sub-regions according to the organ-labels in the target atlas, and the Jacobian matrix \( J_a^{(k)} \) and \( J_s^{(k)} \) is replaced by the reduced ones

\[
\mathbf{J}^{(k)} = [J_a^{(k)} G J_s^{(k)} G]
\]  

(9)

where \( G \) is a \( N_a \times N_o \) mapping matrix

\[
G_{ij} = \begin{cases} 1 & \text{if } i \in \Xi_j \\ 0 & \text{otherwise} \end{cases}
\]  

(10)

and \( \Xi_j \) (j = 1,2,...,\( N_o \)) is the j-th labeled- organ in the target atlas. Therefore, Eq. (8) is reduced to the imaging equation for recovering the organ-oriented tissue optical properties, as follows:

\[
R - F(\tilde{\mu}^{(k)}) = \bar{\mathbf{J}}^{(k)} \tilde{\Delta} \mu^{(k)}, \quad \tilde{\mu}^{(k+1)} = \tilde{\mu}^{(k)} + \tilde{\Delta} \mu^{(k)}
\]  

(11)

where \( \tilde{\mu}^{(k)} \) now represents the optical properties in the \( N_o \) organ regions at the k-th iteration stage and \( \tilde{\Delta} \mu^{(k)} \) their perturbations. Equation (11) is solved with the algebraic reconstruction technique [24].
3. Simulative investigations

Numerical validations focus on the acquisition of \textit{a priori} anatomical structures and \textit{a priori} organ-oriented tissue optical properties are performed on a virtual target mouse, which is generated from the Digimouse: the virtual target volume and atlas are constructed by identically applying the affine transformation and non-rigid deformation to the standard ones and corrupting them by adding Gaussian noise with a signal-to-noise ratio (SNR) of 30 dB. The virtual target atlas is used as an organ-labeled mesh to simulate the TD-DOT measurements, as explained below.

The torso section of a height of 30 mm in the virtual target atlas is chosen as the domain of interest, which contains 6 organ regions: muscle, heart, lungs, liver, stomach and kidneys, whose optical properties are assigned, as listed in Table 1 [4, 5, 36]. The underlying domain is assumed to be embedded in a cylindrical chamber of 25-mm diameter and 30-mm height, as shown in Fig. 3(a). To ensure a good optical match between the mouse torso and chamber, the remaining volume is assumed to be filled with matching fluid with the optical properties of $\mu_a = 0.05\, \text{mm}^{-1}$ and $\mu_s' = 1.0\, \text{mm}^{-1}$. The measured data-types, \textit{i.e.}, the Laplace-transformed TD-DOT measurements with real-domain frequencies of $\rho_{l,2} = \pm 0.02\mu_a c$ (where $\mu_a$ is the absorption coefficient of the matching fluid and $c$ is light velocity in tissue), are directly simulated for a CT-analogous scanning mode, as shown in Fig. 3(b). In this scenario, 5 detectors are assumed to evenly distribute near the surface of the imaging chamber from 112.5° to 247.5°, opposite to an incidence at the source position (0°), and collect 5 samples of the diffusive light “projection”. The imaging chamber is rotated counter-clockwise over 360° at an angle interval of 22.5°, leading to 16 projections on an imaging plane. DOT measurements are successively collected at 8 imaging planes, which are evenly distributed from $Z = 23.75\, \text{mm}$ to $Z = 46.25\, \text{mm}$, with a total of 640 measurements are available for the DOT reconstruction.

![Figure 3](image)

**Fig. 3.** CT-analogous scanning mode for DOT measurement: (a) Sketch of the mouse model for simulation; (b) configuration of the source and detectors.

Laplace-transformed DOT measurements $\Gamma$ can be readily simulated with the finite-element method (FEM) solution to the DE [24], and corrupted by additive Gaussian noise: $\Gamma_i = \Gamma_i \cdot (1 + R_G \cdot 10^{-\text{SNR} / 20})$, where $\Gamma_i$ is the $i$-th measurement, $R_G \in [-1,1]$ is the Gaussian random number, and $\text{SNR}$ is the SNR that is decided according to the actual intensity and the acceptable minimum $\text{SNR}_{\text{min}}$: $\text{SNR}_i = \text{SNR}_{\text{min}} \cdot \sqrt{\Gamma_i / \min(\Gamma)}$. In this work, $\text{SNR}_{\text{min}}$ is set to 20dB in accordance to the employed system.

