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A Monte Carlo Model of a Benchtop X-Ray Fluorescence Computed Tomography System and Its Application to Validate a Deconvolution-based X-Ray Fluorescence Signal Extraction Method

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Abstract

In this study, we developed and validated a Geant4-based Monte Carlo (MC) model of an experimental bench-top x-ray fluorescence (XRF) computed tomography (XFCT) system for quantitative imaging of metallic nanoparticles such as gold nanoparticles (GNPs) injected into small animals for preclinical testing of various NP-based diagnostic and therapeutic approaches. Detailed hardware components of the current benchtop XFCT system, including the x-ray source, excitation beam collimation and filtration, custom imaging phantoms with GNP solutions, and single/ring/linear array detectors with custom collimation, were incorporated into the MC model. In conjunction with a known CdTe detector response function, a deconvolution-based XRF signal extraction method was also developed in this study, which enabled complete separation of gold K-shell XRF peaks even when they almost overlapped and facilitated extraction of XRF signals from a broadband Compton scattered photon background. The extracted signal-to-background ratios were comparable with those expected using an ideal detector with high enough energy resolution (e.g., 0.1 keV full width at half maximum). Once convoluted with the CdTe detector response function, the MC-calculated spectra for excitation beams or emitted photons and XFCT image spatial resolutions agreed well with those measured experimentally. Thus, the current MC model can be used to optimize the beam/imaging parameters (e.g., beam geometry, excitation x-ray beam energy, x-ray filter material) as well as the design of critical hardware components (e.g., detector collimators) within the current benchtop XFCT system. Also, the current XRF signal extraction method can relax the usual stringent requirement of detector energy resolution while not degrading the sensitivity of benchtop XFCT.

Keywords

Geant4; gold nanoparticles; Monte Carlo simulation; x-ray fluorescence computed tomography; x-ray detector response

I. Introduction

X-ray fluorescence (XRF) analysis is a well-known technique capable of accurately identifying and quantifying the concentrations of elements [1–3]. Combining it with computed tomography (CT) leads to a unique x-ray imaging modality known as x-ray fluorescence CT (XFCT), traditionally implemented using monochromatic synchrotron x-rays [4–9]. In recent years, XFCT implemented on a benchtop setting with ordinary polychromatic x-ray sources (i.e., “benchtop XFCT”) has emerged as a promising quantitative imaging modality to image metal nanoparticles such as gold nanoparticles (GNPs) present in biological samples and small animals during pre-clinical testing of various NP-based diagnostic and therapeutic approaches.

Many of the initial technical challenges with benchtop XFCT such as inefficient XRF photon production/detection arose from the use of polychromatic x-rays (vs. monochromatic x-rays). Despite such challenges, the development towards a practical benchtop XFCT system, especially for imaging of GNPs, has passed several milestones: first use of a polychromatic pencil x-ray beam as an excitation source [10], a polychromatic cone beam as an excitation source [11, 12], multiplexed imaging [13], and postmortem imaging of a tumor-bearing mouse [14]. Additionally, numerous investigations have been conducted to improve the performance of benchtop XFCT as well as to explore various applications of it [15–21]. Of note is that the progress in an overall benchtop XFCT system development has been relatively rapid, but considerable improvement in the detection component of the system (e.g., deployment of array/pixelated detectors) is still required to accomplish routine *in vivo* imaging of small animals while meeting the realistic constraints of scan time, delivered dose, spatial resolution, and detection limit.

Although a benchtop XFCT system can be developed based solely on experimental studies, computational modeling of the system to optimize the detection component may expedite the development process while reducing labor, time, and costs. Monte Carlo (MC) simulation toolkits are perfectly suited and can be validated for optimization of probabilistic systems, such as XRF detectors [19, 22, 23]. Thus, we developed an MC model of the current benchtop XFCT system based on the MCNP5 code [24], which helped improve the XRF signal to scatter background ratio by optimizing the excitation energy spectrum. However, our previous MCNP5 model did not incorporate all components of the current benchtop XFCT system. For instance, it did not include an x-ray tube, requiring measured incident x-ray spectra as essential input data for simulation and restricting characterization of beam parameters, such as scattering from the source collimator, beam uniformity, etc., which could be essential to design optimal source collimators. Also, the previous MC model lacked the flexibility in component design and computational speed necessary to perform large-scale simulations, e.g., a realistic XFCT image reconstruction on a practical time scale.

Therefore, the aim of the present study was to develop a more detailed, stand-alone, and computationally efficient MC model of the current benchtop XFCT system to enable further optimization of the system as well as testing of the new system component designs, for example, detector collimators suitable for array detectors. To that end, we used Geant4 (for GEometry ANd Tracking), an open source software toolkit developed by CERN based on C++ [25–27].

