Shape-parameterized diffuse optical tomography holds promise for sensitivity enhancement of fluorescence molecular tomography

Linhui Wu,1 Wenbo Wan,1 Xin Wang,1 Zhongxing Zhou,1,2 Jiao Li,1,2 Limin Zhang,1,2 Huijuan Zhao,1,2 and Feng Gao1,2,*

1College of Precision Instrument and Opto-electronics Engineering, Tianjin University, Tianjin 300072, China
2Tianjin Key Laboratory of Biomedical Detecting Techniques and Instruments, Tianjin 300072, China

* gaofeng@tju.edu.cn

Abstract: A fundamental approach to enhancing the sensitivity of the fluorescence molecular tomography (FMT) is to incorporate diffuse optical tomography (DOT) to modify the light propagation modeling. However, the traditional voxel-based DOT has been involving a severely ill-posed inverse problem and cannot retrieve the optical property distributions with the acceptable quantitative accuracy and spatial resolution. Although, with the aid of an anatomical imaging modality, the structural-prior-based DOT method with either the hard- or soft-prior scheme holds promise for in vivo acquiring the optical background of tissues, the low robustness of the hard-prior scheme to the segmentation error and inferior performance of the soft-prior one in the quantitative accuracy limit its further application. We propose in this paper a shape-parameterized DOT method for not only effectively determining the regional optical properties but potentially achieving reasonable structural amelioration, lending itself to FMT for comparably improved recovery of fluorescence distribution.

References and links

1. S. V. Patwardhan, S. R. Bloch, S. Achilefu, and J. P. Culver, “Time-dependent whole-body fluorescence tomography of probe bio-distributions in mice,” Opt. Express 13(7), 2564–2577 (2005).
2. V. Y. Soloviev, C. D’Andrea, G. Valentini, R. Cubeddu, and S. R. Arridge, “Combined reconstruction of fluorescent and optical parameters using time-resolved data,” Appl. Opt. 48(1), 28–36 (2009).
3. K. Vishwanath, B. Pogue, and M. A. Mycek, “Quantitative fluorescence lifetime spectroscopy in turbid media: comparison of theoretical, experimental and computational methods,” Phys. Med. Biol. 47(18), 3387–3405 (2002).
4. A. B. Milstein, S. Oh, K. J. Webb, C. A. Bouman, Q. Zhang, D. A. Boas, and R. P. Millane, “Fluorescence optical diffusion tomography,” Appl. Opt. 42(16), 3081–3094 (2003).
5. R. Roy, A. Godavarthy, and E. M. Sevick-Muraca, “Fluorescence-enhanced optical tomography using referenced measurements of heterogeneous media,” IEEE Trans. Imaging 22(7), 824–836 (2003).
6. J. F. Abascal, J. Aguirre, J. Chamorro-Servent, M. Schweiger, S. Arridge, J. Ripoll, J. J. Vaquero, and M. Desco, “Influence of absorption and scattering on the quantification of fluorescence diffuse optical tomography using normalized data,” J. Biomed. Opt. 17(3), 036013 (2012).
7. T. Pyka, R. Schulz, A. Ale, and V. Ntziachristos, “Revisiting the normalized Born approximation: effects of scattering,” Opt. Lett. 36(22), 4329–4331 (2011).
8. B.-Q. Li, F. Maafi, R. Berti, P. Pouliot, E. Rheaume, J. C. Tardif, and F. Lesage, “Hybrid FMT-MRI applied to in vivo atherosclerosis imaging,” Biomed. Opt. Express 5(5), 1664–1676 (2014).
9. M. Niedre and V. Ntziachristos, “Elucidating structure and function in vivo with hybrid fluorescence and magnetic resonance imaging,” Proc. IEEE 96(3), 382–396 (2008).
10. D. Hyde, R. de Kleine, S. A. MacLaurin, E. Miller, D. H. Brooks, T. Krucker, and V. Ntziachristos, “Hybrid FMT-CT imaging of amyloid-β plaques in a murine Alzheimer’s disease model,” Neuroimage 44(4), 1304–1311 (2009).
11. D.-F. Wang, J. He, H.-T. Qiao, X.-L. Song, Y.-B. Fan, and D.-Y. Li, “High-performance fluorescence molecular tomography in the presence of heterogeneities,” Opt. Lett. 38(11), 1903–1905 (2013).

12. Y.-T. Lin, H. Yan, O. Nalcioglu, and G. Gulsen, “Quantitative fluorescence tomography with functional and structural a priori information,” Appl. Opt. 48(7), 1328–1336 (2009).

13. Y.-Y. Tan and H.-B. Jiang, “Diffuse optical tomography with structural-prior-based diffuse optical tomography,” Appl. Opt. 57(12), 2011–2016 (2008).

14. T. Correia, N. Ducros, C. D’Andrea, M. Schweiger, and S. Arridge, “Quantitative fluorescence diffuse optical tomography,” Biomed. Opt. Express 15(3), 8043–8058 (2007).

15. D. Hyde, R. Schulz, D. Brooks, E. Miller, and V. Ntziachristos, “Performance dependence of hybrid x-ray computed tomography/fluorescence molecular tomography on the optical forward problem,” J. Opt. Soc. Am. A 26(4), 919–923 (2009).

16. P. Hiltunen, S. J. D. Prince, and S. Arridge, “A combined reconstruction-classification method for diffuse optical tomography,” Phys. Med. Biol. 54(21), 6457–6476 (2009).

17. Y.-T. Lin, H. Yan, O. Nalcioglu, and G. Gulsen, “Quantitative fluorescence tomography with functional and structural a priori information,” Appl. Opt. 48(7), 1328–1336 (2009).

18. B. W. Pogue, H. Dehghani, C. M. Carpenter, S. D. Jiang, and K. D. Paulsen, “Structural information within regularization matrices improves near infrared diffuse optical tomography,” Opt. Express 15(13), 8043–8058 (2007).

19. P. K. Yalavarthy, B. W. Pogue, H. Dehghani, and K. D. Paulsen, “Weight-matrix structured regularization provides optimal generalized least-squares estimate in diffuse optical tomography,” Med. Phys. 34(6), 2085–2098 (2007).

20. S. C. Davis, H. Dehghani, J. Wang, S. D. Jiang, B. W. Pogue, and K. D. Paulsen, “Image-guided diffuse optical fluorescence tomography implemented with Laplacian-type regularization,” Opt. Express 15(7), 4066–4082 (2007).

21. Q.-Q. Fang, R. H. Moore, D. B. Kopans, and D. A. Boas, “Compositional-prior-guided image reconstruction algorithm for multi-modality imaging,” Biomed. Opt. Express 1(1), 223–235 (2010).

22. B. W. Pogue, T. O. McBride, J. Prewitt, U. L. Osterberg, and K. D. Paulsen, “Spatially variant regularization improves diffuse optical tomography,” Appl. Opt. 38(13), 2950–2961 (1999).

23. G. Boverman, E. L. Miller, A. Li, Q. Zhang, T. Chaves, D. H. Brooks, and D. A. Boas, “Quantitative spectrscopic diffuse optical tomography of the breast guided by imperfect a priori structural information,” Phys. Med. Biol. 50(17), 3941–3956 (2005).

24. L.-H. Wu, H.-J. Zhao, X. Wang, X. Yi, W.-T. Chen, and F. Gao, “Enhancement of fluorescence molecular tomography with structural-prior-based diffuse optical tomography: combating optical background uncertainty,” Appl. Opt. in press.

