Performance evaluation of the simplified spherical harmonics approximation for cone-beam X-ray luminescence computed tomography imaging

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As an emerging molecular imaging modality, cone-beam X-ray luminescence computed tomography (CB-XLCT) uses X-ray-excitable probes to produce near-infrared (NIR) luminescence and then reconstructs three-dimensional (3D) distribution of the probes from surface measurements. A proper photon-transportation model is critical to accuracy of XLCT. Here, we presented a systematic comparison between the common-used Monte Carlo model and simplified spherical harmonics (SP_N). The performance of the two methods was evaluated over several main spectrums using a known XLCT material. We designed both a global measurement based on the cosine similarity and a locally-averaged relative error, to quantitatively assess these methods. The results show that the SP_3 could reach a good balance between the modeling accuracy and computational efficiency for all of the tested emission spectrums. Besides, the SP_1 (which is equivalent to the diffusion equation (DE)) can be a reasonable alternative model for emission wavelength over 692 nm. *In vivo* experiment further demonstrates the reconstruction performance of the SP_3 and DE. This study would provide a valuable guidance for modeling the photon-transportation in CB-XLCT.

Keywords: Cone-beam X-ray luminescence computed tomography; photon-transportation model; simplified spherical harmonics approximation; diffusion equations.

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1. Introduction

X-ray luminescence computed tomography (XLCT) is an attractive imaging modality, with the potential to improve the characterization and treatment response of small tumors.^{1,2} The deep embedded nanophosphor materials in biological tissues emit near-infrared (NIR) luminescence light signals when stimulated by X-rays.³ These materials, such as NaGdF₄:Eu, GOS:Eu, Gd₂O₂S:Eu, EU₂O₃, and Gd₂O₂S:Tb, have been successfully applied to past XLCT study. Generally, these materials contain about 12 emission peaks (607, 615, 618, 620, 623, 627, 667, 692, 700, 703, 720 and 802 nm).⁴⁻⁹

Compared with conventional pre-clinical molecular imaging techniques, i.e., fluorescence molecular tomography (FMT)^{10,11} and bioluminescence tomography (BLT),^{12,13} the advantages of XLCT are manifested in the avoidance of a significant background noise and the ability of imaging deeper tissue.^{3-6,9} XLCT imaging could be achieved either by the pencil-beam XLCT (PB-XLCT)⁵ or the cone-beam XLCT (CB-XLCT) methodologies.⁶ The PB-XLCT has high-resolution at depth but with long time of data acquisition (typically, ≥ 624 s).⁹ Compared with PB-XLCT, the CB-XLCT can decrease the scanning time and fully utilize the X-ray dose by using a cone beam X-ray source (multi-view data scanning: 134 s or single view data scanning: ≤ 1 s).^{5,9}

The establishment of an accurate and practical photon-transportation model is key in XLCT. In optical imaging, photon propagation in tissues can be depicted by the Monte Carlo (MC) method, or by the radiative transfer equation (RTE) theory.¹⁴⁻¹⁶ However, both methods are computationally expensive. The diffusion equations (DE), a low-order approximation of RTE, have been extensively used for three-dimensional (3D) optical imaging (e.g., BLT, FMT, and XLCT.^{4-6,10-13}) because of its computational efficiency. However, DE is not applicable in tissues with low-scattering-low-absorption and low-scattering-high-absorption.¹⁷ Besides, it is not suitable to describe the photon transportation in regions near the light source^{14,15} by DE.

To get a more accurate approximation of RTE, a high-order simplified spherical harmonics (SP_N) approximation has been developed. It exhibits better performance than the DE, thus was introduced in optical imaging.¹⁸ Some studies have proved that the SP_N models can efficiently improve the imaging accuracy, e.g., BLT, FMT.¹⁹⁻²¹ Further,

some hybrid models based on the SP_N have also been proposed to exhibit the applicability in optical imaging.^{22,23} However, SP_N models do not converge to the exact RTE approximation when $N \rightarrow \infty$.¹⁸ Besides, SP_N models yield different best solutions when using different N and different XLCT probes. These two facts lead to the need of individual determination of the optimal N . Therefore, it is necessary to evaluate the performance of SP_N with different N values for CB-XLCT imaging.

