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A framework for optimizing micro-CT in dual-modality micro-CT/XFCT small-animal imaging system

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ABSTRACT

Dual-modality Computed Tomography (CT)/X-ray Fluorescence Computed Tomography (XFCT) can be a valuable tool for imaging and quantifying the organ and tissue distribution of small concentrations of high atomic number materials in small-animal system. In this work, the framework for optimizing the micro-CT imaging system component of the dual-modality system is described, either when the micro-CT images are concurrently acquired with XFCT and using the x-ray spectral conditions for XFCT, or when the micro-CT images are acquired sequentially and independently of XFCT. This framework utilizes the cascaded systems analysis for task-specific determination of the detectability index using numerical observer models at a given radiation dose, where the radiation dose is determined using Monte Carlo simulations.

Keywords: X-ray fluorescence computed tomography (XFCT), computed tomography (CT), small-animal imaging system

1. INTRODUCTION

Several targeted nanoparticles incorporating high atomic number (Z) elements such as gold (Au), silver (Ag) and iodine (I) have been developed and are actively investigated for potential use as diagnostic contrast agents, as therapeutic agents for targeted treatment, and as theranostic agents [1-3]. These nanoparticle-based agents are initially evaluated in preclinical small-animal models to evaluate safety, biodistribution and suitability for subsequent clinical trials. For such studies in preclinical models, there is a need for in vivo imaging of the nanoparticle distribution as an alternative to tissue analysis following euthanasia. Such an imaging system can also allow for monitoring temporal changes of the nanoparticle distribution. X-ray fluorescence computed tomography (XFCT) has the potential to serve this important need [4-8]. For example, benchtop XFCT utilizing a conventional polychromatic x-ray source has shown to be capable of imaging very low concentration of gold nanoparticles (GNPs) present in a mouse on the order of 0.2% to 2% by weight [8]. While XFCT provides for the spatial distribution and allows quantitation of the high Z element concentration, it does not provide anatomical images. A micro-computed tomography (CT) system used in conjunction with benchtop XFCT can allow for co-localization of the anatomy with the spatial distribution of the nanoparticle agent that incorporates a high Z element.

The motivation for this study was that the radiation dose from benchtop XFCT can be in the range of 15 to 20 cGy [7] and is comparable to the radiation dose from micro-CT reported in some studies (e.g., [9]). Hence, a dual-modality micro-CT/XFCT small-animal imaging system has the potential to double the radiation dose. In order to limit the radiation dose, the potential for concurrently acquiring the micro-CT images using the XFCT x-ray beam was investigated. A major challenge is that the x-ray spectrum used for benchtop XFCT is substantially different with x-ray tube peak voltage as high as 125 kV and with heavily filtration using tin (Sn) or lead (Pb) to induce gold K-shell x-ray fluorescence from GNPs. In comparison, micro-CT operates in the 40-90 kV range [9, 10]. The framework presented in here can be readily adapted for both concurrent and sequential micro-CT imaging with benchtop XFCT at a specified radiation dose. The framework can also facilitate task-dependent optimization of image acquisition factors in existing micro-CT systems.

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2. METHODS

2.1 Modeling approach

The modeling approach comprises four major components. First, for a specified imaging geometry and small-animal model, Monte Carlo simulations are used to estimate the radiation dose to the small-animal. Second, for specified imaging geometry, detector specifications and acquisition parameters selected to satisfy the radiation dose limit, cascaded systems analysis is used to determine the objective physics-based imaging metrics such as modulation transfer function (MTF), noise power spectrum (NPS), noise-equivalent quanta (NEQ), and detective quantum efficiency (DQE). Third, an imaging task is specified for task-specific evaluation. Fourth, numerical observer models are then used to determine the detectability index by combining the task function with objective imaging properties.

2.2 Imaging geometry

The distance from the axis of rotation, also referred to as isocenter, to the source for most micro-CT systems are in the range of 100-200 mm. The imaging geometry reported for a cone-beam micro-CT system [10] was used and this cone-beam micro-CT scanner is denoted as the reference system. The source-to-isocenter distance (SCD) and the source to detector distance (SDD) were 154 mm and 265 mm, respectively. This system was assumed to use a PaxScan 1515 (Varex Imaging, Salt Lake City, UT) amorphous silicon flat-panel detector with 200 μ m thick CsI:Tl scintillator. X-ray source, detector and acquisition parameters are summarized in Table 1 for this reference system. For the dual-modality micro-CT/XFCT system, SCD=145 mm and SDD=250 mm were used for simulations, which slightly differs from the SDD=240 mm for the benchtop system. An active-pixel complementary metal-oxide-semiconductor (CMOS) detector (Dexela 1512, Varex Imaging, Salt Lake City, UT) with 150 μ m thick CsI:Tl scintillator was considered based on our current experimental setup. This scanner is referred to as “mCT/XFCT” system with a prefix of “C” or “S”, representing concurrent or sequential micro-CT imaging. The x-ray source, detector and acquisition parameters for the XFCT system are also included in Table 1.