To develop an accurate MC model, validation of MC results against experimental measurements at different operational stages is necessary. For an MC model of any XFCT system, it is even more critical that MC-calculated photon spectra at excitation/emission stages are validated to keep the simulation time manageable. For instance, consider a cone-beam x-ray beam with radiation coverage of 40° that excites a GNP solution with a 1-mm^2 cross-sectional area placed 15 cm away from the source and the emitted XRF (isotopic) and scattered (directional) photons are detected at $(90 \pm 1)^\circ$ at a distance of 10 cm from the GNP solution. Under these conditions, if all excitation photons (energies above the gold K-absorption edge, i.e., 80.7 keV) can produce the gold K-shell XRF photons from GNPs, only about 25 XRF photons will hit the detector for every 1 billion excitation particles. Therefore, performing a full XFCT simulation, including x-ray generation and filtration, while requiring statistically meaningful energy spectra, is impractical. If the MC-calculated photon spectra are validated at excitation/emission stages, however, the generated spectra or phase-space data from previous runs can be used as inputs to the next runs, only including the subsequent system components.

For typical XRF signal extraction, the broadband Compton scatter background is subtracted from the measured XRF and scattered photon spectra using polynomial fitting of the scatter background, and the total net XRF signal over a certain region of interest is calculated [10, 14]. Such signal extraction routines, although perfectly reasonable for an ideal detector with sufficiently high energy resolution, pose a challenge in determining the appropriate energy window for signal extraction if the detector has a relatively low energy resolution [15, 28] or for multiplexed imaging [13] if different NPs emit overlapping XRF peaks. In practice, the energy resolution of a high-energy x-ray detector (e.g., a CdTe detector) is not only limited but also governed by a complex response function [29–32]. For example, the CdTe response function depends on the source energy and is governed by Gaussian broadening (equivalent electronic noise [*ENC*], statistical fluctuations [Fano limit]), and so-called hole tailing which deteriorates the measured energy response by adding an exponential tail toward lower energy [32]. Hence, for accurate estimation of total XRF photon signal, the detector response must be considered in the signal extraction procedure. To address this important issue, we investigated a deconvolution approach in the present study for extracting XRF signals from the measured XRF and scattered photon spectra, in which an energy response function for a CdTe detector based on the model proposed by [32] was incorporated.

II. Experimental Details

A. Benchtop XFCT System

The current benchtop XFCT system (Fig. 1) uses a unipolar tungsten (W)-target x-ray source (MXR-160/22, COMET) for excitation of GNP-filled phantoms. The excitation beam was

collimated using a cone-beam collimator (made of 5 cm thick lead) with diameters of 1 and 2 cm at the beam entrance and exit, respectively. The x-ray tube was operated at a 125-kVp tube potential with maximum tube current (24 mA), and the output beam was filtered using 1.8-mm tin (McMaster-Carr, USA) in addition to inherent 0.8-mm beryllium filtration. GNP-filled phantoms were positioned 15 cm away from the W-target, where the excitation beam coverage was more than 3 cm. XRF and scattered photons from GNP-filled phantoms were detected at 90° (with respect to the excitation beam axis) using a thermoelectrically cooled CdTe x-ray detector (5 mm × 5 mm × 1 mm, XR-100T-CdTe; Amptek, USA) coupled with a custom-made stainless steel collimator (2-mm aperture diameter and 5-cm thickness). The distances from the phantom center to the nearest surface of the collimator and the CdTe detector were about 5 cm and 10 cm, respectively. Unless specified otherwise, the CdTe detector gain was set at 14.56 and the pulse pile-up rejection mode was enabled (i.e., pulses separated by more than the fast channel resolving time [120 ns], and less than the 1.05× rise time are rejected) with a pulse rise time of 32 μ s. The flat top was 3.2 μ s and the thresholds for the fast and slow counters were 240 and 5%, respectively. These parameters were optimized to achieve best energy resolution around 70 keV at a minimum dead time. All measured photon spectra were corrected for photon-counting efficiency of the CdTe detector.

B. GNP Solutions and Phantoms

GNP solutions (AuroVist 15 nm; Nanoprobe, Inc., USA) were prepared in phosphate-buffered saline at different concentrations (0.02–0.50 wt. %) using a serial dilution method from a stock GNP solution (4 wt. %). Two kinds of custom-made cylindrically shaped polymethyl methacrylate (PMMA) GNP phantoms were used: 1) hollow GNP tubes with 1-cm inner diameters (height, 3 cm; wall thickness, ~1 mm) and 2) a three-hole GNP phantom with a 3-cm outer diameter (height, 3 cm) accommodating three 6-mm-diameter holes at a radial distance of 0.9 cm and angular separation of 120°.

C. Direct Beam Measurements

For direct excitation beam measurements, the CdTe detector was placed along the x-ray beam axis. To avoid saturating the detector with an excessive photon count rate, it was placed about 1.5 m away from the W-target followed by successive lead collimators (total thickness, ~25 cm; aperture decreasing from 2 mm to 1 mm), and the x-ray tube current and detector gain were reduced by about one order of magnitude below those used in regular XFCT experiments.