In this paper, we investigated the performance and applicability of the SP_N models for CB-XLCT imaging in detail. More specifically, the performance of the SP_N models was compared with the MC method under the finite element method (FEM), from order $N = 1$ up to order $N = 7$ over several main spectrums for the known XLCT probes. Then, an *in vivo* data was used to further evaluate reconstruction performance of the SP_3 and SP_1 .

The outline of this paper is as follows. Section 2 presents the theory and method of this paper. Then, the experimental results were demonstrated based on a 3D digital mouse model and an *in vivo* experiment in Sec. 3. Finally, we conclude the paper and discuss relevant issues in Sec. 4.

2. Method

2.1. SP_N model

Higher-order SP_N models result in a significant increase in time-consumption. Thus, the SP_N up to SP_7 were investigated. Equations (1) give the 3D SP_7 equations. The SP_5 , SP_3 and SP_1 (equals to DE) can be easily obtained from SP_7 .¹⁸

$$\left\{ \begin{aligned} & -\nabla \cdot \frac{1}{3\mu_{a1}} \nabla \varphi_1 + \mu_a \varphi_1 = S + \left(\frac{2}{3} \mu_a \right) \varphi_2 - \left(\frac{8}{15} \mu_a \right) \varphi_3 \\ & + \left(\frac{16}{35} \mu_a \right) \varphi_4 - \nabla \cdot \frac{1}{7\mu_{a3}} \nabla \varphi_2 + \left(\frac{4}{9} \mu_a + \frac{5}{9} \mu_{a2} \right) \varphi_2 \\ & = -\frac{2}{3} S + \left(\frac{2}{3} \mu_a \right) \varphi_1 + \left(\frac{16}{45} \mu_a + \frac{4}{9} \mu_{a2} \right) \varphi_3 \\ & - \left(\frac{32}{105} \mu_a + \frac{8}{21} \mu_{a2} \right) \varphi_4 - \nabla \cdot \frac{1}{11\mu_{a5}} \nabla \varphi_3 \\ & + \left(\frac{64}{225} \mu_a + \frac{16}{45} \mu_{a2} + \frac{9}{25} \mu_{a4} \right) \mu_{a3} \\ & = \frac{8}{15} S - \left(\frac{8}{15} \mu_a \right) \varphi_1 + \left(\frac{16}{45} \mu_a + \frac{4}{9} \mu_{a2} \right) \varphi_2 \\ & + \left(\frac{128}{525} \mu_a + \frac{32}{105} \mu_{a2} + \frac{54}{175} \mu_{a4} \right) \varphi_4 - \nabla \cdot \frac{1}{15\mu_{a7}} \nabla \varphi_3 \\ & + \left(\frac{256}{1225} \mu_a + \frac{64}{245} \mu_{a2} + \frac{324}{1225} \mu_{a4} + \frac{54}{175} \mu_{a6} \right) \varphi_4 \\ & = -\frac{16}{35} S + \left(\frac{16}{35} \mu_a \right) \varphi_1 - \left(\frac{32}{105} \mu_a + \frac{8}{21} \mu_{a2} \right) \varphi_2 \\ & + \left(\frac{128}{525} \mu_a + \frac{32}{105} \mu_{a2} + \frac{54}{175} \mu_{a4} \right) \varphi_3 \end{aligned} \right. \quad (1)$$

where $\mu_{an} = \mu_t(x) - \mu_s(x)g^n$ is the n th order absorption coefficient, μ_s is the scattering coefficient, and g is the anisotropy parameter. S is the XLCT source density, and φ_n is the composites of the n th order Legendre moments, which is defined as follows:

$$\begin{cases} \varphi_1 = \phi_0 + 2\phi_2, \\ \varphi_2 = 3\phi_2 + 4\phi_4, \\ \varphi_3 = 5\phi_4 + 6\phi_6, \\ \varphi_4 = 7\phi_6. \end{cases} \quad (2)$$