Table 1. Acquisition parameters, x-ray source and detector specifications for reference cone-beam micro-CT system, concurrent micro-CT/XFCT (C-mCT/XFCT) imaging using the XFCT source and sequential micro-CT/XFCT (S-mCT/XFCT) imaging.

Parameters/Specifications	Reference	C-mCT/XFCT	S-mCT/XFCT
<i>Imaging geometry</i>			
Source-to-isocenter distance (SCD)	154 mm	145 mm	145 mm
Source-to-detector distance (SDD)	265 mm	250 mm	250 mm
<i>X-ray source</i>			
Focal spot	5 μ m	400 μ m	400 μ m
KV	90	125	90
Anode	W	W	W
Be window	0.15 mm	0.8 mm	0.8 mm
X-ray beam filtration	0.06 mm Cu + 0.5 mm Al	2 mm Sn	0.06 mm Cu + 0.5 mm Al
<i>Detector</i>			
Pixel pitch	127 μ m	75 μ m	75 μ m
Fill factor	0.57	0.84	0.84
CsI:Tl thickness	200 μ m	150 μ m	150 μ m
System noise	3945 e-	362 e-	362 e-
<i>Acquisition parameters</i>			
Number of projections	512	64	512
Dose limit	16 mGy	150 mGy	16 mGy
Reconstruction	FBP (ramp)	FBP (ramp)	FBP (ramp)

2.3 Monte Carlo simulations

Monte Carlo simulations were performed using the GEANT4 toolkit using the Livermore low-energy physics model. For x-ray photon interactions, photoelectric effect, Compton and Rayleigh scattering were considered similar to prior studies [11-15]. One million monoenergy x-ray photons from 10 to 125 keV, in 1 keV increments were used in the simulation. The small-animal was approximated as a water-equivalent cylinder of 30 mm diameter and 100 mm length. Each x-ray photon was tracked and the dose per incident x-ray photon of specified energy was determined. For a given x-ray spectrum, the aforementioned dose per incident photon was weighted after normalizing the spectrum to unit area. Figure 1 shows the x-ray spectra for the reference cone-beam micro-CT system and that used for XFCT imaging.

Figure 1. X-ray spectra used for imaging with reference cone-beam micro-CT system and XFCT. Each spectrum is normalized to unit area.

2.4 Cascaded systems analysis

Cascaded systems analysis that models the signal and noise transfer properties in the spatial frequency domain through each step of the image formation chain was used to obtain objective imaging metrics such as MTF, NPS, NEQ and DQE [16, 17]. The specific implementation of the model accounted for emission of characteristic x-rays and reabsorption within the scintillator [18-20]. Such models have been well-validated in projection space and have been extended to reconstructed image space. For image reconstruction, ramp-filtered back projection without apodization and bilinear interpolation of voxels were modeled.

2.5 Task-specific evaluation

The purpose of the micro-CT component of the dual-modality micro-CT/XFCT imaging system is to provide anatomical images of the small animal. Hence, the tasks considered were detection of 0.5 to 3 mm diameter spheres with CT numbers ranging from 5 to 200 HU. In each simulation, the sphere was considered to be centered at the isocenter, defined as the intersection of the central-ray (0° cone and fan angles) with the axis of rotation. At a specified dose limit (Table 1), the x-ray fluence integrated over the entire 360° cone-beam scan was determined and equally divided among the projections. The parallel-cascades systems model was used to determine the objective imaging metrics in reconstructed object domain. The ICRU-recommended detectability index (d') was computed by combining the imaging task with the objective imaging metrics using an ideal numerical observer model.

3. RESULTS AND DISCUSSION

Figure 2 shows the radiation dose to the water-equivalent cylindrical phantom approximating a small animal for monoenergy x-ray photons from 10 to 125 keV reported in units of dose in μGy per x-ray photon. The data are shown for SCD of 100 and 200 mm that spans the range of imaging geometries used in micro-CT systems. The slight increase in dose with the larger SCD is expected due to the longer path-length for oblique rays through the object. Upon weighting with the normalized 90 and 125 kV spectra, the doses in μGy per x-ray photon are 5.5×10^{-7} and 5.4×10^{-7} , respectively.

Figure 2. Radiation dose in μGy per incident x-ray photon for monoenergy x-rays for source-to-isocenter distances (SCD) of 100 and 200 mm.

