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High-speed X-ray-induced luminescence computed tomography

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Abstract

X-ray-induced luminescence computed tomography (XLCT) is an emerging molecular imaging. Challenges in improving spatial resolution and reducing the scan time in a whole-body field of view (FOV) still remain for practical in vivo applications. In this study, we present a novel XLCT technique capable of obtaining three-dimensional (3D) images from a single snapshot. Specifically, a customized two-planar-mirror component is integrated into a cone beam XLCT imaging system to obtain multiple optical views of an object simultaneously. Furthermore, a compressive sensing based algorithm is adopted to improve the efficiency of 3D XLCT image reconstruction. Numerical simulations and experiments were conducted to validate the single snapshot X-ray-induced luminescence computed tomography (SS-XLCT). The results show that the 3D distribution of the nanophosphor targets can be visualized much faster than conventional cone beam XLCT imaging method that was used in our comparisons while maintaining comparable spatial resolution as in conventional XLCT imaging. SS-XLCT has the potential to harness the power of XLCT for rapid whole-body in vivo molecular imaging of small animals.

Graphical Abstract

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Keywords

computed tomography; luminescence; XLCT; X-ray

1 | INTRODUCTION

X-ray-induced luminescence computed tomography (XLCT) is an emerging molecular imaging technique based on the radioluminescence effect by which light is produced in a material using ionizing radiation. Through detection of photon emissions, the three-dimensional (3D) X-ray excitable phosphor distribution can be obtained using tomographic reconstruction [1–7]. XLCT imaging shows promising higher molecular sensitivity over conventional X-ray CT imaging while maintaining the higher spatial resolution of X-ray CT imaging. Moreover, compared to traditional light excited fluorescence imaging like fluorescence molecular tomography (FMT) [8–15] or pure optical imaging such as diffuse optical tomography (DOT) [16] and bioluminescence tomography (BLT) [17–21], XLCT has superb tissue penetration and less excitation light interference, allowing for whole-body molecular imaging in high spatial resolution.

The first XLCT image was obtained using a customized XLCT system consists of X-ray source, X-ray detector and optical detector in a way similar to the first X-ray CT scanner [1, 2]. The samples containing X-ray excitable nanophosphor were selectively irradiated by a sequence of X-ray pencil beams. While inspiring, due to the selective excitation mechanism including raster and rotatory scanning around the sample, the imaging speed is slow, which limits its practical application for in vivo imaging. Cone-beam XLCT [22, 23], limited angle XLCT [24], multiple narrow beam XLCT [25] have been proposed and investigated to improve the imaging speed thus enhancing the practical application. Nevertheless, scanning around the sample is still necessary, which limits further improvement of XLCT imaging speed for real time applications such as detecting dynamic physiological responses. For example, in cone-beam XLCT [23, 26–30], either sample or optical detector (camera) needs to be rotated in order to obtain multi-view projections for three-dimensional (3D) image reconstruction. Theoretically, the more views of data are acquired, making the inverse problem in XLCT image reconstruction less ill-conditioned, the higher spatial resolution can be achieved. Many investigations have been continuously carried out to improve the spatial resolution and sensitivity through advanced algorithms to solve the ill-conditioned inverse problem in cone-beam XLCT 3D image reconstruction [28, 29]. In multiple narrow beam XLCT [25], a multiple pinhole collimator was carefully designed to offer multiple pencil X-ray beams simultaneously within a scan. It maintains the high spatial resolution as in single pencil beam XLCT. The scanning mechanism includes point-to-point translational and rotatory scanning is still necessary, thus the acceleration of data acquisition is limited. Recently, a novel X-ray excitation geometry called coded aperture compressive X-ray luminescence tomography (CAC-XLCT) has been proposed to overcome the challenges associated with the long data acquisition time in pencil-beam XLCT and reduced spatial resolution and inferior image quality in cone-beam XLCT [31]. Instead of illuminating the entire sample in the conventional cone-beam XLCT, CAC-XLCT obtains each optical projection image from a specific subset of pencil beam excitations corresponding to the open

elements of a coded-aperture. Meanwhile, the coding information is collected and incorporated into the reconstruction algorithm to make the XLCT reconstruction inverse problem less ill-conditioned. Multiple optical projection images can be acquired by using multiple coded-aperture masks with different patterns. Apart from performing spatial encoding of the X-ray excitation, coded aperture imaging also facilitates the application of sparse data reconstruction in XLCT. While inspiring, rotatory scanning is still necessary and fabricating the coded-aperture masks is quite challenge practically. Recently, the feasibility of a single-view CT imaging via deep learning has been demonstrated [32]. Few-view cone-beam XLCT was reported [26]. However, the spatial resolution was deteriorated and not comparable to traditional narrow beam XLCT. At present, challenges are still remaining when short scan time, good spatial resolution and whole-body field of view (FOV) are considered simultaneously.