By setting $\phi_6 = 0$ and solving Eq. (1), the SP_5 can be obtained. Similarly, the SP_3 can be obtained by setting $\phi_6 = \phi_4 = 0$ and DE (SP_1) can be obtained by setting $\phi_6 = \phi_4 = \phi_2 = 0$. The boundary conditions of the SP_N model can be found in Klose's work.¹⁸

For the case of $N = 1$ and $N = 3$, the DE (SP_1) and SP_3 were shown in Eqs. (3) and (4) respectively:

$$-\nabla \cdot \frac{1}{3\mu_{a1}} \nabla \phi_0(r) + \mu_a(r)\phi_0(r) = S(r), \quad (3)$$

where r is the position vector.

$$\begin{cases} -\nabla \cdot \frac{1}{3\mu_{a1}} \nabla \phi_1(r) + \mu_a \phi_1(r) - \left(\frac{2}{3}\mu_a\right)\phi_2(r) = S, \\ -\nabla \cdot \frac{1}{7\mu_{a3}} \nabla \phi_2(r) + \left(\frac{4}{9}\mu_a + \frac{5}{9}\mu_{a2}\right)\phi_2(r) \\ -\frac{2}{3}\mu_a \phi_1(r) = -\frac{2}{3}S. \end{cases} \quad (4)$$

Using the FEM and Green's first formula,²⁴ the SP_N model can be discretized to the matrix-form equation. For the case of $N = 3$, SP_3 matrix-form equation can be obtained:

$$\begin{bmatrix} M_{1\varphi_1} & M_{1\varphi_2} \\ M_{2\varphi_1} & M_{2\varphi_2} \end{bmatrix} \begin{bmatrix} \varphi_1 \\ \varphi_2 \end{bmatrix} = \begin{bmatrix} S \\ -\frac{2}{3}S \end{bmatrix}. \quad (5)$$

In Eq. (5), the unknown source S is approximated as $S(r) \approx \sum_{p=1}^T \Phi_p X_p \nu_p(r)$, where X_p is the unknown material distribution, $\nu_p(r)$ is the base function for node p and T is the total number of the discretized nodes. Then, the following equation can be obtained:

$$\begin{bmatrix} M_{1\varphi_1} & M_{1\varphi_2} \\ M_{2\varphi_1} & M_{2\varphi_2} \end{bmatrix} \begin{bmatrix} \varphi_1 \\ \varphi_2 \end{bmatrix} = \begin{bmatrix} E_\Phi & 0 \\ 0 & E_\Phi \end{bmatrix} \begin{bmatrix} X \\ -\frac{2}{3}X \end{bmatrix}. \quad (6)$$

2.2. CB-XLCT imaging model based on the SP_N method

The CB-XLCT imaging model includes three steps which are shown as follows:

First, X-rays are emitted from the cone-beam X-ray source. According to Beer-Lambert's law, X-rays suffer from attenuation in tissues as follows:

$$X(r) = X_0 \exp \left\{ - \int_{r_0}^r \mu_x(\tau) d\tau \right\}, \quad (7)$$

where $X(r)$ is the X-ray source intensity at position r , X_0 is the X-ray source intensity at the initial position r_0 , and μ_x is the X-ray attenuation coefficient which can be obtained by the attenuation-based CT technique.

Second, XLCT probes excited by X-rays emit visible or NIR light. This can be expressed as follows:

$$S(r) = \varepsilon X(r)\rho(r), \quad (8)$$

where ρ is the material density, and ε is the light yield.

Finally, the CCD camera captures the emitted photons which reach the surface of biological tissues. The photon-transportation in biological tissues can be modeled by the SP_N method and expressed as follows:

$$J^+ = A_{SP_N} X, \quad (9)$$

where J^+ is the exiting partial current measurement.