D. XRF and Scattered Photon Spectra

The GNP-filled tubes described in section II.B were placed in air and irradiated for 30 seconds to measure XRF and scattered photon spectra at 90° (with respect to the excitation beam axis). To examine the XRF signal extraction routine at different CdTe detector energy responses, spectra from GNP solutions were measured at varying detector pulse rise times of 19.2 – 32.0 μ s while keeping the rest of the detector settings the same as described in section II-A. All measurements were repeated 10 times.

E. XFCT Imaging with the Three-Hole GNP Phantom

The three-hole GNP phantom (Section B) filled with 0.5, 0.3, and 0.1 wt. % GNP solution was scanned in a total of 30 angular projections in incremental 12° steps. At each projection, the CdTe detector (coupled with a collimator) was translated in 11 steps with a 3-mm step size. At each position, the phantom was irradiated, and the spectrum was accumulated for 15 seconds.

III. MC Model

A. Geometric Components

The MC model was developed using the Geant4 toolkit (release 10.3, patch-01, multi-threaded). The model (Fig. 2) includes the following subsystems: x-ray generation (Fig. 2a), beam collimation and filtration (Fig. 2b), and excitation of the GNP phantom by a filtered cone beam and detection of XRF/scattered photons through an appropriate detector collimator (Fig. 2c). The geometric dimensions of the source collimator, filter, and GNP phantoms along with their locations and materials were matched with those used in the present benchtop XFCT system (Fig. 1). All system components were placed in air (density, 0.0012 g/cm^3 ; ionization potential, 85.7 eV). Unlike colloidal GNP solutions used in the experimental XFCT work, GNP solutions were created applying a uniform mixture model of water and gold [33, 34]. The x-ray source and the photon detector were modified from those used in the experimental benchtop XFCT system, due to lack of information about the internal structure of the x-ray tube or to increase photon detection efficiency, respectively. The details of modification are presented below.

X-ray source: The x-ray source (Fig. 2a; designed as a rectangular parallelepiped instead of a cylindrical shape for convenience in simulation) was filled with low-density gas (10^{-25} g/cm^3 ; ionization potential, 21.8 eV) and included a virtual monoenergetic electron source (filament with a diameter of 2 cm), a cylindrical W-target (1-cm diameter, 1-cm length at the longest side) cut at a 20° angle, and a beryllium window (inherent filter) with a thickness of 0.8 mm and diameter of 2.45 cm. The electron beam from the filament was generated in a converging momentum direction such that it hit the W-target within a spot size of 5.5 mm to potentially mimic the operating conditions for the benchtop x-ray tube in this study, for which the chosen focal spot size was 5.5 mm (EN 12543).

Detectors: The detectors used in the MC model were made of CdTe (47% Cd and 53% Te, available in Geant4 material database) crystals. For each simulation, two x-ray spectra were scored from the crystals: i) kinetic energy of any photon that hits the crystal, a spectrum that would be scored by an ideal detector with the energy resolution of 0.1 keV full width at half maximum (FWHM) and ii) energy deposited in the crystal, a spectrum that would be scored by CdTe crystal with perfect charge collection. The geometric structures of the detectors tested in the simulation consisted of a single crystal (Fig. 2c-i), as is used in the present benchtop XFCT system; a ring detector (Fig. 2c-ii); and a linear array detector (Fig. 2c-iii). The detector collimator material (stainless steel), hole diameter (2 mm), and thickness (5 cm) were kept the same for all three detectors. Also, the distance from the phantom's central axis to the first collimator surface was fixed (5 cm). Beryllium windows with the same

thickness (0.1 mm) were placed in front of the crystals in all detectors. The crystal size for the single and ring detectors was $5\text{ mm} \times 5\text{ mm} \times 1\text{ mm}$, the same as that for the CdTe detector used in the experimental benchtop XFCT system. The ring detector included a total of 107 crystals (coupled with the collimator including 107 holes) placed radially in a uniform manner with crystal center-to-center distance of 6.0 mm. For the linear array detector, the crystal size was reduced to $2.5\text{ mm} \times 2.5\text{ mm} \times 1.0\text{ mm}$ to maintain a crystal center-to-center distance of 3 mm (to mimic the 3-mm translational movement used in the experimental XFCT scan). The linear array detector included 11 crystals coupled with a collimator with 11 holes. The crystals in the array detectors were separated by air, thus charge sharing between the neighboring detectors was not considered [30, 31]. For the relatively large crystal (or pixel) sizes considered in this study, the charge sharing effect could be negligible [35].

B. Component assembly and Scoring

1) Excitation beam generation: For Bremsstrahlung and characteristic x-ray generation from the W-target; only the x-ray tube was included (Fig. 2a). For x-ray filtration; x-rays following the previously scored x-ray spectrum (generated from the focal spot on the W-target in the cone-beam momentum direction with a radiation coverage of 40° to mimic the output beam of the experimental x-ray tube) was transmitted through the tin filter (Fig. 2b). For both the x-ray generation and filtration, x-rays scored in the CdTe crystal placed 1.5 m away from the W-target were recorded. For these simulations, 100 billion photons histories were used. The 125-kVp, 1.8-mm tin-filtered x-ray photons were used for the excitation of GNPs in this study (Fig. 2b).