25. A. Ale, V. Ermolayev, E. Herzog, C. Cohrs, M. H. de Angelis, and V. Ntziachristos, “FMT-XCT: in vivo animal studies with hybrid fluorescence molecular tomography-X-ray computed tomography,” Nat. Methods 9(6), 615–620 (2012).

26. F. Stuker, C. Baltes, K. Dikaiou, D. Vats, L. Carrara, E. Charbon, J. Ripoll, and M. Rudin, “Hybrid small animal imaging system combining magnetic resonance imaging with fluorescence tomography using single photon avalanche diode detectors,” IEEE Trans. Med. Imaging 30(6), 1265–1273 (2011).

27. D.-F. Wang, J. He, H.-T. Qiao, X.-L. Song, Y.-B. Fan, and D.-Y. Li, “High-performance fluorescence molecular tomography through shape-based reconstruction using spherical harmonics parameterization,” PLoS ONE 9(4), e94317 (2014).

28. K. Liu, X. Yang, D. Liu, C.-H. Qin, J.-T. Liu, Z. J. Chang, M. Xu, and J. Tian, “Spectrally resolved three-dimensional bioluminescence tomography with a level-set strategy,” J. Opt. Soc. Am. A 27(6), 1413–1423 (2010).

29. S. Babaeizadeh and D. H. Brooks, “Electrical impedance tomography for piecewise constant domains using boundary element shape-based inverse solutions,” IEEE Trans. Med. Imaging 26(5), 637–647 (2007).

30. A. D. Zacharopoulos, M. Schweiger, V. Kolehmainen, and S. Arridge, “3D shape based reconstruction of experimental data in diffuse optical tomography,” Opt. Express 17(21), 18940–18956 (2009).

31. A. D. Zacharopoulos, “Three-dimensional shape-based reconstructions in medical imaging,” PhD thesis, 2004.

32. A. Aghasi, M. Kilmer, and E. L. Miller, “Parametric level set methods for inverse problems,” SIAM J. Imaging Sci. 6(2), 618–650 (2011).

33. F. Larusson, S. Fantini, and E. L. Miller, “Parametric level set reconstruction methods for hyperspectral diffuse optical tomography,” Biomed. Opt. Express 3(5), 1006–1024 (2012).

34. M. Schweiger, O. Dorn, and S. R. Arridge, “3-D shape and contrast reconstruction in optical tomography with level sets,” J. Phys. Conf. Ser. 124, 012043 (2008).

35. F. Larusson, P. G. Anderson, E. Rosenberg, M. E. Kilmer, A. Sassaroli, S. Fantini, and E. L. Miller, “Parametric estimation of 3D tubular structures for diffuse optical tomography,” Biomed. Opt. Express 4(2), 271–286 (2013).

36. A. D. Zacharopoulos, S. R. Arridge, O. Dorn, V. Kolehmainen, and J. Sikora, “Three-dimensional reconstruction of shape and piecewise constant region values for optical tomography using spherical harmonic parameterization and a boundary element method,” Inverse Probl. 22(5), 1509–1532 (2006).

37. J. Sikora, A. D. Zacharopoulos, A. Douiri, M. Schweiger, L. Horesh, S. R. Arridge, and J. Ripoll, “Diffuse photon propagation in multilayered geometries,” Phys. Med. Biol. 51(3), 497–516 (2006).
1. Introduction

Fluorescence molecular tomography (FMT) in the near-infrared (NIR) range is becoming a powerful modality for mapping the three-dimensional (3-D) distribution of fluorochromes in live small animals [1, 2]. Quantum yield and fluorescing lifetime reconstructed by FMT quantitatively reveal conditions of diseased tissues and provide information useful for diagnoses [3]. In FMT, the accuracy of reconstructed fluorescence distributions highly depends on the knowledge of the tissue optical heterogeneities for correct modeling of the light propagation [4, 5]. The common approach is to assume a homogeneous optical background, which definitely exerts adverse effects on the reconstruction sensitivity and accuracy. Abascal et al. demonstrated that the normalized Born approximation approach tolerates uncertainty in the absorption heterogeneity to some extent, but fails to compensate for the effect of the unknown scattering heterogeneity in the model [6, 7]. Another strategy is to fuse the structural information from anatomical imaging modalities such as X-ray CT and MRI to the modeling process [8–10], and to assign the experimentally measured or literature-published optical properties to different tissue regions [11]. This approach, despite considerably improving the images, usually leads to noticeable quantification errors because of the individual variations. The advanced method uses diffuse optical tomography (DOT) to estimate the optical property distributions within tissues in vivo, which are then incorporated into the FMT inversion to improving the quality of reconstructed images [12–14]. Tan et al. directly reconstructed optical heterogeneities using DOT and applied them to the FMT [13].

To improve accuracy, Correia et al. proposed a method that reconstructed the diffusion coefficient using continuous-wave (CW) DOT with the assist of a prior estimation of the homogeneous background absorption [14]. Although, it has been demonstrated that the simultaneous unique recovery of the scattering and absorption coefficients might not be feasible using a CW-DOT measurement, it is still an open problem whether this nonuniqueness might be effectively suppressed in a reasonably-regularized or well-posed inversion process, where a solution with acceptable accuracy is uniquely generated [15]. Furthermore, due to the strong scattering nature of most tissue types and limited availability of the data, the traditional voxel-based DOT involves a severely ill-posed inverse problem, and in general suffers from low resolution and accuracy [15, 16].

To improve the inferior fidelity intrinsic to the conventional DOT, a regularization strategy is generally incorporated into its inversion formulation, which enhances the spatial resolution and the quantitative accuracy of DOT reconstruction by constraining the relevant...
optimization issue in terms of structural or anatomical \textit{a priori} information [17–21]. Spatially varying Tikhonov regularization was used to reduce high frequency noises in the reconstructed images by Pogue et al [22]. Boverman et al. evaluated the effect of prior segmentation of breast into glandular and adipose tissues [23]. Yalavarthy et al. regularized the inverse solution by use of MRI-derived breast geometry [17]. In our previous work a structural-prior-based method was proposed for \textit{in vivo} obtaining the background optical property sets of the tissue regions [24]. This method uses prior structural information from X-ray CT and/or MRI modalities to impose either a hard or a soft constraint on the reconstruction process, referred to as hard- and soft-prior schemes, respectively. The major advantage of using a hard-prior scheme is that the total number of unknowns is dramatically reduced, making the inversion better-posed and thereby significantly enhancing the DOT reconstruction quality. However, its stability is critically dependent on the accuracy of the structural priors, and the performance degraded when incomplete or distorted structural priors are employed. In contrast, the soft-prior scheme is robust and unbiased in the presence of uncertainty in structural priors, but exhibits an inferior performance in the quantitative accuracy to the hard-prior one as the confidence in the prior structural information is high.

In multi-modality imaging applications such as XCT-DOT or MRI-DOT, it is possible to segment the small animal into a small number of sub-domains with constant piecewise optical properties [25, 26]. The whole domain to be imaged can be fairly parameterized by decomposing the surfaces that bound those sub-domains over a spatial basis and therefore describing them in a finite number of shape coefficients. With this strategy the DOT issue reduces to a “coarse-grain” version that jointly recovers the shape-coefficient and optical-property sets associated with the sub-domains, referred to as shape-parameterized DOT. Since the number of unknowns is greatly reduced, which in turn alleviates the ill-posedness of the inverse issue, an acquisition of the domain optical structure can be achieved with improved accuracy. In a broad sense, the shape-parameterized inversion methodology in tomography regime provides an effective way of combating the ill-posedness of the voxel-based scheme through parametric decomposition of the sub-domain surfaces and homogeneity assumption on the sub-domain physical properties, and has been successfully applied to FMT [27], bioluminescence tomography [28], electrical impedance tomography [29], and DOT [30, 31]. An alternative to the above shape-parameterized DOT is the parametric level-set method that implicitly defines the object shape to be the zero level set of a parameterized Lipschitz continuous object function and estimates both the piecewise constant optical properties in the anomaly and background and the weight coefficients in the object function expansion [32, 33]. This method has been adopted to counter the ill-posedness of DOT inversion [33, 34], and recently used to estimate 3-D complex tubular structures in breast tissue [35]. Nevertheless, application of the method to capturing the highly heterogeneous optical background of a realistic domain (such as the whole body small animal) involves a whole blind, multi-level and multi-geometry problem and the technical aspects, in particular the choice of the object function and its expansion basis, need to be crucially tackled.