With the standard-to-target registration process described in Section 2, \textit{a priori} anatomical structures can be obtained including both the volume and atlas, where the temperature parameter in the $i$-th iteration is chosen to be $T = 0.5 \cdot 0.93^i$ and $\lambda$ set to the same value as $T$ in the pre-registration step; the width of the feature blocks are set to be 15 voxels in the
post-registration step. The accuracy of the registration is evaluated by 2-D correlation coefficients between the final registered standard volume and the target volume, which are calculated on a set of transverse slices across the torso. Prior to the registration, an evident dissimilarity between the target volume and standard one are observed according to the fused slices, as selectively shown in Fig. 4(a). During the pre-registration and the post-registration, the standard volume is transformed into the registered standard volume, with the fused slices of its finally registered volume illustrated in Fig. 4(b). Figure 4(c) calculates correlation coefficients on the fused slices, and a strong correlation between the registered standard volume and the virtual target volume is now achieved.

Figure 5(a) and Fig. 5(b) qualitatively illustrate that the registered standard atlas is in excellent coincidence with the virtual target atlas after the registration. For an enhanced demonstration of the inner organ registration, we further quantitatively compare in Fig. 5(c) the similarities between the standard and target atlases before and after the registration, by calculate the mean Euclidean distance of the organs

$$d^{(k)} = \left( \sum_{n=1}^{N_k} \left\| \xi_n^{(k)} - \xi_v^{(k)} \right\| \right) / N_k$$

where $\xi_n^{(k)}$ and $\xi_v^{(k)}$ are the coordinates of the $n$-th node in the $k$-th organ of the standard and virtual target atlases, respectively; $N_k$ is the number of nodes in the $k$-th organ. By the definition, a smaller $d^{(k)}$-value means the higher registration accuracy. Therefore calculations in Fig. 5(c) indicate a strong similarity between the registered standard atlas and the virtual target one, where the mean Euclidean distances of $<$1.331 mm have been reached for all the organ regions after the registration, contrast to those of $>$5.63 before the registration. The above evaluations on both the volumes and atlases indicate that, the registration method
proposed herein well performs in registering the standard volume to the target volume, and effectively works as an easy-to-operate approach for the target atlas acquisition.

With the target atlas obtained, the optical properties of the organ regions can be reconstructed with the organ-constrained DOT algorithm aforementioned. In the DOT reconstruction process, initial optical properties of each organ region are set to be those of the matching liquid. As listed in Table 1, the results show that the absorption and reduced scattering coefficients of each organ can be recovered with reasonable accuracies, although its improvement is still requested.

![Atlas registration](image)

**Fig. 5. Atlas registration:** (a) Fused atlases before registration (b) Fused atlases after registration (c) Mean Euclidean distances of each organ before and after registration. For clearly showing the inner organs of atlases, muscle is not included.

**Table 1. Simulated reconstruction of mouse organ optical properties with the atlas-registration.**

| Region   | $(\mu_a, \mu_s')$ [mm$^{-1}$] | True    | Initial   | Reconstructed | Relative Error(%) |
|----------|-------------------------------|---------|-----------|---------------|------------------|
| Heart    | (0.0104, 0.99)                | (0.0128, 1.09) | (0.0128, 1.09) | (0.0128, 1.09) | (-22.87, -10.33) |
| Liver    | (0.0176, 0.65)                | (0.0175, 0.588) | (0.0175, 0.588) | (0.0175, 0.588) | (50.9, 53)        |
| Lung     | (0.0203, 1.95)                | (0.0211, 1.91) | (0.0211, 1.91) | (0.0211, 1.91) | (-3.77, 2.00)    |
| Stomach  | (0.007, 1.36)                 | (0.005, 1.34) | (0.005, 1.34) | (0.005, 1.34) | (28.57, 1.39)    |
| Kidney   | (0.038, 2.02)                 | (0.0325, 1.64) | (0.0325, 1.64) | (0.0325, 1.64) | (14.42, 18.69)   |
| Muscle   | (0.0068, 1.03)                | (0.0063, 1.073) | (0.0063, 1.073) | (0.0063, 1.073) | (7.23, 5.56)     |

4. Experimental validations

Experimental validations on full body mice involve two imaging measurements: XCT for the target volume acquisition and TD-DOT for recovery of the optical properties.