2) XRF/Scatter detection : To examine the spectral properties of the x-ray spectra emitted by GNPs (no imaging), GNP-filled tubes placed in air were irradiated using a filtered cone beam. In addition to the single crystal detector (Fig. 2c-i), possibility of improving detection efficiency using a ring detector (Fig. 2c-ii) was tested with the GNP tube rotated by 90° (to maintain the radial symmetry) and shortened in length (equal to the tube diameter, to ensure the same amount of excitation beam attenuation). For the ring detector, the x-rays detected in all crystals were accumulated to obtain the final spectrum. As all the crystals in the ring detector were at 90° with respect to the excitation beam, identical spectra were detected in the single crystal and ring detector except counting 107 times more photons in the ring detector for the same number of excitation photons (120 billion 125 kVp, 1.8-mm Sn filtered x-rays) as shown in Fig. 2c-iv. Thus, the detection cross-section increased 107-fold and the simulation time decreased accordingly. For the subsequent simulations using the ring detector, a total of 10 billion photon histories were used.

3) XFCT imaging: For XFCT image reconstruction (Fig. 2c-iii), a three-hole GNP phantom filled with 0.5, 0.3, and 0.1 wt. % GNP solution (described in section II-B) was rotated around the y-axis in a total of 30 angular projections in incremental 12° steps. At each projection, the phantom was bombarded with 125-kVp, 1.8-mm tin-filtered x-rays collimated to become a cone-beam, and the XRF/scattered photon spectra were scored using the linear array detector. Each crystal was set to measure a separate spectrum to mimic the detector's translational movement in the experiment.

To estimate the number of 125-kVp, 1.8-mm tin-filtered x-ray photons needed in the simulation to produce the same number of XRF photons in the experiment under identical conditions, the following test was performed: the number of XRF photons detected from the three-hole phantom (at 0° rotation) at the central crystal of the linear array detector was accumulated for the increasing number of excitation photons and compared with that measured in the experiment for 30 s of irradiation/acquisition time. Based on the test, about 88 billion filtered excitation photons produced the same number of XRF photons as was measured in the experiment with 30 s irradiation/acquisition time as shown in Fig. 2c-v. Thus, 88 billion photons were used for the irradiation of the three-hole phantom at each projection.

MC simulations were performed in multi-thread mode using the High Performance Computing (HPC) cluster at The University of Texas MD Anderson Cancer Center. The average simulation time taken to run one billion particles in a computing node with 23 CPUs (2.2–2.5 GHz clock speed) for the simulations involving x-ray generation from the W-target bombarded by electrons was ~ 30 h and that for photon irradiation of GNPs was ~ 6 h.

C. Physics List and Energy Cuts

The particle (photon or electron) interactions and transportations were modeled using the Penelope low energy electromagnetic physics list. For photon transport, the photoelectric effect, Compton scattering, and Rayleigh scattering were included in the physics list, whereas for electron transport, the multiple scattering, Coulomb scattering, ionization, and bremsstrahlung x-ray production were included. The range cuts (threshold stopping range) were chosen such that particles with energy > 1 keV are tracked regardless of material of passage.

IV. Spectral data processing and image reconstruction

A. Correction for Escape Peaks

To correct the MC-calculated or experimental x-ray spectra detected by the CdTe detector for the so-called escape events owing to the Cd and Te XRF emissions, the stripping algorithm [32, 36] was applied. Briefly, due to the Cd K-shell XRF emissions at $E_j = 23.2$ and 26.1 keV and Te emissions at $E_j = 27.5$ and 31.0 keV, if the incident photon energy E is greater than the CdTe absorption edges, it is detected at $(E - E_j)$ and results in distortion in the detected spectrum. To correct for this effect, the fractions $f_\lambda(E)$ of the incident photons escaping the crystal were calculated via MC simulation as follows: the CdTe crystal was uniformly bombarded with a monoenergetic photon beam and for each incident photon, i) the energy deposited inside the crystal and ii) the number of photons emitted at the four escape peaks were recorded. The procedure was repeated over energies ranging from 0 – 160 keV, with ~ 47 million photons for each energy. From this dataset, the fractions $f_\lambda(E)$ were calculated. Based on these functions and CdTe detection efficiency, both simulated and experimental spectra were corrected.

B. CdTe Detector Response Function

Based on the detailed physics-based model proposed by [32], an analytical function was tested to characterize the response of the currently used CdTe detector as shown in (1). Here, E_m is the deposited energy, E_s is the monoenergetic source or incident photon energy (i.e. XRF from GNP), σ is the standard deviation of the measured response associated with Gaussian broadening only, and γ is the hole-tailing parameter. The first term in the right-hand side of (1) considers the Gaussian broadening as a function of σ , with the energy dependence of σ characterized as $\sigma(E_s) = \sqrt{a + bE_s}/2.35$. Here, a ($=ENC^2$) accounts for electronic noise, and bE_s accounts for the Fano limit at source energy E_s . The second term in the right-hand side of (1), which is a convolution of an exponential function tailing toward lower energy and step functions, considers hole tailing as a function of γ above a cutoff energy $E_{\gamma c}$, as hole tailing is not as prominent at low energy as it is at high energy. The greater the γ , the more dominant the hole-tailing effect.