In this paper, we consider employing a shape-parameterized DOT scheme for effectively obtaining the background optical structure (\textit{i.e.}, the geometrical and optical priors) to improve the sensitivity of FMT. To enhance the robustness of the reconstruction, an iterative two-step scheme is proposed for joint estimation of the optical properties and shape coefficients, where, alternately, a hard-prior regularized optical-reconstruction is used in the first step for acquiring the optical properties of the sub-domains with the aid of some structural priors, and a shape-reconstruction is followed in the second step for achieving reasonable structural amelioration based on the spherical harmonics parameterization of the interior sub-domains [27, 30, 36]. Since the introduction of some imperfect structural priors is inevitable in practice to the optical-reconstruction due to uncertainties in the image segmentation or performance limitations of the anatomical imaging modality, a geometrical adjustment of the sub-domains is crucial to improving accuracy of the optical-reconstruction, and accordingly the global
convergence of the shape-reconstruction in the second step could also be accelerated with the improved optical-reconstruction – both the steps promote each other in such a robust way to approach the true optical structure of imaging domain. For a methodological validation, simulations and experiments are conducted where the background optical structure obtained with the shape-parameterized DOT is put to use for sensitivity enhancement of FMT. The comparative investigations demonstrate the notable advantage of the proposed method over the previously developed hard- or soft-prior DOT schemes.

2. Methods

2.1 Parametric description of domain shapes

It is feasible to fairly parameterize a closed domain by expanding its boundary over the spherical harmonics basis of different degrees, depending on the regularity and smoothness of the surface [27, 30, 36]. Assuming that \( L \) disjoint sub-domains \( \{ \Omega_\ell \} \), \( \ell = 1 \ldots L \) with piecewise constant optical properties \( \{ \mu_{\ell,0}, \mu'_{\ell,0} \} \), representing the inner organs, are segmented from the whole body (imaging domain) of a small animal \( \Omega \) (the remaining muscle sub-domain and its optical property set are denoted by \( \Omega_0 = \Omega \setminus \bigcup_{\ell \neq \ell'} \Omega_\ell \) and \( \{ \mu_{0,0}, \mu'_{0,0} \} \), respectively), i.e., \( \bigcup_{\ell=1}^{L} \Omega_\ell \subset \Omega \) and \( \Omega_\ell \cap \Omega_{\ell'} = \emptyset (\ell \neq \ell') \), these sub-domains are then geometrically characterized by their respective closed and relatively smooth boundaries \( \partial \Omega_\ell \), which, within the framework of the spherical harmonics, can be further parametrically described in terms of its boundary location \( r_\ell = (x_\ell, y_\ell, z_\ell) \), by the following representation [30, 36]

\[
V_\ell(\theta, \phi) = \sum_{m=0}^{W} \sum_{l=0}^{m} C_{m}^{(l, m)} Y_{m}^{(l)}(\theta, \phi), \forall \in \{ x, y, z \} \tag{1}
\]

where \( C_{m}^{(l, m)} \) denotes the expansion coefficient set for the \( \ell \)-th sub-domain, \( Y_{m}^{(l)}(\theta, \phi) \) is the real-valued basis functions taken from the real part \( m \leq 0 \) or imaginary part \( m > 0 \) of the complex spherical harmonics functions \( Y_{m}^{(l)}(\theta, \phi) \) [30, 36], and \( W \) is the maximum degree of spherical harmonics used for the specific representation. In particular, the 0-th degree \( (W = 0) \) shape coefficients \( C_{0}^{(l, 0)} \) are Cartesian coordinates of the center of the \( \ell \)-th sub-domain. Thus, a single sub-domain can be geometrically described by \( (W+1)^2 \times 3 \) expansion coefficients for up to \( W \)-degree spherical harmonics. In addition to the sub-domain optical properties, a total of \( L((W+1)^2 \times 3) \) shape coefficients could model the \( L \) disjointed sub-domains, denoted by \( \gamma \). Although a spherical harmonics expansion with higher degree describes more complicated geometry and therefore yields better shape description, it accordingly brings greater computational burden and potentially aggravates the ill-posedness of reconstruction due to rapid increase in the expansion coefficient number. As a demonstration of the methodology, we simply use a 2-degree \( (W = 2) \) spherical harmonics expansion throughout the study.

2.2 Forward calculation

Since the CW method is technically the simplest scheme and potentially offers greater parallelism at lower cost, we hence choose the CW mode in my work. In CW-FMT regime, based on the assumption of multi-domain geometries and the piecewise constant optical properties in each sub-domain \( \Omega_\ell \) \( (\ell = 0 \ldots L) \), the following coupled Helmholtz equations [30, 36], i.e., the equivalent transform of the diffusion equations in a piecewise homogeneous
medium, with the Robin boundary conditions for the outermost boundary \( \partial \Omega \) as well as the joint flux-continuity and radiance-continuity interface conditions for the inner boundaries \( \partial \Omega, \ell = 1 \ldots L \) have been widely used to describe the excitation \( (\nu=x) \) or emission \( (\nu=m) \) light propagation in tissues

\[
\begin{align*}
\nabla^2 \Phi_{\nu}(r) + \sigma_{\nu}(r)\Phi_{\nu}(r) &= q_{\nu}(r)/\kappa_{\nu}, \quad r \in \Omega, \quad \ell = 0 \ldots L, \\
\Phi_{\nu}(r) &= \Phi_{\nu}\big|_{\partial \Omega}(r), \quad r \in \partial \Omega, \quad \ell = 1 \ldots L, \\
\kappa_{\nu}\big(\hat{n}(r) \cdot \nabla \Phi_{\nu}(r)\big) &= \kappa_{\nu}\big(\hat{n}(r) \cdot \nabla \Phi_{\nu\partial}(r)\big), \quad r \in \partial \Omega, \quad \ell = 1 \ldots L, \\
c\Phi_{\nu\partial}(r) + 2\kappa_{\nu}\big(\hat{n}(r) \cdot \nabla \Phi_{\nu\partial}(r)\big) &= 0, \quad r \in \partial \Omega,
\end{align*}
\]  

(2)

where \( \Phi_{\nu}(r) \) is the photon density in \( \Omega \); \( q_{\nu}(r) \) is the source term: \( q_{\nu\partial}(r) = \delta(r-r')\big|_{\nu \in \partial \Omega} \), \( q_{\nu\partial}(r) = 0 \) \( \ell = 1 \ldots L \), and \( q_{\nu\partial}(r) = \Phi_{\nu\partial}(r)\eta_{\nu}(r) \) with \( \eta_{\nu} \) being the fluorescence yield in \( \Omega \); \( \hat{n}(r) \) and \( \hat{n}(r) \) are the outward unity vectors normal to the \( \ell \)-th sub-domain boundary \( \partial \Omega \), \( \ell = 1 \ldots L \), and to the outermost boundary \( \partial \Omega \), respectively; \( K = \big(1+R_{\nu}\big)/\big(1-R_{\nu}\big) \) with \( R_{\nu} \) being the internal reflection coefficient at \( \partial \Omega \); the \( \sigma_{\nu} = \sqrt{\mu_{\nu} c / \kappa_{\nu}} \) is the wave number associated with the Helmholtz equation in the \( \ell \)-th sub-domain \( \partial \Omega \), \( \ell = 0 \ldots L \); \( c \) is the light velocity in tissue; \( \kappa_{\nu} = c\sqrt{3 \big(\mu_{\nu} + \mu'_{\nu}\big)} \) is the diffusion coefficient with \( \mu_{\nu} \) and \( \mu'_{\nu} \) being the absorption and reduced scattering coefficients, respectively, in each sub-domain. For simplicity, we assume \( \mu_{\nu\partial} = \mu_{\nu} = \mu_{\nu}' \) and \( \mu'_{\nu\partial} = \mu'_{\nu} = \mu'_{\nu} \).