For the reconstruction, due to the ill-posedness of CB-XLCT problem and the noise in the measured data, it is impractical to solve the unknown material distribution X directly.^{6,9} Meanwhile, XLCT materials are sparsely distributed. Therefore, the L_1 regularization can be applied to CB-XLCT imaging as follows:

$$\min \|A_{SP_N} X - J^+\|_2^2 + \tau \|X\|_1, \quad (10)$$

where τ is the regularization parameter.

3. Experiments and Results

3.1. Forward simulation

To test the accuracy of the SP_N model based on 12 emission spectrums of the known XLCT materials for CB-XLCT imaging, we conducted numerical experiments of forward modeling. These experiments compare the SP_N model including DE

Fig. 1. The results of the MC method: (a) The tested mouse model used for comparison, containing six organs: heart, lung, stomach, liver, kidney and muscle. (b) A local area of the surface where the photo distributes densely. (c) The simulation results of 12 spectrums by the MC method based on the MOSE platform.¹⁵

(SP_1), SP_3 , SP_5 , SP_7 with the MC method which is known as the gold standard in photon-transportation modeling.^{16,25} All experiments were performed on a desktop computer with 3.40 GHz Intel® Xeon® Processor E3-1231 and 12 GB RAM.

In the numerical experiments, a digital mouse model²⁶ was discretized into tetrahedral mesh (10151 nodes and 55581 tetrahedrons). A cylindrical light source with a radius of 0.5 mm and a height of 1.5 mm was positioned at (17.8, 6.6, 16.4) mm to simulate different materials, as shown in Fig. 1(a). A local area of the surface where the photo distribute densely was shown in Fig. 1(b). The optical properties μ_a and μ_s of different organs were calculated by Alexandrakis' work.²⁷ The X-ray source was set to 50 kVp voltage and 1 mA current. The mass of the simulated target was set to 1 μ g. By setting the photon number as 10^8 , the simulation results of MC method from the software of molecular optical simulation environment (MOSE)¹⁶ are shown in Fig. 1(c).

Figure 2 demonstrates the results of three examples each with a commonly used spectrum in CB-XLCT imaging (i.e., 627, 700 and 802 nm, respectively). Particularly, we computed the

normalized surface energy of two extracted lines ($x = 17$ mm, $z = 16$ mm), and sorted the surface energy of five models in descending order. Figure 3 is the corresponding results of the top 50 largest points of the five models based on two lines. In comparison with MC method, it is clear that SP_3 , SP_5 and SP_7 models get better results than DE (SP_1).

To quantitatively assess the simulation results, a global measurement based on the cosine similarity $G_{\cos}$ was designed. It is noted that the greater $G_{\cos}$ is, the greater the similarity of the two models is.

$$G_{\cos} = \frac{\sum_{k=1}^M j_{1,k} \cdot j_{2,k}^{\text{MC}}}{\sqrt{\sum_{k=1}^M (j_{1,k})^2} \cdot \sqrt{\sum_{k=1}^M (j_{2,k}^{\text{MC}})^2}}, \quad (11)$$

where $j_{1,k}$ is flux of the k th nodes, $j_{2,k}^{\text{MC}}$ is the corresponding MC's flux and M is the total number of nodes on the surface.

Meanwhile, a locally-averaged relative error (L_{are}) is designed to compare the density distribution of surface flux between MC and other forward models. The local area is shown in Fig. 1(b). L_{are} is

Fig. 2. Three examples of the results for 627, 700 and 802 nm which used different forward models.

defined as follows:

$$L_{\text{are}} = \frac{\sum_{i=1}^{N_L} \text{abs}(j_i^{\text{MC}} - j_i) / \max(j_i^{\text{MC}})}{N_L}, \quad (12)$$

where j_i^{MC} and j_i are flux of the i th nodes on the surface of the MC and other forward models respectively, and N_L is the total number of nodes on the local area.