$$F(E_m, E_s, \sigma, \gamma) = \frac{1}{\sqrt{2\sigma}} \exp(-(E_m - E_s)^2 / 2\sigma^2) \quad (1) \\ + \gamma \exp(E_m - E_s + \gamma\sigma^2) \\ \times \operatorname{erfc}((E_m - E_s)/\sigma) \\ \times (1 - \operatorname{erfc}(E_m - E_{\gamma c})/2)$$

C. Compton Scatter Background

The background photon counts due to Compton scattering, which, when detected at 90° for a polychromatic excitation beam, is usually shaped as an asymmetrical broadband peak, was fitted using the asymmetric double sigmoidal function shown in (2), where A , E_{mc} , w_1 , w_2 , and w_3 refer to the peak amplitude, position of the peak maximum, FWHM, variance of the low-energy side and the variance of high-energy side, respectively of the peak-shaped background. This function was chosen based solely on the observed shape of the background and was preferred over typical polynomial fitting to reduce degrees of freedom and influence of Poisson noise on the fitted background.

$$N_{scat}(E_m) = \frac{A}{1 + e^{-\frac{E_m - E_{mc} + w_1/2}{w_2}}} \times \left(1 - \frac{1}{1 + e^{-\frac{E_m - E_{mc} + w_1/2}{w_3}}} \right) \quad (2)$$

D. Convolution of Simulated Spectra

To compare the MC spectra with the measured spectra, the simulated photon counts $N(E_s)$ at each energy E_s were convoluted using the CdTe response function as shown in (3): photon counts at each energy were distributed into appropriate numbers (function of energy) of

energy bins E_m , preserving the total photon counts. The convoluted spectra were then fitted against the experimentally measured spectra, and the best fit parameters (σ , γ) were calculated using a constrained non-linear multivariable solver (MATLAB, R2006a; MathWorks, USA).

$$N'(E_m, E_s, \sigma, \gamma) = N(E_m) \frac{F(E_m, E_s, \sigma, \gamma)}{\sum_m F(E_m, E_s, \sigma, \gamma)} \quad (3)$$

E. Deconvolution of Measured XRF Photons

A deconvolution method was tested for extraction of XRF photons from the measured XRF and scattered photon spectra from GNP solutions taking into account the CdTe detector response function in (1). As shown in (4), the deconvolution method consisted of three steps: i) fitting of the Compton scattered photon counts (i.e., the entire spectrum excluding the regions around the XRF peak positions was fitted using (2), ii) addition of the detector response functions F_i to N_{scat} centered at XRF peak positions (e.g., at ~67 keV for K_{a2} and ~68.8 keV for K_{a1} , etc., K-shell XRF peaks for gold) multiplied by the respective scaling factors (k_s), and iii) fitting of the entire measured spectrum using the combined function and calculation of the best fit parameters (σ , γ , k_s) using a constrained nonlinear multivariable solver (MATLAB, R2006a; MathWorks). For the best fit parameters, the second term in the right-hand side of (4) indicates the total (from all XRF peaks) measured XRF photon counts.

$$N_{fit}(E_m, E_s, \sigma, \lambda) = N_{scat}(E_m) \quad (4)$$

$$+ \sum_s k_s \frac{F(E_m, E_s, \sigma, \gamma)}{\sum_m F(E_m, E_s, \sigma, \gamma)}$$

F. Estimation of XRF Signal and Background

For both experimental and MC spectra, the Compton scattered photon counts at the XRF peak energies E_s , referred to here as background (B), were interpolated as $B = N_{scat}(E_s)$. For the measured spectra, the photon counts from individual XRF peaks, referred to here as XRF signal (S), were calculated as $S = k_s$ based on the best fitted spectrum obtained using (4). For the MC spectra, the signals were estimated by directly subtracting the backgrounds from the respective scored photon counts at E_s . The respective signal-to-background ratio (SBR) was then calculated as S/B .

G. Image Reconstruction

For both experimental and simulated XFCT imaging of the three-hole phantom, sinograms were calculated using total XRF photons at all gold K-shell peaks and the images were reconstructed using a maximum-likelihood iterative reconstruction algorithm similar to the algorithm presented by [12]. The correction for attenuation inside phantom was performed

based on *a priori* attenuation coefficients of PMMA at the intensity-weighted mean energy of excitation beam and at XRF photons energies. At each iteration, the images were filtered using Gaussian smoothing filter built-in in MATLAB. The results converged in 6–8 iterations within ~10 s. For ease in visual comparison of reconstructed images based on experimental and simulated data, the pixel size of each reconstructed image was reduced from 3 mm × 3 mm to 1 mm × 1 mm using spline interpolation.