A boundary element method (BEM) can be naturally adopted as a computationally efficient solution to Eq. (2), which, based on the Green's second theorem, transforms the volume integral regarding to the interior photon density \( \Phi_{\nu}(r) \big|_{\nu \in \Omega} \) to a boundary integral regarding to the boundary photon density \( \Phi_{\nu\partial}(r) \big|_{\nu \in \partial \Omega} \) [37]. Reliable boundary mesh for each sub-domain as required by the BEM can be readily generated by mapping the mesh on a spherical surface onto the sub-domain surface according to its spherical harmonics coefficients. We finally obtain a set of linear equations with regard to the photon density \( \Phi_{\nu\partial}(r) \) on the boundary mesh

\[
T\big[\mu_{\nu}(R),\mu'_{\nu}(R),\gamma\big] \Phi_{\nu\partial} = q_{\nu\partial}.
\]  

(3)

Where the system matrix \( T\big[\mu_{\nu}(R),\mu'_{\nu}(R),\gamma\big] \) is in a form of densely asymmetric blocks and depends nonlinearly on the shape coefficients \( \gamma \) and the sub-domain optical properties \( \mu_{\nu}(R),\mu'_{\nu}(R) = \big[\mu_{\nu\partial},\mu'_{\nu\partial}\big] \big| \ell = 0 \ldots L \); \( q_{\nu\partial} \) represents the source term. According to the boundary integral equation, the photon density \( \Phi_{\nu\partial}(r) \) for an arbitrary interior point \( r \in \Omega \) by definition could be calculated directly through the boundary integral of the photon density over \( \partial \Omega \) [37], from which the measurable flux at the boundary sites can be obtained by applying Fick's law.
2.3 Inverse problems

In the most general case, an adjunct DOT procedure is needed to acquire the background optical properties of the imaging domain, prior to the FMT reconstruction [4]. This definitely optimizes the light propagation model and enables high-fidelity reconstruction of fluorescence target. Under the regional homogeneity assumption on the background optical properties and the spherical harmonics parameterization of the sub-domains aforementioned, both DOT and FMT inversions can be derived within the BEM framework.

DOT reconstruction

Use of the hard- or soft-prior DOT scheme has been investigated for obtaining the background optical properties and demonstrated a strong dependency on confidence of the anatomical priors. To suppress the adversity, we present a novel shape-parameterized DOT scheme for effectively acquiring the background optical structure. The three schemes can be expressed as follows:

Soft – prior: \[ \{\mu_s(r), \mu'_s(r)\} = F_i^{-1}\left[I_s, \mu_s^{(0)}(r), \mu'_s^{(0)}(r), \gamma(0)\right], \tag{4} \]

Hard – prior: \[ \{\mu_s(R), \mu'_s(R)\} = F_i^{-1}\left[I_s, \mu_s^{(0)}(R), \mu'_s^{(0)}(R), \gamma(0)\right], \tag{5} \]

Shape – parameterized: \[ \{\mu_s(r), \mu'_s(R), \gamma\} = F_i^{-1}\left[I_s, \mu_s^{(0)}(R), \mu'_s^{(0)}(R), \gamma(0)\right]. \tag{6} \]

Where, \( I_s \) is the column vector numerating the \( M \) excitation measurements on the boundary \( \partial\Omega \), \( F_i \) is the forward operator describing the photon migration, \( \gamma(0) \) is the initial expansion coefficient set of the sub-domain geometries, which is estimated from the structural a priori information, and \( \{\mu_s^{(0)}, \mu'_s^{(0)}\} \) denotes the initial background optical properties of the imaging domain, which are commonly assumed to be homogeneous and set to those of muscle. The two former schemes are essentially derived from a voxel-based DOT, with the soft-prior one modifying the minimization functional to include a penalty term for the structural priors and tolerating the prior imperfect to some extent at the cost of low quantitativeness, while the hard-prior one utilizing the regional homogeneity assumption of the optical properties to reduce the voxel-oriented reconstruction to the domain-oriented inversion and being only unbiased for accurate priors [38]. In the soft-prior scheme, Eq. (4), each voxel is regarded as an element with its position indicated by \( r \). While in the hard-prior scheme, Eq. (5), the reconstruction is based on the organ-relevant sub-domains, which, in contrast, are indexed by \( R \). The details on the hard- and soft-prior schemes can be found in Ref [24, 38]. We herein focus on the shape-parameterized case.

For the shape-parameterized DOT reconstruction, the nonlinear inverse problem in Eq. (2) (\( \nu = x \)) is linearized to construct the following Newton-Raphson iterative procedure

\[
\mathbf{b}^{(k)} = J^{(k)} \delta \chi^{(k)}; \quad \chi^{(k+1)} = \chi^{(k)} + \lambda \delta \chi^{(k)}, \tag{7}
\]

where, \( \mathbf{b}^{(k)} = I_s - F_i [\chi^{(k)}] \); \( \chi^{(k)} = \{\mu^{(k)}, \gamma^{(k)}\} \) denotes the optical property and expansion coefficient set, \( \mu^{(k)} = \{\mu_s^{(k)}(R), \mu'_s^{(k)}(R)\} \), and \( \delta \chi^{(k)} = \{\delta \mu^{(k)}, \delta \gamma^{(k)}\} \) denotes the perturbation at the \( k \)-th iteration with \( \delta \mu^{(k)} \) and \( \delta \gamma^{(k)} \) being the optical and shape perturbations, respectively; \( \lambda \) is the relaxation factor in range of \([0,1]\); \( J^{(k)} = [J^{(k)}_{\mu} J^{(k)}_{\gamma}] \) is the Jacobian...
matrix with $J^{(k)}_{\mu}$ and $J^{(k)}_{\gamma}$ being the sub-matrices regarding the optical properties and shape coefficients, respectively.

Although, it is naturally feasible to simultaneously reconstruct the optical property and shape coefficient sets with a single iterative formulation of inversion, a satisfactory solution might be difficult to find without a proper weight-scaling measure because of different orders of magnitude sensitivities of the measurements to both the parameters. To avoid this difficulty, we split the reconstruction procedure into two successive steps: the part of optical-reconstruction and the part of shape-reconstruction. This eventually leads to an iterative alternating scheme for joint estimation of the optical properties and shape coefficients, as shown in Fig. 1. The two-step reconstruction procedure is repeated until the relative change in the forward calculation $F_x$ between two successive iterations drops down below a threshold $\varepsilon$, i.e.,

$$\frac{\|F_x^{(k+1)} - F_x^{(k)}\|}{\|F_x^{(k)}\|} \leq \varepsilon.$$  (8)

At the $k$-th iteration of the two-step reconstruction procedure, the optical-reconstruction is performed with the hard-prior DOT scheme to obtain the optical properties for the $(k+1)$-th iteration: $\mu^{(k+1)}$, on the basis of the structural $a$ priori information for the $k$-th iteration: $\gamma^{(k)}$, and then the shape-reconstruction step is conducted with the parameterization for obtaining the spherical harmonics coefficients for the $(k+1)$-th iteration: $\gamma^{(k+1)}$, based on the updated optical properties: $\mu^{(k+1)}$.