In this study, a novel XLCT technique, namely, single-snapshot X-ray-induced luminescence computed tomography (SS-XLCT), capable of obtaining 3D images with a single X-ray snapshot was investigated. Specially, two planar mirrors were used to create multiple optical views of an object, combining with the capability of small animal (such as mouse) whole-body field of view using a cone-beam XLCT system, within a single snapshot, a full set of 3D XLCT data can be acquired without any mechanical scanning. Thus, SS-XLCT significantly speeds up XLCT data acquisition. Moreover, sparse data reconstruction strategy using compressive sensing was adopted for 3D XLCT image reconstruction. Numerical simulations and phantom experiments were conducted to validate SS-XLCT imaging. The results show that the 3D distribution of the nanophosphor targets can be visualized much faster than conventional cone-beam XLCT imaging that was used in our comparisons while maintaining a comparable image quality.

2 | MATERIAL AND METHODS

2.1 | Two-planar-mirror scene geometry and multiple-view optical data acquisition

As shown in Figure 1A, two planar mirrors (m_1 , m_2) are positioned side-to-side with an angle of 72° between each other. Theoretically, more than five views can be created by choosing a smaller angle between the mirrors, but in this work, we restrict ourselves to the five-view case [33]. Hence, a scene consisting of one real object (r) and four virtual objects (v_1 , v_2 , v_{12} , v_{21}) is created. Two of the virtual objects (v_1 , v_2) are reflections of the real object (indicated by red arrows in Figure 1A), and the other two virtual objects (v_{12} , v_{21}) are formed through multiple reflections by the mirrors. Each of these five objects (r , v_1 , v_2 , v_{12} , v_{21}) can be used to define a reference frame. In addition, the normal of the two mirrors can be used to transform viewing directions between these reference frames, which follows:

$$d_R = d - 2\hat{m}(\hat{d} \cdot \hat{m}) \quad (1)$$

where, d_R is the reflected direction of the direction d in one reference frame, $\hat{d}$ is a unit direction in the reference frame and $\hat{m}$ is unit normal of the mirror for reflection.

As an example, Figure 1B shows the viewing directions in the reference frame of a real object. The five red arrows indicate the viewing direction in the real object (r) and its

corresponding directions in the other four virtual objects (v1, v2, v12, v21), respectively. Each viewing direction corresponds to a silhouette. Thus, in each reference frame, five different silhouettes are available. Considering all the five objects (real object r, virtual objects v1, v2, v12, v21), thereafter, in total, 25 silhouette poses of the real object can be computed [33]. With these silhouettes, a visual hull which is a geometric entity is created through the shape-from-silhouette 3D reconstruction algorithm [34–36]. In visual hull model, it assumes that the foreground object in an image can be separated from the background. Under this assumption, a binary silhouette is obtained from the original image by applying an intensity threshold. The camera viewing parameters (position, focal length, etc.), and the silhouette define a back-projected generalized cone containing the actual object. Thus, a silhouette is essentially a two-dimensional (2D) projection of the 3D object. Visual hull defines the maximal object that has the same silhouettes of all the projections of the object.

Here, two 8-in. square protected aluminum mirrors (ME8S-G01, Thorlabs) are used as the planar mirrors, and a plastic base was 3D printed for assembling the mirrors. In the wavelength of 450 nm to 2 μ m range, the mirrors exhibit average reflectance in excess of 90%. Figure 2A shows the photograph of a bottle placed in the front of the two-planar-mirror component. Different views of the bottle can be clearly seen from the image taken from one single snapshot. The image is firstly converted to a binary image using a threshold (Figure 2B). The silhouettes of the object are extracted and computed. Then a visual hull model from the silhouettes is created to get the approximation of the 3D shape of the object (as shown in Figure 2C). Figure 2D shows the real object for comparison, we can see, the 3D shape of the object is obtained with a high precision. The results show the feasibility of acquiring surface light signals by using the two-planar-mirror structure.