The comparative results of G_{cos} and L_{are} for different models are shown in Fig. 4. Tables 1 and 2 give numerical results of G_{cos} and L_{are} , respectively. Table 3 gives the average time-consumption of five models.

As is illustrated in Fig. 4(a) and Table 1, the G_{cos} of all models were below 70% when the spectrum was under 627 nm. Meanwhile, a great improvement of G_{cos} can be obtained by the increase of wavelength. The SP_3 , SP_5 and SP_7 models were superior than DE (SP_1) over all 12 spectrums, and their G_{cos} values were almost the same. Due to high computational cost of SP_5 and SP_7 models as listed in Table 3, the two models were discarded in the following comparisons and analysis. The difference of G_{cos} between DE (SP_1) and SP_3 model varied from 0.11% to 17.58% when spectrum was between 607 nm and 802 nm, and dropped to 0.94% when

spectrum came to 692 nm. This was mainly caused by the high-scattering-low-absorption properties of soft tissue. For the results of L_{are} , we can see in Fig. 4(b) and Table 2 that tendency of the four SP_N models are similar from 607 nm to 802 nm, and the error of DE (SP_1) is larger than that of the other three models. Compared with DE (SP_1) model, the SP_3 model was more superior than over all spectrums, and their difference of L_{are} dropped to 0.33% when spectrum increased to 692 nm.

3.2. In vivo experiments

In this section, we evaluated the performance of DE (SP_1) and SP_3 in inverse reconstruction with *in vivo* experimental data.⁶ In the experiments, a female eight-week-old mouse was used. The homogeneous absorption coefficient was 0.3 mm^{-1} and the reduced scattering coefficient was 10 mm^{-1} .²⁸ A plastic capillary (radius: 1 mm, height: of 2 mm) with $\text{Gd}_2\text{O}_2\text{S:Tb}$ nanophosphors filled in was implanted into the abdomen of the mouse. The light yield ε of $\text{Gd}_2\text{O}_2\text{S:Tb}$ nanophosphors was 5×10^9 photons/Gy $\times$ mg. The concentration of $\text{Gd}_2\text{O}_2\text{S:Tb}$ nanophosphors was 0.015 g/mL. The voltage and current of X-ray source (Apogee, Oxford

Fig. 3. The corresponding results of the largest 50 points of the five models based on the two lines. (a) The result of $x = 17$ cm. (b) The result of $z = 16$ cm.

Instruments, USA) with a micro 55 mm f/2.8 lens (Nikkor, Nikon, Japan) were set to 50 kVp and 1 mA, respectively. A highly sensitive CCD camera (PIXIS 2048, Princeton Instruments, USA) with a micro 55 mm f/2.8 lens (Nikkor, Nikon, Japan) was mounted vertical to the X-ray axis to capture the optical data (620 nm). The CCD binning was set to 2×2 and the integrating time of CCD was set to 30 s. The micro-CT imaging was performed (360 views with 1° intervals) using a flat-panel detector (C7921CA-02, Hamamatsu, Japan) to get the structural information. The 3D reconstruction of XCT projections was performed employing the Feldkamp–Davis–Kress (FDK) method.²⁹

The mouse was excited by a cone beam X-ray source from different directions with 45° intervals to acquire the luminescent photons. Figure 5(a) shows the distribution of forward photon on the surface. The micro-CT result at $z = 6.8$ mm is demonstrated in Fig. 5(b).

In reconstruction, we used the incomplete variables truncated conjugate gradient (IVTCG) algorithm proposed in our work.¹² The IVTCG algorithm is based on L_1 regularization framework, and has been widely applied to optical molecular imaging, e.g., BLT, FMT and XLCT.^{6,30,31} We used location error (LE), recovered density and relative quantity error to analyze the results.⁶

(a)

(b)

Fig. 4. The results of $G_{\cos}$ and L_{are} : (a) The global comparison results between SP_N model and MC method based on cosine similarity. (b) The local average relative error between SP_N model and MC method.

Table 1. The $G_{\cos}$ between the SP_N model results and MC model results.