Figure 6 illustrates the TD-DOT setup. A picosecond (ps) pulse laser system is utilized as the source, where a controller (PDL-828, PicoQuant, Germany) drives a 670-nm fiber-tailed laser diode (LD) head (LDH-P-670, PicoQuant, Germany) working at a repetition rate of 20 MHz, a power of > 5 mW, and a pulse width of <70 ps. The beam is delivered to the source fiber with a core diameter of 62.5 μm and a numerical aperture (NA) of 0.22, and then
collimated to impinge the boundary of the imaging chamber. 5 detection fibers with a core diameter of 500 μm and NA = 0.37 are evenly placed on the surface of the imaging chamber from 112.5° to 247.5°, opposite to an incidence of the source fiber (0°). The transmitted light is collected by the 5 detection fibers and coupled to 5 photomultiplier tube (PMT) photon counting heads (PMC-100, Becker & Hickl, Germany), whose output single-photon pulses are thereafter analyzed by a multi-dimensional time-correlated single photon counting (TCSPC) module (SPC130, Becker & Hickl, Germany) through encoding of a router (HRT-81, Becker & Hickl, Germany) [37]. As with the simulation scenario, the system works in a CT-analogous scanning way where DOT measurements are collected by rotating the imaging chamber at an angular interval, in one or several planes selected by vertically translating the imaging chamber.

Fig. 6. Schematic of the CT-analogous scanning DOT setup.

A lab-equipped micro-CT imaging system is employed for the XCT acquisitions. The system is developed by adding a rotating mechanism to a commercial Digital Specimen Radiography System (Pixarray-100, Bioptics). It uses a 1024 × 1024 CMOS imager with 50 μm × 50 μm pixel size and gray levels of 14 bits, and a tungsten source with 0.2 mm beryllium filtration and 50 μm focus size. The imaging chamber is rotated at the required angular interval by a motorized rotational stage to generate different X-ray projection angles, and a software is programmed for generating the target volumes based on the Feldkamp-Davis-Kress (FDK) cone-beam reconstruction Algorithm [38].

To obtain statistically reasonable optical properties in vivo, two 4-week-old and three 3-week-old male KM mice are utilized in the mouse experiments. Each of them is anesthetized with 10% chloral hydrate and hung in a polyformaldehyde cylinder chamber with a diameter of 25 mm, a height of 95 mm and a wall thickness of 0.3 mm. The remaining volume of the imaging chamber is filled with mixture solution of India ink and Intralipid with the optical properties of $\mu_a = 0.05$ mm$^{-1}$ and $\mu_s' = 1$ mm$^{-1}$. The DOT measurements are collected at 11 imaging planes, evenly distributed from Z = 35 mm to Z = 85 mm. On each imaging plane, the imaging chamber is rotated at an angular step of 9°, producing 40 projections over the full angle of 360°. For the TCSPC analysis, the range of the time-to-amplitude converter is set to 50 ns, which is then resolved by a 12-bit analog-to-digital converter and leads to a time-bin of ~12.2 ps. An integration time of 2.5 s is used, which ensures an acceptable SNR of the maximal source-detector distance.

The matching fluid is then sucked from the imaging chamber for XCT measurement, where the source is operated at 45 kVp and 0.5 mAs, and the exposure time set to 3 s. The projections are collected at an interval of 2.88°, leading to a total of 125 projections for the FDK reconstruction of the target volume.
Prior to registration, the image chamber in the target volume is manually segmented, and it is removed from the target volume. The standard volume is scaled to the target one to ensure a uniform voxel size in the standard and target volumes. In the point-matching process, 1000 bone landmarks and 1000 surface landmarks are selected from each XCT volume, the temperature parameter in the \( i \)-th iteration is also chosen to be \( T = 0.5 \times 0.9^i \) and \( \lambda \) set to the same value as \( T \). In the block-matching process, the width of the feature blocks is set to be 15 voxels. Thereafter, the standard volume is registered to the target volume to finally acquire the target atlas, with the same controlling parameters as in the numerical simulation. Figure 7 shows the fused sagittal slices across the spine for the 5 experiments. As illustrated in Fig. 7 the proposed method can achieve an acceptable registration between the standard and the target volume, where the bones and surfaces in the standard and target volumes are geometrically fitted.

The obtained target atlases are used as the anatomical structures for the organ-constrained DOT reconstruction. Similar to the simulation, a torso section with a height of 35 mm of the target atlas is chosen as the domain of interest. Only the measurements within the domain of interest are used as the effective data for reconstruction. Box-plot of the recovered optical properties is listed in Fig. 8. In addition, their mean values compared with those in two groups of literature publications in Table 2.
Fig. 8. Box-plot about the recovered (a) absorption coefficients and (b) reduced scattering coefficients of the main regions in KM mice.