2.2 | SS-XLCT imaging system

The SS-XLCT imaging system is schematically shown in Figure 3A. The system consists of an X-ray source, a high-sensitivity CCD camera for excellent optical detection, a sample stage and a home-made two-planar-mirror component. The experimental setup is identical to conventional cone-beam XLCT imaging system except the scanning stages (linear translational stage and rotator). Here, a commercially available small animal cabinet X-ray irradiator (X-RAD 320, Precision) was adopted. The cabinet irradiator can generate X-ray up to 320 kVp. An InGaAs camera (NIRvana 640, Princeton Instruments) which has a broad spectrum of 900 to 1700 nm is used for light detection. The two planar mirrors (8 in. protected aluminum, Thorlabs) which are mounted on a 3D printed plastic stage, and the sample stage are fixed in the cabinet. The reflection efficiency of the planar mirror is more than 90% in the light wavelength range of 450 to 2000 nm. The light emission by X-ray excitation in the cabinet was detected by the InGaAs camera which is fixed in an adjustable tripod through a transparent lead glass window sealed with a black aluminum foil. The foil is to minimize the interference from environment light (as shown in Figure 3B). All the components of the system shown in Figure 3A except the InGaAs camera were mounted within the X-ray irradiator cabinet in Figure 3B.

2.3 | SS-XLCT 3D image reconstruction

Rare-earth nanophosphors used in this study emit light centered at the wavelength of 1180 nm [37]. In this spectrum window, the reduced scattering coefficient and the absorption coefficient are comparable in the biological tissues, therefore, the widely used diffuse equation. (DE) is not accurate enough to model the light propagation in the biological tissue. Here, a steady-state RTE (2) with the vacuum boundary condition (3) is adopted to mathematically model the light propagation in the biological tissue.

$$\begin{aligned} & \hat{s} \cdot \nabla \Psi(\vec{r}, \hat{s}) + (\mu_a + \mu_s) \Psi(\vec{r}, \hat{s}) \\ &= \mu_s \int_{\hat{S}^{n-1}} f(\hat{s} - \hat{s}') \Psi d\hat{s}' + q(\vec{r}, \hat{s}), \vec{r} \in \Omega, \hat{s} \in \hat{S}^{n-1} \end{aligned} \quad (2)$$

$$\Psi(\vec{r}, \hat{s}) = 0, \vec{r} \in \partial\Omega, \hat{s} \cdot \hat{n} < 0 \quad (3)$$

where, μ_s is the scattering coefficient, μ_a is the absorption coefficient, $\Psi(\vec{r}, \hat{s})$ is the photon flux depends on space $\vec{r}$ and angle $\hat{s}$, $q(\vec{r}, \hat{s})$ is the light source, $\hat{n}$ is the outer normal at boundary $\partial\Omega$ of domain Ω and the angular space $\hat{S}^{n-1}$ and $f(\hat{s}, \hat{s}')$ is the Henyey-Greenstein scattering function which can be expressed as for 3D [38]:

$$f(\theta) = \frac{1 - g^2}{4\pi(1 + g^2 - 2g\cos\theta)^{1.5}} \quad (4)$$

where, θ is the angle between $\hat{s}$ and $\hat{s}'$, g is the anisotropic factor indicating the strength of forward-peaking scattering, having a range from 0 to 1. The RTE (2) with vacuum boundary condition (3) can be solved numerically using a multigrid solver [38]. In this study, a compressive sensing based algorithm as shown in details in our previous work [37] was adopted for SS-XLCT 3D image reconstruction.