$G_{\cos}$ (%)	607	615	618	620	623	627	667	692	700	703	720	802
DE (SP_1)	52.67	42.79	44.99	46.92	49.91	55.10	89.02	96.09	96.80	97.41	97.79	98.38
SP_3	67.91	60.37	58.10	60.10	63.83	69.87	93.15	97.03	97.46	97.69	98.26	98.49
SP_5	68.24	60.84	58.90	60.14	64.34	70.39	93.05	96.98	97.42	97.66	98.24	98.48
SP_7	68.45	61.41	59.66	60.95	65.00	70.84	93.07	96.98	97.42	97.66	98.24	98.48

Table 2. The L_{are} between the SP_N model results and MC model results.

L_{are} (%)	607	615	618	620	623	627	667	692	700	703	720	802
DE (SP_1)	2.54	1.37	1.17	1.15	1.09	1.00	1.95	2.89	3.59	3.81	4.96	8.37
SP_3	1.58	0.56	0.39	0.36	0.32	0.33	1.30	2.56	3.41	3.65	4.88	8.29
SP_5	1.52	0.53	0.37	0.34	0.31	0.31	1.26	2.47	3.39	3.63	4.87	8.28
SP_7	1.48	0.49	0.36	0.31	0.31	0.29	1.23	2.47	3.37	3.62	4.86	8.28

Table 3. The average time-consumption of the five models.

Model	DE (SP_1)	SP_3	SP_5	SP_7	MC
Average time-consumption (s)	23.23	138.92	430.58	1081.53	2316.57

Fig. 5. (a) The distribution of forward photon on the surface. (b) The micro-CT result at $z = 6.8$ mm.Table 4. The reconstruction results of DE (SP_1) and SP_3 .

Model	Real position center (mm)	Location error (mm)	Recovered density (g/ml)	Relative quantity error (%)
DE (SP_1)	(12.0, 13.2, 6.8)	1.65	0.009	40.00
SP_3		0.92	0.011	26.67

Table 4 gives the reconstruction results of SP_3 and DE (SP_1), respectively. Figure 6 gives the transverse view of results along with corresponding CT slices ($z = 6.8$ mm). As shown in Table 4 and Fig. 6, results of SP_3 have lower LE, larger recovered density and lower relative quantity error compared with DE (SP_1). The final quantitative results clearly demonstrated that SP_3 had more

Fig. 6. The transverse view of the results along with corresponding CT slices. (b) and (c) The cross-sectional views of reconstruction results obtained by SP_3 model and DE (SP_1) model, respectively. (a) and (d) The $z = 6.8$ mm micro slices corresponding to (b) and (c).

accurate reconstruction results than DE (SP_1) had in the inverse problem of CB-XLCT.

4. Discussion and Conclusion

In this paper, the performance and applicability of different SP_N models of CB-XLCT were compared with MC model over all spectrums based on several main XLCT probes that have been successfully applied in this field up till now. The *in vivo* experiment was conducted to further demonstrate the

reconstruction performance of the SP_3 and DE (SP_1). Several useful conclusions could be drawn from the experiments. Firstly, to balance accuracy and computational efficiency, the SP_3 model was the best choice for CB-XLCT imaging based on all known probes. Secondly, 692 nm can be viewed as the dividing line between the SP_3 model and the DE (SP_1) model, above which their difference was small. Finally, considering the time-consumption and ignoring their difference, the DE (SP_1) model can be employed for CB-XLCT imaging when the wavelength is above 692 nm.

In summary, this study would provide a detailed guidance for the choice of either SP_3 or DE (SP_1) depending on different XLCT probes. Particularly, this study would also be helpful for the study of photon-transportation models for the CB-XLCT imaging. In addition, because dynamic XLCT imaging was proven useful for metabolic processes of nanophosphors-based drugs,⁹ further research will focus on accelerating the computations of the photon-transportation model and applying them to a single-view reconstruction for fast CB-XLCT imaging.

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