V. Results

A. Correction for CdTe escape peaks and efficiency

Fig. 3 shows the correction for the escape peaks and detection efficiency of CdTe detector as applied to an MC-calculated 125 kVp x-ray spectrum for the W-target, where the inset shows the fractions of photons escaped at the four CdTe XRF peaks. The fractions estimated here are about half of that estimated by [32] most probably due to the use of a thicker crystal in this study (1.0 mm instead of 0.75 mm). The energy deposited in the CdTe crystal clearly shows the absorption edges of CdTe and distortion due to escape events, which are significantly removed after the correction and the incident spectrum is nearly reproduced (χ^2 between the spectra reduced by one order of magnitude).

B. Validation of MC Spectra and Detector Response Function

1) X-Ray Spectrum from the W-Target: Fig. 4a shows a comparison between the experimentally-measured 125-kVp (currently used in the experimental benchtop XFCT system) unfiltered (apart from the inherent beryllium filter) bremsstrahlung x-ray spectrum including characteristic WXRF peaks and MC-calculated spectrum before and after convolution using the CdTe detector response function as shown in (3). The measured W-XRF peaks, in addition to the inevitable electrical noise and Gaussian broadening, suffered from hole tailing, which became more prominent at higher energy. Also, a residual effect of the so-called escape events [32] can be observed as the absorption edges of the Cd and Te at about 27 keV and 32 keV. Although the MC spectrum, as scored before convolution, reproduces the relative fluence of the measured bremsstrahlung x-ray spectrum and identifies the center of W-XRF peaks, it displays much greater relative XRF peak intensities than that observed in the measured spectrum. After the CdTe model is applied, as the energy resolution deteriorates, the convoluted spectra nearly replicate the measured spectra with a good coefficient of determination ($R^2 > 0.99$) and the same intensity-weighted mean energies (36.92 keV and 36.89 keV for experimental and simulated spectra, respectively). We also observed similar agreement between the experimentally-measured and MC-calculated spectra at other tube voltages, such as 60, 140, and 160 kVp (detailed results not shown here).

2) Beam Hardening Using Tin Filter: Fig. 4b shows a comparison of experimentally-measured 125-kVp x-ray spectrum hardened using a 1.8-mm tin filter (currently used in the experimental benchtop XFCT system) with that calculated from the MC model before and after convolution using the CdTe detector response function. Once convoluted using the CdTe detector response function, the MC-calculated spectrum exhibited good agreement with the measured data ($R^2 > 0.99$), most importantly in terms of the intensity-weighted

mean energies, which were 94 keV and 95 keV for the experimental spectrum and simulated spectrum, respectively. We observed similar agreement between the experimentally-measured and MC-calculated spectra at other filter thicknesses, such as 0.9 and 2.7 mm (detailed results not shown here).

3) XRF and Scattered Photon Spectra from GNPs: Fig. 4c shows the XRF and scattered photon spectra from a 1 wt. % GNP solution irradiated by the 1.8-mm tin-filtered 125kVp beam. Comparison of the measured spectrum and MC-calculated spectrum with 0.1 keV FWHM energy resolution clearly indicated that the ratio of the gold K-shell XRF intensity to the Compton scattered background decreased by about one order of magnitude owing to the CdTe detector energy resolution. Not only had the XRF peaks overlapped, a considerable number of photons also created a tail from the K_{α} peaks toward lower energy owing to hole tailing. Again, after it was corrected with the CdTe detector response function, the MC-calculated spectrum agreed with the measured spectrum very well ($R^2 > 0.99$).

4) CdTe Detector Response: Fig. 5 shows the CdTe detector responses at different characteristic W- XRF peak energies as calculated based on the best fit parameters obtained from the spectrum comparison in Fig. 4a. The indicated values represent full width at tenth maximum (FWTM) instead of the typically reported FWHM to include broadening due to hole tailing. As reported previously [32], electronic noise was the most dominant source of peak broadening at lower energy (<20 keV), and the statistical broadening and hole-tailing effect dominated at higher energies. The average FWTM of the W K-shell XRF peaks (58–69 keV) due only to Gaussian broadening was about 1.2 keV, whereas that observed with the inclusion of hole-tailing, was about 2.7 keV. Thus, while validating the CdTe detector response function, these findings demonstrated that in conjunction with the MC spectra with 0.1 keV FWHM energy resolutions and a test detector response function, the energy resolution of an experimental x-ray detector can be characterized over a range of energies using a polychromatic x-ray beam from a benchtop x-ray tube, without requiring any standard radioactive sources.

C. Extraction of Gold XRF Photons

The measured x-ray spectra from a 0.5 wt. % GNP solution at different CdTe detector pulse rise times along with the fitted model as shown in (4) and the respective extracted XRF peaks are shown in Fig. 6. As the rise time increased from 19 to 32 μ s, the average FWTM of the gold $K_{\alpha 2}$ or $K_{\alpha 1}$ peaks decreased from about 3.6 keV to 2.6 keV. Regardless of whether the two $K_{\alpha 2}$ and $K_{\alpha 1}$ peaks are, in comparison with energy separation of the two peaks $E = 1.8$ keV, almost overlapped (FWTM = $2.0 \times E$) as in Fig. 6c or almost resolved (FWTM = $1.4 \times E$) as in Fig. 6d, the CdTe detector response function enabled characterization of the measured spectra very well ($R^2 > 0.99$), and the XRF peaks were completely resolved. Thus, this deconvolution procedure bypasses the need for choosing an appropriate energy window for signal extraction by identifying all XRF photon counts distributed over a finite energy range (~ 4 keV).