---

**Initialization**

1. Initialization of the optical properties:
   - Set $\mu^{(0)}$ homogeneously to be the background values.

2. Initialization of the shape coefficients:
   - Set $\{C_i\}$ to be the center coordinates of the sub-domains.
   - Determine the details $\{C_i\}$, $j = 1, ..., W$ using a least-squares fitting between the boundaries of the sub-domains and the spherical harmonics approximation.

**Optical-reconstruction**

Obtain the optical properties $\mu^{(k)}$ using the hard-prior DOT with the structural $a$ priori $\gamma^{(k)}$ by solving the relevant linear inversion: $b^{(k)} = J^{(k)}(\mu^{(k)}, \gamma^{(k)})\delta\mu^{(k)}$.

**Shape-reconstruction**

Obtain the shape coefficients $\gamma^{(k)}$ using the shape reconstruction with the optical properties $a$ priori $\mu^{(k)}$ by solving the relevant linear inversion: $b^{(k)} = J^{(k)}(\mu^{(k)}, \gamma^{(k)})\delta\gamma^{(k)}$.

---

Fig. 1. Flowchart of the Newton-Raphson scheme for alternating optical and shape reconstructions.
Optical-reconstruction

For the optical property reconstruction, Eq. (7) for the voxel-based DOT becomes

$$\mathbf{b}^{(k)} = J^{(k)}_\mu \delta \boldsymbol{\mu}^{(k)}; \quad \bar{\mu}^{(k+1)} = \bar{\mu}^{(k)} + \lambda_\mu \delta \bar{\mu}^{(k)};$$

(9)

where $\mathbf{b}^{(k)} = \mathbf{I}_s - \mathbf{F}_s \left[ \boldsymbol{\mu}^{(k)} \right]_\mu; \quad \delta \boldsymbol{\mu}^{(k)}$ are 2$N \times 1$ column vectors denoting the optical properties and their perturbations, respectively, at the $N$ discretizing voxels; $\lambda_\mu$ is the relaxation factor; $J^{(k)}_\mu = \left[ \mathbf{J}^{(k)}_\mu \mathbf{J}^{(k)}_\mu \right]$ is the Jacobian matrix of $\mathbf{F}_s$ with $\mathbf{J}^{(k)}_\mu$ being the $M \times N$ sub-matrices regarding the absorption and reduced scattering coefficients, respectively, which can be conventionally calculated from the photon density and the Green's function values at the $N$ voxels that are obtained with BEM through the boundary integral equation [37].

With the regional optical homogeneity assumption for the hard-prior scheme, Eq. (9) is reduced to a $2(L+1)$ matrix equation for estimating the sub-domain optical property sets $\mu^{(k+1)}$ with the aid of structural a priori information $\gamma^{(k)}$

$$\mathbf{b}^{(k)} = J^{(k)}_\mu \delta \boldsymbol{\mu}^{(k)}; \quad \bar{\mu}^{(k+1)} = \bar{\mu}^{(k)} + \lambda_\mu \delta \bar{\mu}^{(k)};$$

(10)

where $\mathbf{b}^{(k)} = \mathbf{I}_s - \mathbf{F}_s \left[ \boldsymbol{\mu}^{(k)} \right]_\mu; \quad J^{(k)}_\mu = \left[ \mathbf{J}^{(k)}_\mu \mathbf{R} \mathbf{J}^{(k)}_\mu \mathbf{R} \right]$ is the reduced Jacobian matrix with $\mathbf{R}$ being a $N \times (L+1)$ voxel-to-region mapping matrix with its entry given as [19]

$$\Sigma_r = \begin{cases} 1 & \text{if } \mathbf{r}_i \in \Omega_r, \\ 0 & \text{otherwise} \end{cases}$$

where $\mathbf{r}_i$ is the positional vector of the $i$-th voxel. $\delta \boldsymbol{\mu}^{(k)}$ is a $2(L+1) \times 1$ vector denoting the optical property perturbation sets in the $L+1$ sub-domains. As with the voxel-based case, Eq. (10) can be universally solved by the algebraic reconstruction technique (ART) [39, 40].

Shape-reconstruction

With the optical properties $a$ priori $\mu^{(k+1)}$ being reconstructed in the previous optical-reconstruction step, the shape-reconstruction at the $k$-th iteration is for updating the spherical harmonics coefficients: $\gamma^{(k+1)}$. The inverse problem in Eq. (7) is solved with a framework of nonlinear cost-minimization Levenberg-Marquardt method [17, 18, 39]

$$\gamma^{(k+1)} = \gamma^{(k)} + \lambda_\gamma \left( J^{(k)}_\gamma J^{(k)}_\gamma + \alpha \mathbf{D}^{(k)} \mathbf{D}^{(k)} \right)^{-1} J^{(k)}_\gamma \mathbf{b}^{(k)};$$

(11)

where $\mathbf{b}^{(k)} = \mathbf{I}_s - \mathbf{F}_s \left[ \gamma^{(k)} \right]_\gamma; \quad \lambda_\gamma$ is the relaxation factor; the Jacobian matrix $J^{(k)}_\gamma = \partial \mathbf{F}_s \left[ \gamma^{(k)} \right]_\gamma / \partial \gamma^{(k)}$ is constructed using a perturbation method based on the BEM forward calculation: $J^{(k)}_\gamma = \lambda_\gamma \mathbf{E}_s \left[ \gamma^{(k)} \right]_\gamma / \partial \gamma^{(k)}$; $\mathbf{D}$ is a regularization matrix of diagonal form with its diagonal elements being the norm of each column of $J^{(k)}$; and $\alpha$ is the regularization parameter.

Since the different types of the shape coefficients contribute differently to the measurement data, we adopts a “center-priority” strategy for the shape coefficients.
reconstruction, i.e., the low degree coefficients such as those representing the center positions of the sub-domains were reconstructed at the first iterations for stabilizing the algorithm, and the high degree coefficients for describing the finer details of the sub-domain shapes are then appended to the reconstruction process at the later iterations. This technique can effectively enhance the robustness of the reconstruction procedure against the initial conditions, and will be further discussed later in the discussion section.