Table 2. Comparison of the recovered and published optical properties of mice

| Region     | recovered $\mu_a$, $\mu'_s$ [mm$^{-1}$] | Literature #1 $\mu_a$, $\mu'_s$ [mm$^{-1}$] | Literature #2 $\mu_a$, $\mu'_s$ [mm$^{-1}$] |
|------------|----------------------------------------|---------------------------------------------|---------------------------------------------|
| Heart      | (0.101,1.67)                           | (0.0104,0.99)                              | (0.0863,0.4291)                            |
| Liver      | (0.122,0.96)                           | (0.0176,0.65)                              | (0.0583,0.9639)                            |
| Lung       | (0.0503,1.65)                          | (0.0203,1.95)                              | (0.3489,0.6781)                            |
| Stomach    | (0.011,1.4)                            | (0.007,1.36)                               | (0.1948,0.1739)                            |
| Kidney     | (0.0255,1)                             | (0.038,2.02)                               | (0.0113,1.4369)                            |
| Muscle     | (0.0431,1.25)                          | (0.0068,1.03)                              | (0.0654,2.253)                            |

#1: The optical properties are suggestive values at 600-650 nm for manufacturing phantoms [39] or numerical simulations [4,5,40], according to the in vitro or in vivo optical properties of rat, human, pig, dog et al in a few wavelengths [41].

#2: The optical properties at 670 nm are calculated with empirical formula that is generated from the in vivo or in vitro optical properties of mouse, pig, canine, human et al [42].

5. Discussion and conclusions

In this paper, a region-based diffuse optical tomography with the registered atlas is presented for the sake of obtaining a priori organ-oriented tissue optical properties of the target mouse in vivo, which is oriented toward the improvement of reconstruction quality in the model-based optical tomography modalities.

Numerical investigations have been performed on a virtual target XCT volume that is transformed from the standard one. The comparisons (Fig. 4) clearly show that a correlation coefficient of >0.9 has been achieved for the torso slices between the registered standard volume and the virtual target one. This observation is supported by atlas comparisons (Fig. 5) where the registered standard atlas has demonstrated a good coincidence with the virtual target one after registration. It is concluded that, the registered standard atlas can be regarded as an effective approximation to the target anatomical structures. Under this premise, the registered standard atlas is applied in the organ-constrained DOT reconstruction for iteratively extracting the optical properties of the inner organs. The results (Table 1) show that the absorption and reduced scattering coefficients can be recovered from homogenous optical background, with relative errors of <28.57% and <18.69%, indicating effectiveness of the proposed methodology.

Synergetic DOT and XCT experiments have also been conducted on a statistically-reasonable group of mouse for further validation of the method. As the results shown in Fig. 7, an acceptable registration between the standard and the realistic target volumes can be achieved with the proposed method. The obtained target atlases are used to recover optical properties of the main organs. The results provide a group of in vivo measurements of the optical properties at 670 nm for the major organs. The comparisons with the literature published optical properties (Table 2) show the reasonability of the reconstructions. It should be noted that the experiments just provide a group of references to the mean optical properties.
of the main organs, abundant trials are required to improve fidelity of the results. Nevertheless, with consideration on the individual variations, it may be more meaningful for instantaneously obtaining optical properties of each individual in practice.

Although the feasibility of the region-based continuous-wave DOT scheme has been demonstrated for the goal [4], the TD-DOT scheme is believed to better separate the absorption from the scattering with an improved quantification. Moreover, to avoid the time-origin sensitivity and reference measurement with using the full time-resolved data, the GPST-based reconstructions are performed in this study for more robust reconstructions. Since the DOT system based on PMT-TCSPC is sensitive, it can measure weak signals from thick tissues. Therefore, the proposed method may also be employed to the acquisition of rat optical properties acquisition in vivo [43].

In conclusion, both of the numerical simulations and the mouse experiments reveal that the a priori anatomical structures and the a priori organ-oriented tissue optical properties can be effectively obtained in vivo with atlas-registration-based DOT strategy. Nevertheless, since the diffuse equation might behave ineffectively for the regions with low scattering such as the liver, an accurate model for modeling photon migration, e.g. the Monte Carlo simulation, could be employed in DOT reconstruction in the future work. In addition, more work need to be concentrated on applying the proposed approach to in vivo small animal imaging within XCT/DOT/FMT multi-modality.

Funding

National Natural Science Foundation of China (81271618, 81371602, 61475115, 61475116, 81401453, 61575140, 81571723); Tianjin Municipal Government of China (13JCZDJC28000, 14JCQNJC14400, 15JCZDJC31800, 15JCQNJC14500).