Fig. 7 shows a comparison of the SBRs at the gold K-shell XRF peaks as a function of GNP concentration estimated in the experiment (rise time of 32 μ s) and via simulation. For all

peaks, we observed a linear response ($R^2 > 0.99$) in the extracted signal and the slopes of the fitted curves agreed with those observed for the simulated data within fitting uncertainty. Thus, the total SBR over all gold K-shell XRF peaks can be used for quantification of GNP concentration.

Of note is that the focus of testing different detector settings was to merely produce different energy resolutions to examine the flexibility of CdTe detector response function, not to find the best detector settings. Besides, we did not consider the potential loss of linearity in output count rate at high input count rate (the measured input count rate for this study was ~ 4000 counts/s) and at high rise times [37].

D. Validation of the MC Model via XFCT Images

Fig. 8 shows the reconstructed images obtained from the XFCT scan of a three-hole phantom filled with 0.5, 0.3, and 0.1 wt. % GNP solution based on experimentally-measured XRF/scattered photon spectra and those calculated from MC simulations

A pixel-to-pixel regression analysis demonstrated that the GNP concentrations calculated from the simulation had a linear relationship ($R^2 > 0.99$) with that measured in the experiment. The blue lines marking the outer edges of the phantom (large circle) and GNP-filled regions (small circles) indicate that we detected the XRF signals beyond the boundaries of the GNP-filled regions in both the experiment and simulation. This was due to using a rather large detector collimator aperture. The mean FWHM calculated using two-dimensional Gaussian fitting (different standard deviations in the x- and z-directions) applied considering only the regions of interest around individual GNP-loaded regions were 7.1 ± 0.2 mm and 7.0 ± 0.2 mm (the values following $\pm$ indicates standard errors) in the experiment and in the simulation, respectively, regardless of direction (x- or z-direction).

VI. Discussion

In this study, we developed and validated a detailed MC model of an experimental benchtop XFCT system for quantitative imaging of GNP distributions in small animals or biological samples. Although they were by no means exhaustive, our experiments clearly indicated that the current MC model is an accurate and versatile tool that can facilitate our ongoing development of a practical benchtop XFCT system and a more robust XRF signal extraction method.

The array detector we used in the simulated XFCT scan is a simple, viable option that can be implemented with XFCT systems instead of detector translation to reduce the scan time. As we found, however, to achieve spatial resolution of about 1 mm, the collimator aperture size must be reduced, possibly at the expense of increased scan time. Further studies can help identify the best array detector configuration in terms of optimal scan time and spatial resolution. Because the x-ray source is reliably incorporated into the current MC model, different source collimator designs and materials can be tested in our future study to optimize the divergence of the excitation beam according to the size of imaging object and/or to minimize the production of scattered or unwanted XRF photons from the source

collimator itself. Moreover, the output and spectrum of the excitation beam can also be further optimized by testing different beam energy and filter materials and/or thicknesses.

In principle, the XRF signal extraction method described herein could be developed independently of MC simulation. The only difficulty in relying solely on the experimental spectra for such development is a lack of a reference to compare the extracted XRF signal with the expected value using an ideal detector (e.g., the one with the energy resolution of 0.1 keV FWHM) at the energies of interest. The comparison of the extracted signal with that achievable with an ideal detector, only possible in MC simulation, allows an assessment of the performance of the current detector and an estimation of how much improvement in the detection limit can be expected with the detector development. In the present study, in conjunction with the deconvolution procedure, the CdTe detector nearly mimicked the performance of a detector with an energy resolution of 0.1 keV FWHM. Although the CdTe detector response function must be determined for a wide range of detector designs, it was demonstrated that the deconvolution procedure, in general, relaxed the stringent requirement of high-energy resolution usually needed for an x-ray detector in highly sensitive benchtop XFCT imaging. In principle, adoption of such a deconvolution method may allow the use of detectors with lower energy resolution, such as, conventional photon counting detectors with energy resolution of few keVs [30] for benchtop XFCT, while achieving comparable sensitivity. Also, if the XRF peaks from different elements somewhat overlap during multiplexed imaging with benchtop XFCT, an immediately discernable way to resolve them would be a deconvolution-based approach. In general, a deconvolution method such as the one presented herein eliminates the necessity to carefully choose an XRF energy window to achieve the best signal-to-background ratio.