Initialization

It is vital for the Newton-Raphson iterative procedure to be properly initialized. In the scheme, the initial optical properties \( \mu^{(0)} \) are homogeneously set to be those of the primary constituent in the imaging domain, such as the muscle sub-domain in animal experiments or the background material in phantom experiments. The initialization of the shape coefficients \( \gamma^{(0)} \) could be divided into two parts: Firstly, the 0-degree coefficients, \( \left\{ C_{0,i}^{(0)} \right\} \), for each sub-domain are naturally set to be its center coordinates by definition

\[
\begin{bmatrix}
C_{0,i}^{(0)}, C_{0,j}^{(0)}, C_{0,k}^{(0)}
\end{bmatrix} = \frac{1}{N(\Omega_i)} \sum_{i=1}^{N(\Omega_i)} \mathbf{r}_i
\]

where \( N(\Omega_i) \) is the number of the discretizing voxels in the sub-domain \( \Omega_i \), and \( \mathbf{r}_i \) is positional vector of the \( i \)-th voxel. Secondly, the higher-degree coefficients, \( \left\{ C_{l,m}^{(0)} \right\}, l=1,...,L, m=-l,...,l \), for the shape description, are determined for each sub-domain using a least-squares fitting between its a priori boundary and spherical harmonics approximation [31]

\[
\min \sum_i \left[ v_i(\theta_i, \phi_i) - \sum_l \sum_{m=-l}^{m=l} C_{l,m}^{(0)} \tilde{Y}_l^m(\theta_i, \phi_i) \right]^2
\]

where, \( v_i(\theta_i, \phi_i) \) is the coordinates of the \( i \)-th vertice on the boundary of the \( l \)-th sub-domain with \( \theta_i \in [0, \pi] \) and \( \phi_i \in [0, 2\pi] \) being the corresponding altitude and azimuth angles, respectively.

With the aforementioned methodology, we could finally acquire the background optical structure of the imaging domain: \( \left\{ \mu, \gamma \right\} \).

FMT reconstruction

In the FMT reconstruction, the fluorescence map \( \eta(\mathbf{r}) \) is recovered on basis of the obtained optical structure: \( \left\{ \mu, \gamma \right\} \), using the following linear system [6, 41]

\[
\mathbf{I}_{\text{sd}} = \mathbf{W}[\mu, \gamma] \eta
\]

where \( \mathbf{I}_{\text{sd}} = \left[ I_{s1}^{(0)}, I_{s1}^{(1)}, I_{s1}^{(2)}, ..., I_{sM}^{(M)} \right] \) is the normalized Born data with \( I_{s1}^{(m)} \) and \( I_{s1}^{(M)} \) \( (m=1,2,\ldots,M) \) being the measured flux for the \( m \)-th source-detector combination, respectively; \( \eta = [\eta_1, \eta_2, \ldots, \eta_N]^T \) is the vector numerating the fluorescent yield at the \( N \) voxels, and \( \mathbf{W}[\mu, \gamma] \) is a \( M \times N \)-dimensional weighting matrix, which again implicitly derived from the BEM-calculated photon density and Green's function values at the \( N \) voxels. A reasonable solution to Eq. (14) is also achieved by the ART [41].
3. Simulative validations

3.1 Numerical model

Simulation validations are performed on a cylindrical domain of turbid medium with 17 mm radius and 35 mm height, as shown in Fig. 2. The domain is divided into five sub-domains with different optical properties to emulate heart, liver, lungs, and muscle of a mouse torso embedded in a cylindrical imaging chamber full of the matching fluid. The geometries (shapes and positions) of the organs are extracted from the Digimouse, a 3-D digital mouse model that is developed from the CT images and cryosection data and provides a simplified atlas of mouse anatomy [42]. These organ geometries are approximated with the 2-degree spherical harmonics, respectively, leading to 27 shape coefficients to be reconstructed for each organ. A cylindrical fluorescent target with 3.5 mm radius and 6 mm height is placed in the liver with its center at \((x = -4 \text{ mm}, y = 0 \text{ mm}, z = 11 \text{ mm})\) and optical properties being the same as those of liver.

![Simulation model with a fluorescence target in the liver. Sub-domains index 1-5 represent the muscle, heart, liver, left lung, and right lung, respectively.](image)

Table 1. Reconstructed sub-domain optical properties for the simulation model

| Sub-domain | \(\mu'_a/\mu'_s \text{ (mm}^{-1}\) |
|-----------|-------------------------------|
| **True**  | **Initial**                  | **Hard-Prior** | **Soft-Prior** | **Shape-Parameterized** |
| Muscle    | 0.0068/1.03                  | 0.0066/0.97    | 0.0065/0.95    | 0.0069/1.01             |
| Heart     | 0.0104/0.99                  | 0.0189/1.41    | 0.0082/0.83    | 0.0095/1.04             |
| Liver     | 0.0176/0.65                  | 0.0232/0.82    | 0.0131/0.72    | 0.0193/0.68             |
| Left Lung | 0.0203/1.95                  | 0.0338/2.62    | 0.0114/1.67    | 0.0199/2.02             |
| Right Lung| 0.0203/1.95                  | 0.0273/1.66    | 0.0120/1.41    | 0.0195/1.88             |

3.2 DOT for background optical structures

For better demonstrating the superiority of the proposed shape-parameterized DOT method over the previous structural-prior-based DOT with either the hard- or soft-prior scheme for acquiring the background optical structure to improving FMT, the optical properties of the sub-domains are obtained using the three schemes, with the initial optical properties...
homogeneously set to be the typical values of living muscle: $\mu_\nu^{(0)} = 0.0040$ mm$^{-1}$ and $\mu'_\nu^{(0)} = 0.80$ mm$^{-1}$. For mimicking scenario with imperfect structural priors in practice, we distort all the initial shape coefficients of the four sub-domains (heart, liver, left lung, and right lung) that are extracted with the aforementioned least-squares fitting, by randomly adding errors of $\pm 15\%$, which is in the typical deviation range of a successful organ segmentation according to our practice. These initial shape coefficients are also used to construct the structural a priori information for the hard- and soft-prior regularizations. Here the relaxation factors $\lambda_\nu$ and $\lambda'_\nu$ are chosen to be 0.75 and 0.8, respectively. Table 1 lists the reconstructed sub-domain optical properties results in contrast to the true ones [43–45] (mean values of $\mu_\nu$ and $\mu'_\nu$ in each sub-domain for the soft-prior one). Figure 3 shows the relative errors of the reconstructed absorption and reduced scattering coefficients for the five different sub-domains in Table 1. From the results it is clearly observed that, the proposed shape-parameterized DOT method has a notable advantage over the previous hard- and soft-prior schemes for obtaining the sub-domain optical properties – nevertheless, its performance is still not perfect. As can be noticed in Fig. 3(a), the reconstructed absorption coefficients of the liver and heart exhibit large deviations from their true values, and the reduced scattering coefficient of the heart has a little large disparity with its true one, as shown in Fig. 3(b).

Fig. 3. Relative errors of the reconstructed (a) absorption and (b) reduced scattering coefficients of the five sub-domains in Table 1.

The iterative process of estimating the shape coefficients of the four sub-domains (heart, liver, left lung, and right lung) is shown in Fig. 4, where the red meshes denote the reconstructed sub-domain geometries. As shown in the figure, the result is very promising with good convergence for the associated shape coefficients. Of course, because of the presence of the measurement noise and the inaccuracy of the reconstructed optical properties (Table 1 and Fig. 3), fully accurate recovery of the true geometries is impossible to achieve.

Fig. 4. The iterative process of estimating the shape coefficients of the four sub-domains (heart, liver, left lung, and right lung) from noisy simulated data. The red surfaces denote the reconstructed results.
To assess the effectiveness of the DOT reconstruction, two metrics are defined: one calculating the residue between the simulated data and the forward model for the overall performance, referred to as residue-metric

$$\varepsilon_1(k) = \frac{1}{M} \sum_{m=1}^{M} \left( I_x^{(n)} - F_x^{(n)} \left[ I_x^{(k)}, \gamma^{(k)} \right] / I_x^{(n)} \right)^2,$$

and the other calculating the distance between the reconstructed and true shape coefficients for the shape-reconstruction, referred to as shape-metric

$$\varepsilon_\gamma (k) = \| \hat{\gamma} - \gamma^{(k)} \|,$$

where $\hat{\gamma}$ denotes the set of true shape coefficients in the simulation model. Figures 5(a) and 5(b) show the residue-metric $\varepsilon_1$ and the shape-metric $\varepsilon_\gamma$ versus the iteration index $k$, respectively. It is seen that both the metrics, $\varepsilon_1$ and $\varepsilon_\gamma$, are decreased rapidly in the first iterations, since the measurements are especially sensitive to the low degree coefficients of the sub-domains, and then they reach their minimums, respectively, thanks to the successful recovery of the finer details. The results demonstrate that the applicability of the shape-parameterized DOT method in acquiring the optical structure and also its performance superiority over the previous hard- and soft-prior ones.