3 | RESULTS AND DISCUSSION

3.1 | Numerical simulations

Numerical simulations were firstly conducted to assess the performance of SS-XLCT. A 3D simulation model was built using a digimouse atlas [39]. A mesh generation toolbox iso2mesh [40] was adopted to discretize the mouse model. Here, a partial body of the mouse model was used to save the computational resource (as shown in Figure 4A). Different optical properties (absorption and scattering coefficients) were attributed to background tissue (indicated in black color in Figure 4A, absorption coefficient $\mu_a = 0.08 \text{ mm}^{-1}$, reduced scattering coefficient $\mu'_s = 0.7 \text{ mm}^{-1}$), liver (blue, $\mu_a = 0.1 \text{ mm}^{-1}$, $\mu'_s = 0.9 \text{ mm}^{-1}$) and kidney (red, $\mu_a = 0.12 \text{ mm}^{-1}$, $\mu'_s = 0.95 \text{ mm}^{-1}$) [41, 42]. Within the partial mouse model, two cylinders with a size of 2 mm in diameter and 2 mm in height were inserted as the two simulated targets (as shown in Figure 4B).

In each simulation, the signals from all the optical detectors in the boundary of the simulation model was acquired as the measured data for 3D image reconstruction in two

steps: first, given the nanophosphor distribution, solve the forward problem described in Equations (2) and (3) to get the optical fluence in each detection position; second, these detections were then added to 20% random Gaussian noise (which is used to approximate the noise in realistic system including light to electrical signal convention, data acquisition, natural light interference, et al.) to obtain final computed detector measurements. Here, we investigate two cases with different edge-to-edge distance (d). One is 2 mm and the other one is 4 mm.

Figure 5A,B show the representative cross-sectional image from the reconstructed images with the target edge-to-edge distances of 2 and 4 mm, respectively. For comparison, these cases were also simulated with conventional cone-beam XLCT using 24 rotatory scanning view angles. Figure 5C,D show the reconstructed images sharing the same colormap information as that in SS-XLCT images. The reconstructed intensities in the images were normalized to the maximum intensity, therefore, the colormap range from 0 to 1 represents the normalized pixel intensity. In these images, black circles indicate the true nanophosphor distribution. For quantitative comparison, the profiles along the center of the targets were plotted for SS-XLCT (blue), conventional cone-beam XLCT (green) and the ground truth (red) as shown in Figure 5E,F, respectively. As seen in Figure 5, SS-XLCT has comparable results in target localization accuracy and spatial resolution as cone-beam XLCT, but all the data can be acquired in a single snapshot. In these images, we can see some artifacts, which might come from the large percentage (20%) of random noise adding to the simulated luminescence data in the forward solution. It is worth noting that very similar artifacts also exist in CB-XLCT reconstructed images, which used the same reconstruction algorithm as SS-XLCT in this work. Thus, from this perspective, SS-XLCT can provide good image quality without significant distortion.

3.2 | Phantom experiments

Tissue-mimicking phantom experiments were then conducted to further assess the performance of SS-XLCT. Home synthesized rare-earth nanophosphors (RENPs) were used as contrast agents for X-ray luminescence [43]. Conventional RENPs emit light around 1500 nm where water has a strong absorption peak thus highly deteriorate the imaging penetration depth [43]. The RENPs used in this study were tuned by doping lanthanide element Holmium which emit light at the peak of 1180 nm. In brief, a two-step synthetic procedure was involved in the synthesis of RENPs. The first step was to decompose the rare-earth trifluoroacetate precursors in presence of surfactants at the high temperature (325°C) to obtain the monodisperse cores. The second step is identical to the first step, but, only Yttrium trifluoroacetate was used as a precursor for formation of the shell during the solvothermal decomposition reaction. Due to the relatively low quantum yield of the RENPs, for the purpose of verification for our proposed method, compressed RNP powders were sealed as targets.

The phantom background has a cylindrical shape with a size of 26 mm in diameter and 40 mm in height. The phantom was made of 2% Agar mixed with TiO_2 as light scatterer and India ink as light absorber. Ref to [43], in the spectrum around 1180 nm region, the reduced scattering coefficient is about 0.7 mm^{-1} and the optical absorption coefficient is around 0.12

mm^{-1} , which were used in phantom studies. The two centrally embedded targets were made of two pieces of transparent glass tubing filled with nanophosphors. The targets have a cylindrical shape with a size of 2.2 mm in diameter and 4 mm in height. The phantom was then mounted on the sample stage in the SS-XLCT imaging system. Differences in edge-to-edge distance of the two targets were studied: (1) 1 mm, (2) 3.5 mm. Again, for comparison, conventional cone-beam XLCT experiments were done right after each SS-XLCT experiment. The data of conventional cone-beam XLCT were acquired using 24 rotatory scanning view angles. For all these experiments, the X-ray irradiator were set with the following parameters: 320 kVp and 12.5 mA.