Figures 3A through 3C show the MTF for the reference system, sequential micro-CT (S-mCT/XFCT) imaging and concurrent (C-mCT/XFCT) imaging. In each plot, the following color-coding scheme is utilized: red – focal spot MTF inclusive of the system magnification associated blur, cyan – MTF associated with the emission and reabsorption of characteristic x-rays, green – scintillator blur, yellow – pixel aperture function, black – the projection space MTF that combines all of the above, blue – bilinear interpolation used during image reconstruction, and magenta – the MTF in the reconstructed object domain. In Figure 3A for the reference system, the focal spot MTF is close to unity over the entire spatial frequency range due to the use of a $5 \mu\text{m}$ micro-focus x-ray tube. The major contributor to the reduction in overall system MTF (magenta curve) in Fig. 3A is the scintillator associated blur. Comparing Figure 3A with Figure 3B, there is a reduction in limiting spatial resolution (10% MTF) from 4.5 cycles/mm for the reference system to 3.5 cycles/mm for sequential micro-CT imaging. Although the S-mCT/XFCT (Figure 3B) utilizes a thinner scintillator compared to the reference system ($150 \mu\text{m}$ vs. $200 \mu\text{m}$) and has a finer pixel pitch ($75 \mu\text{m}$ vs. $127 \mu\text{m}$), there is reduction in overall system MTF due to the substantially larger x-ray tube focal spot size ($400 \mu\text{m}$ vs. $5 \mu\text{m}$). Comparing Figure 3B with Figure 3C, there is minimal difference in the limiting spatial resolution, as the major contributing factor to the overall MTF is the x-ray tube focal spot size. For concurrent micro-CT/XFCT (Figure 3C), the larger focal spot size is unavoidable as XFCT requires a focal spot capable of providing sufficient fluence rate to complete the exam in a reasonable duration. However, for sequential micro-CT/XFCT (Figure 3B), it is potentially possible to use a second x-ray tube with a smaller focal spot size for micro-CT imaging. Such an approach also provides flexibility for choosing the appropriate technique factors for micro-CT imaging without the constraints of XFCT imaging.

Figure 4 shows the detectability index computed using an ideal observer model for 0.5 to 3 mm diameter spheres with CT numbers ranging from 5 to 200 HU. The color-coding scheme for the curves represents objects (spheres) of diameters ranging from $500 \mu\text{m}$ to 3 mm and is matched between the reference (Ref) system, sequential micro-CT (S-mCT) imaging and concurrent (C-mCT) imaging. Comparing the reference system to sequential micro-CT imaging,

there is an improvement in detectability index, primarily due to the significantly lower noise characteristics of the CMOS sensor compared to the amorphous silicon detector (3945 e- vs. 362 e-). It is relevant to note that both these systems use 90 kV spectrum and similar acquisition factors (Table 1) and are matched in terms of radiation dose to the small-animal. Comparing concurrent micro-CT/XFCT imaging (C-mCT) with the reference system and with sequential micro-CT/XFCT imaging, there is a significant improvement in the detectability index. This improvement in detectability index is due to an approximately ten-fold increase in radiation dose with concurrent micro-CT/XFCT imaging. It is relevant to note that this is not additional radiation dose to the animal.

Figure 3. The overall system MTF along with the components of the imaging chain that contribute to the overall system MTF are shown for (a) the reference system, (b) for sequential micro-CT/XFCT imaging, and (c) for concurrent micro-CT/XFCT imaging. In each panel, the following color-coding is used: red – focal spot MTF inclusive of the system magnification associated blur, cyan – MTF associated with the emission and reabsorption of characteristic x-rays, green – scintillator blur, yellow – pixel aperture function, black – the projection space MTF that combines all of the above, blue – bilinear interpolation used during image reconstruction, and magenta – the MTF in the reconstructed object domain.

Computing the slope for each curve and comparing it between the reference system, concurrent, and sequential micro-CT/XFCT imaging shows that the slope for concurrent micro-CT/XFCT imaging is higher and increases with object diameter. This is readily supported by visual analysis of Figure 4. It can thus be inferred that concurrent micro-

CT/XFCT imaging is preferable when the objective of micro-CT imaging is to provide gross anatomical imaging of high-contrast structures such as the skeleton for co-localization with XFCT. However, if the intent is to visualize low-contrast, high-resolution structures then sequential micro-CT imaging using an additional dedicated micro-focus x-ray tube, based on the observation in Figure 3, would be preferable.

Figure 4. The detectability index computed using an ideal observer model for the reference system, denoted as “Ref”, for sequential micro-CT/XFCT imaging, denoted as “S-mCT”, and for concurrent micro-CT/XFCT imaging, denoted as “C-mCT”.

4. CONCLUSION

The results from this study provide a clearer picture of the trade-off between concurrent and sequential micro-CT imaging in dual-modality micro-CT/XFCT. If the intent of the micro-CT imaging is to provide gross anatomical images for co-localization with XFCT, then concurrent micro-CT/XFCT imaging is preferable. However, if the intent of micro-CT imaging is to provide high-resolution anatomical images similar to stand-alone micro-CT systems, then sequential micro-CT imaging with a micro-focus x-ray tube dedicated to micro-CT imaging would be of benefit.

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