### 3.3 FMT reconstruction

The obtained optical structures for the simulation model are then used directly in the BEM forward calculation in the FMT reconstruction. Figure 6 illustrates the sliced yield-images at $z = 11$ mm obtained using the five kinds of the optical structures (true, initial, hard-prior, soft-prior, and shape-parameterized, respectively) for the two fluorescent TBCs. To facilitate the comparison of the reconstructed images with the true ones, the cut-lines along the X axis in the reconstructed images, i.e., the X-profiles, are extracted, as shown in Fig. 6(f). From Fig. 6(b), it is obvious that the image obtained using the initial homogeneous optical background has a large deviation of the target location for the contrast of 3:1. Because the hard-prior scheme produces significant errors in the optical properties reconstruction with the imperfect initial structural a priori information, and the soft-prior one yields underestimated optical property values for almost all the sub-domains (Table 1 and Fig. 3), the fluorescence reconstructions with these defective optical structures result in inferior performances in terms of the location and especially quantitative accuracy of the target, as shown in Figs. 6(c) and 6(d), respectively. Comparatively, images obtained with the shape-parameterized DOT reconstructed optical structure reasonably disclose the target for all the two TBCs, as shown in Fig. 6(e), which clearly perform better than the other techniques presented.
Fig. 6. Reconstructed yield-images at $z = 11$ mm, using the optical structures: (a) true, (b) initial, (c) hard-prior, (d) soft-prior, and (e) shape-parameterized DOT reconstructed, and (f) their X-profiles, for the fluorescent TBCs of (top) 5:1 and (bottom) 3:1, respectively. The black circles and dashed lines indicate target location.

4. Experimental validations

4.1 Instrumentation and phantom

A phantom experiment is performed using a CW-FMT system of photon-counting mode, as shown in Fig. 7(a). The system uses a 660 nm diode laser (LTC100/LPS-660-FC, Thorlabs), specially for Cy5.5 dye with its peak excitation and emission wavelengths at 670 and 710 nm, respectively. The excitation light from the laser with intensity is adjusted appropriately by a variable attenuator (FVA-3100, EXFO, Canada), is coupled into a source fiber with $62.5 \, \mu m$ core diameter and $0.22$ numerical aperture (NA). The transmitted light is collected by 8 detection fibers of $500 \, \mu m$ core diameter and $NA = 0.37$, evenly distributed on the surface of the phantom from $101.25^\circ$ to $258.75^\circ$ opposite to the incidence position ($0^\circ$) with their tips being $1$ mm apart from the phantom surface, i.e., in a noncontact configuration, as shown in Fig. 7(b), and coupled into an $8 \times 1$ fiber-optic switch with its output collimated for normal incidence to a successive motorized filter wheel housing a bandpass interference filter (Cy5.5-A Emitter, Semrock). The filtered light, finally, enters into a PMT photon-counting head (H7155-01, Hamamatsu, Japan) coupled with a counting unit for the photon-counting detection. By rotating the phantom at an angular interval and translating it at a vertical displacement, a 3-D spatial sampling process can be achieved with a programmed pattern. The whole experimental set is placed in a dark environment to shield the stray light.

A cylindrical solid phantom with $15$ mm radius and $80$ mm height is fabricated from polyformaldehyde, with its background optical properties being $\mu_a^{(0)} = 0.0040 \, mm^{-1}$ and $\mu_s^{(0)} = 0.80 \, mm^{-1}$ at $660 \, nm$ [Fig. 7(b)]. Three cylindrical holes, referred to as sub-domains #2, #3, and #4 (the solid phantom referred to as sub-domain #1), with radii of 5, 4, and 3 mm and heights of 40, 30, and 20 mm, are drilled $6$ mm away from the cylinder central-axis, respectively, as shown in Fig. 8. In our experiments, 3-D data sets are acquired at $5$ imaging planes of $z = 20, 30, 40, 50, \text{and} 60$ mm, respectively, with an angular interval of $22.5^\circ$, which provides $16$ equally spaced projection angles for each scanning plane. As a result, two sets of $M = 640$ measurements are acquired at the excitation and emission wavelengths using integration times of $100$ and $500$ ms, respectively. Under the above experimental setup, the minimal photon counting numbers in the excitation and emission measurements are $1.75 \times 10^4$ and $2.32 \times 10^3$, respectively. This means that the used system can achieve $<1\%$ and $<3\%$ noisy levels (inversely proportional to square root of the photon count) for the excitation and emission measurements, respectively, in agreement with the simulation case.
4.2 DOT reconstruction

To construct an optically heterogeneous background, the phantom sub-domains #2 and #3 are filled with mixture of India ink and Intralipid solution with the absorption/reduced scattering coefficients of 0.008/1.6 mm⁻¹ and 0.012/2.4 mm⁻¹, respectively. A fluorescent target is formed by filling sub-domain #4 with mixture of Intralipid solution, Indian Ink and Cy5.5-dyes of ~2 μM and ~0.5 μM concentrations, respectively, making that the optical properties of sub-domain #4 are approximately the same as those of sub-domain #1. The reconstructions are achieved using a difference imaging scheme with a reference phantom that is geometrically and optically equivalent to the background one.

| Sub-domain | \( \mu_a \) / \( \mu_s' \) (mm⁻¹) |
|------------|-------------------------------|
| #1         | True 0.0040/0.80             |
|           | Initial 0.0043/0.87           |
|           | Hard-Prior 0.0042/0.85        |
|           | Soft-Prior 0.0069/1.34        |
|           | Shape-Parameterized 0.0041/0.82 |
| #2         | 0.0080/1.60                   |
|           | 0.0040/0.80                   |
|           | 0.0102/1.81                   |
|           | 0.0069/1.34                   |
|           | 0.0075/1.64                   |
| #3         | 0.0120/2.40                   |
|           | 0.0137/1.75                   |
|           | 0.0089/1.78                   |
|           | 0.0109/2.19                   |

The initial shape coefficients of the two sub-domains (#2 and #3) are extracted also with the aforementioned least-squares fitting and then deviated by randomly adding errors of ±15% similar to the simulation case. The choice of the relaxation factors are consistent with the simulations. Table 2 lists the reconstructed sub-domain optical properties of the phantom using the hard-prior, soft-prior, and shape-parameterized DOT methods, respectively. The relative errors of the reconstructed absorption and reduced scattering coefficients for the three sub-domains in Table 2 are shown in Fig. 9. The experimental reconstruction similarly shows the superiority of the proposed shape-parameterized DOT method over the previous hard- and
soft-prior schemes in the optical structure acquisition of the imaging domain, while the same
defects as those in the simulations are still observed: the reconstructed absorption coefficients
of the sub-domains #2 and #3 exhibit a certain amount of errors, as shown in Fig. 9(a), and
the reconstructed reduced scattering coefficient of the sub-domain #3 has a little bit large
deviation comparing with its corresponding true one, as shown in Fig. 9(b). Figure 10 shows
the iterative process of estimating the shape coefficients of the sub-domains #2 and #3. The
residue-metric and the shape-metric versus the iteration index $k$ are presented in Figs. 11(a)
and 11(b), respectively, to demonstrate the reasonability and convergence of the
reconstruction.