Figure 6A,B show the reconstructed images of SS-XLCT in the cases that the two targets have the edge-to-edge distances of 1 and 3.5 mm between each other, respectively, while Figure 6C,D show the corresponding images of conventional rotatory multi-view cone-beam XLCT reconstruction. For quantitative comparison, the profile crossing the two targets were plotted in Figure 6E, F. In these plots, the profile of SS-XLCT reconstructed targets is plotted in blue, while the profile of cone-beam XLCT is plotted in green, and the red curve shows the real target. Again, in Figure 6A-D, the black dotted lines indicate the position and shape of the real targets. From these results, comparable image quality can be achieved by SS-XLCT as conventional cone-beam XLCT for mapping the nanophosphor distribution. The results of the case where the edge-to-edge distance is 1 mm demonstrated that the spatial resolution of our proposed method can achieve as high as 1 mm. In addition, in the experiments, the exposure time of the SWIR camera was set to be 30 seconds, which shows the temporal resolution of our proposed system can be as fast as 30 seconds. Compared to these images in numerical simulation studies (Figure 5), our experimental results (Figure 6) show fewer artifacts in background. One potential reason is that the phantom structure is much more complex in simulation studies than experimental studies.

4 | CONCLUSION

In this study, we investigated a novel geometry of X-ray-induced luminescence CT, namely, single snapshot XLCT (SS-XLCT). SS-XLCT is intriguing in that it offers a strategic way to tackle the challenge of XLCT for practical in vivo molecular imaging applications when short scan time, good spatial resolution and whole-body FOV are considered simultaneously. In SS-XLCT, all data are acquired in static status without any mechanical scanning or rotation, thus real-time imaging is achievable while maintain a comparable image quality as conventional cone-beam XLCT. Moreover, with reduced X-ray exposure time, the ionizing dose to the object can also be highly reduced. More detailed measurement of the reduction in dose delivered to the object will be one of our future investigations. In our validation studies, rare-earth nanophosphors were used. However, our proposed method is generic and not restricted to these rare-earth nanophosphors only, any other nanophosphors such as near infrared emitting nanophosphors can also be used. SS-XLCT promises to have two immediate biomedical application. First, it affords an effective way for in vivo small animal molecular imaging with high temporal and spatial resolution. High temporal resolution is helpful for studies on tumor dynamics and radiation dose reduction to the animals. Second, the system may be suitable for dosimetric applications, offering real-time monitoring of

delivered dose of external beam radiation therapy [44–46], which is highly desirable for accurate beam targeting.

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FIGURE 1.

Two-planar-mirror scene geometry. A, the schematic, B, various viewing directions under the reference frame of real object

FIGURE 2.
An object fixed in the two-planar-mirror component. A, the photograph, B, binary silhouette, C, reconstructed 3D shape, D, the photograph of the real object

FIGURE 3.
SS-XLCT imaging system. A, the schematic, B, the photograph

FIGURE 4.

The 3D simulation model for SS-XLCT. A, partial mouse finite element mesh, B, two cylindrical targets inserted into the model, d, edge-to-edge distance of the two targets

FIGURE 5.

Numerical simulation results. SS-XLCT reconstructed images of targets with the edge-to-edge distance of 2 mm, A, and 4 mm, B, cone-beam XLCT reconstructed images of targets with edge-to-edge distance of 2 mm, C, and 4 mm, D, E, profile plots of 2 mm case, F, profile plots of 4 mm case. SS-XLCT: single snapshot XLCT, CB-XLCT: cone beam XLCT

FIGURE 6.

Phantom experiment results of two different edge-to-edge distances of 1 mm (case 1) and 3.5 mm (case 2). SS-XLCT reconstructed images of case 1, A, and case 2, B, cone-beam XLCT reconstructed images of case 1, C, and case 2, D, (E) profile plots of case 1, F, profile plots of case 2. SS-XLCT: single snapshot XLCT, CB-XLCT: cone beam XLCT