VII. Conclusions

In this study, we developed and validated a Geant4-based MC model of a novel experimental benchtop XFCT system and a gold XRF signal extraction method. We characterized the energy resolution of a CdTe x-ray detector based on the MC spectra with 0.1 keV FWHM energy resolution and tested the CdTe detector response function. In conjunction with the CdTe response function and our proposed deconvolution method, gold K-shell XRF signals were extracted completely over a large Compton scatter background, even when the XRF peaks almost overlapped, thus relaxing the usual stringent requirement of detector energy resolution while not degrading the sensitivity of benchtop XFCT. The MC spectra, convoluted with the CdTe detector response function, agreed well with the experimentally-measured unfiltered/filtered excitation beam spectra and XRF/scattered photon spectra from GNPs. We further validated the MC model in terms of the absolute SBR at the gold XRF peaks and spatial resolution of the experimental benchtop XFCT system. Therefore, our MC model can be useful for future optimization of the design of different critical hardware components within our experimental benchtop XFCT system, and also for assessment of some critical constraints in determining the feasibility to perform *in vivo* animal imaging with it, such as the delivered dose versus detection limit and spatial resolution versus scan time.

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Fig. 1.
Photograph of the current benchtop XFCT system.

Fig. 2.

Schematic for the current MC model showing the system components used in the model at different stages of simulation along with exemplary x-ray spectra. The red and green trajectories indicate electron and photon trajectories, respectively. (a) The x-ray tube and the x-ray spectrum from W-target for 125 kVp tube voltage. (b) The collimation/filtration components and the filtered spectrum obtained using 1.8 mm Sn filter at 125 kVp tube voltage. Excitation and detection of x-ray spectra from GNP tube/phantom using (c-i) single detector, (c-ii) ring detector, and (c-iii) linear array detector. (c-iv) Comparison between the x-ray spectra obtained using single crystal and ring detector (upon excitation of 1 wt.% GNP solution using 120 billion 1.8 mm Sn filtered 125 kVp x-ray photons). (c-v) Comparison between the x-ray spectra from three-hole phantom obtained in the experiment using irradiation time of 30 s and that obtained in simulation using 88 billion filtered x-ray photons (estimated using the correlation shown in inset). The average statistical uncertainty (square root) in the MC-calculated photon counts in (a) is 3% over 5–125 keV, (b) 2% over 50–125 keV, (c-iv) 9% for single crystal and 0.9% for ring detector over 50–100 keV, and (c-v) 9.7% over 50–100 keV.

Fig. 3. Correction for escape peaks as applied to MC-calculated 125 kVp x-ray spectrum for W-target. The inset shows the calculated fractions of escape events at four CdTe XRF peaks used for the correction. The average statistical uncertainties in the spectra are $<5\%$.

Fig. 4.

Comparison between experimentally-measured and the MC-calculated x-ray spectra before and after convolution using the CdTe detector response function for (a) unfiltered and (b) 1.8 mm tin-filtered 125-kVp W-target excitation beam measured/simulated along the beam axis. (c) XRF and scattered photon spectrum from a 1 wt. % GNP solution (excited using 125-kVp W-target 1.8 mm tin-filtered beam) measured/simulated at 90° with respect to the beam axis. The spectra were normalized to the mean photon counts over the energy range (a) 5–125 keV, (b) 50–125 keV, (c) 50–100 keV, where the average statistical uncertainty (square root) in the unprocessed MC-calculated photon counts is 3%, 2%, and 4%, respectively.

Fig. 5.

Responses of the CdTe detector at different energies, where the indicated values represent full width at tenth maximum (keV- FWTM). The estimated relationship for Gaussian broadening was: $\sigma(E) = \sqrt{2.12 \times 10^5 + 2402E/2.35}$ eV and $\gamma = 1.02$.

Fig. 6.

Extraction of XRF signals from x-ray spectra (from a 0.5 wt. % GNP solution) measured using a CdTe detector with different pulse rise times. a-b) The measured signal and fitted models. c-d) The respective deconvoluted gold K-shell XRF peaks ($K_{\beta 3,1}$ indicates the sum of $K_{\beta 3}$ and $K_{\beta 1}$) and total XRF. The parameters related to Compton background are: $A = 470$ counts, $E_{mc} = 82.4$ keV, $w_1 = 24$ keV, $w_2 = 7.2$ keV, $w_3 = 2.8$ keV; the parameters related to XRF counts, k are the area of the deconvoluted peaks shown in c-d.

Fig. 7.

Calibration of the SBR at the gold XRF peaks (data points for K_{β} represent total SBR from $K_{\beta 1-3}$ peaks) as a function of GNP concentrations with excitation of GNP-filled cylindrical tubes using a 1.8-mm tin-filtered 125-kVp beam (30-second irradiation using the benchtop XFCT system and use of 10 billion filtered x-ray photons in the MC model). The error bars indicate standard deviations of the mean SBR based on 10 repeated measurements in the experimental data and propagated statistical uncertainty in the MC model.

Fig. 8.

Comparison of the reconstructed images (pixels values indicate the GNP concentrations) of a three-hole phantom filled with GNP solutions of 0.5, 0.3 and 0.1 wt. % obtained using (a) the experimental benchtop XFCT system and (b) the MC model. The large blue circle indicates the phantom's outer edge, while the small circles indicate the GNP solution position and size (6 mm in diameter).