![Fig. 9. Relative errors of the reconstructed (a) absorption and (b) reduced scattering
coefficients of the three sub-domains in Table 2.](image)

![Fig. 10. The iterative process of estimating the shape coefficients of the sub-domains #2 and
#3. The green surfaces are the actual shapes, and the red ones denote the reconstructed results.](image)

![Fig. 11. Metrics used for assessment of the reconstruction performance, plotted as functions
of the iterations: (a) the residue-metric, and (b) the shape-metric.](image)

### 4.3 FMT reconstruction

Figure 12 shows the obtained yield-images at $z = 48$ mm using the five optical structural
backgrounds (true, initial, hard-prior, soft-prior, and shape-parameterized) for the two Cy5.5
concentrations (~2 μM and ~0.5 μM), and also their X-profiles, respectively. The results are
consistent with the previous observations in the simulations: Fig. 12(b) shows that the approach of assuming a homogeneous optical background is unable to correctly recover the size and location of the target for the low concentration. Although, the shape-parameterized DOT method with a low degree spherical harmonics might still perform imperfectly in obtaining the phantom optical structure (Table 2 and Fig. 10), the FMT reconstruction with the aid of this DOT scheme generates consistently acceptable results, as shown in Fig. 12(e), which can be potentially optimized with higher degree approximations. Nevertheless, the hard- and soft-prior schemes, despite of their comparatively inferior performances in obtaining the background optical properties (Table 2 and Fig. 9), also provide an effective means of enhancing the FMT reconstructions, as shown in Figs. 12(c) and 12(d), and might even be better quantitative for the optical-reconstruction, especially in the case that the highly confident structural a priori is available.

5. Discussions

In practice, a successful application of the proposed shape-parameterized DOT method is dependent on two crucial factors: one is the availability of the reasonably accurate structural a priori; the other is completeness of the shape parameterization. The former normally requires a support from the anatomical imaging modalities with high soft tissue contrast, such as MRI or phase-contrast X-ray CT [8, 46], and also can be potentially obtained by registry between the conventional micro-CT images and a standard digital mouse atlas. In both the methods some errors are inevitably introduced. The latter requires a high degree representation of the organ domains that means a significant increase in the shape coefficient number and therefore a degradation in the inversion condition.

In order to assess the performance of the proposed shape-parameterized DOT scheme with increase in the spherical harmonics degree while without changing the measurement number, herein, we compare the DOT reconstructions with 2- and 3-degree spherical harmonics approximations.
approximation for the surface descriptions, respectively. This time, the chambered Digimouse model is simplified to a medium with two sub-domains containing liver and muscle, as shown in Fig. 2. Figure 13 shows the surface of liver domain approximated with 2- and 3-degree spherical harmonics, leading to 27 and 48 shape coefficients, respectively. Table 3 lists the reconstructed optical properties of the two sub-domains, and the evolving process of the liver reconstruction with the two kinds of degrees of the spherical harmonics approximation are shown in Figs. 14 and 15, respectively. It is seen from the figures that, the results are satisfactory for both the cases and although the involvement of the low-degree approximation provides more overall accurate optical-reconstruction and faster shape coefficients convergence (Fig. 14), the high-degree approximation increases the fidelity of describing the liver geometry (Fig. 15). The FMT reconstructions with the obtained optical structures are compared for the same fluorescent target as in the simulations, as shown in Fig. 16, where the yield-images with the true optical structure, as shown in Fig. 16(a), are used as a gold-standard. It is clearly observed that the proposed scheme with the 3-degree spherical harmonics approximation has a better performance for improving the sensitivity of FMT than that with the 2-degree description.

Table 3. Reconstructed values of the sub-domain optical properties with different degrees of spherical harmonics

| Sub-domain | $\mu_s/\mu'_t$ (mm$^{-1}$) | True | Initial | $W=2$ | $W=3$ |
|------------|-----------------|------|---------|-------|-------|
| Muscle     | 0.0068/1.03     | 0.0040/0.80 | 0.0069/1.01 | 0.0070/1.02 |
| Liver      | 0.0176/0.65     | 0.0175/0.66 | 0.0180/0.68 |

Fig. 14. The evolving process of the liver geometry with 2-degree spherical harmonics approximation. The red surfaces denote the reconstructed results.

Fig. 15. The evolving process of the liver geometry with 3-degree spherical harmonics approximation. The red surfaces denote the reconstructed results.
Although the number of unknowns in the shape-parameterized DOT reconstruction is greatly reduced, attention should be paid to further optimization of the shape-reconstruction to balance the different contributions of the shape coefficients to the measurement data, which, if simply recovered simultaneously without being properly scaled, probably fails the reconstruction. To do so, a “center-priority” strategy for the shape coefficients reconstruction is adopted as aforementioned. An intuitive explanation for use of this strategy is that, for a sub-domain, deviations in its center position and expansion coefficients influence the boundary measurements in different ways: the center position deviation alters the distance from the domain to the domain boundary, and thus re-distributes the photon density over the whole domain; in contrast, the deviation of a expansion coefficient changes the sub-domain shape and mainly changes the fine pattern of the boundary flux. This significant difference in the contributions requires the center position and the expansion coefficients to be handled differently. In particular, the center position needs to be estimated firstly to grasp the coarse configuration of the boundary measurements, and stabilizes the later reconstruction process for the expansion coefficients.

The proposed shape-parameterized DOT guided FMT method is specially suitable for imaging the chest and abdomen regions. In these regions, however, there are also some other organs, mainly the bones, which might not be easily modeled by spherical harmonics approximation. Nevertheless, due to the significantly higher density of the bones than the surrounding tissue, nearly accurate structural a priori of these high-contrast regions could be obtained from the anatomical images. As a result, to include the bones, only the optical-reconstruction is required in the whole procedure, based on the accurate structural a priori.

6. Conclusions

In the paper we proposed an shape-parameterized DOT method for obtaining the background optical structure to improving the sensitivity of FMT. Both the numerical simulations and phantom experiments reveal the superiority of the scheme over the previously developed hard- and soft-prior ones, in the case of some low confident initial structural a priori information. Furthermore, a comparative investigation is performed for a single liver sub-domain described with the 2- and 3-degree spherical harmonics and demonstrates the performance improvement of the proposed scheme with increase in the degree of the geometry approximation. Although higher degree spherical harmonics describes more complicated geometry and therefore yields better shape description, it accordingly brings greater computational burden and potentially aggravates the ill-posedness of the inverse.
problem, therefore, a balance between the condition of the inverse problem and complexity of the shape approximation should be made in applications. Future work will focus on applying the proposed approach to \textit{in vivo} small animal imaging, with support of anatomical imaging modalities, and more complex examples such as reconstruction of multiple domains with higher degree (≥3-degree) spherical harmonics approximation are also of interest. Finally it is worthy to point out that, although the approach used for the shape coefficient initialization is easy and automatic to application without any challenging or trivial form of the problem, some other ways, such as initializing the shape of the sub-domains by computing the soft-prior reconstruction, thresholding the reconstruction, and then fitting a low order spherical harmonic expansion to the resulting characteristic function, would be appreciated in further work.

**Acknowledgment**

The authors acknowledge the funding supports from the National Natural Science Foundation of China (81101106, 61108081, 81271618, 81371602), Research Fund for the Doctoral Program of Higher Education of China (20120032110056), and Tianjin Municipal Government of China (13JCZDJC28000, 12JCQNJC09400).