Improving x-ray fluorescence signal for benchtop polychromatic cone-beam x-ray fluorescence computed tomography by incident x-ray spectrum optimization: A Monte Carlo study

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(Received 17 April 2014; revised 22 July 2014; accepted for publication 22 August 2014; published 17 September 2014)

Purpose: To develop an accurate and comprehensive Monte Carlo (MC) model of an experimental benchtop polychromatic cone-beam x-ray fluorescence computed tomography (XFCT) setup and apply this MC model to optimize incident x-ray spectrum for improving production/detection of x-ray fluorescence photons from gold nanoparticles (GNPs).

Methods: A detailed MC model, based on an experimental XFCT system, was created using the Monte Carlo N-Particle (MCNP) transport code. The model was validated by comparing MC results including x-ray fluorescence (XRF) and scatter photon spectra with measured data obtained under identical conditions using 105 kVp cone-beam x-rays filtered by either 1 mm of lead (Pb) or 0.9 mm of tin (Sn). After validation, the model was used to investigate the effects of additional filtration of the incident beam with Pb and Sn. Supplementary incident x-ray spectra, representing heavier filtration (Pb: 2 and 3 mm; Sn: 1, 2, and 3 mm) were computationally generated and used with the model to obtain XRF/scatter spectra. Quasimonochromatic incident x-ray spectra (81, 85, 90, 95, and 100 keV with 10 keV full width at half maximum) were also investigated to determine the ideal energy for distinguishing gold XRF signal from the scatter background. Fluorescence signal-to-dose ratio (FSDR) and fluorescence-normalized scan time (FNST) were used as metrics to assess results.

Results: Calculated XRF/scatter spectra for 1-mm Pb and 0.9-mm Sn filters matched ($r \geq 0.996$) experimental measurements. Calculated spectra representing additional filtration for both filter materials showed that the spectral hardening improved the FSDR at the expense of requiring a much longer FNST. In general, using Sn instead of Pb, at a given filter thickness, allowed an increase of up to 20% in FSDR, more prominent gold XRF peaks, and up to an order of magnitude decrease in FNST. Simulations using quasimonochromatic spectra suggested that increasing source x-ray energy, in the investigated range of 81–100 keV, increased the FSDR up to a factor of 20, compared to 1 mm Pb, and further facilitated separation of gold XRF peaks from the scatter background.

Conclusions: A detailed MC model of an experimental benchtop XFCT system has been developed and validated. In exemplary calculations to illustrate the usefulness of this model, it was shown that potential use of quasimonochromatic spectra or judicious choice of filter material/thickness to tailor the spectrum of a polychromatic x-ray source can significantly improve the performance of benchtop XFCT, while considering trade-offs between FSDR and FNST. As demonstrated, the current MC model is a reliable and powerful computational tool that can greatly expedite the further development of a benchtop XFCT system for routine preclinical molecular imaging with GNPs and other metal probes. © 2014 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4895004>]

Key words: x-ray fluorescence, computed tomography, gold nanoparticles, Monte Carlo method

1. INTRODUCTION

In recent years, a traditionally synchrotron based technique known as x-ray fluorescence computed tomography (XFCT)^{1–4} has emerged as a valuable quantitative imaging tool which can be used to determine the biodistribution of high-Z metal probes such as iodine, gadolinium, platinum, and gold. While

monochromatic x-rays are considered ideal⁵ for XFCT, the impracticality of using synchrotrons in typical biomedical laboratory settings, especially for *in vivo* imaging of small animals, has motivated the implementation of XFCT on a benchtop setting using a polychromatic diagnostic energy-range x-ray source (viz., “benchtop XFCT”). Through a series of studies,^{6–8} we have shown that benchtop XFCT is capable of localizing

gold nanoparticles (GNPs) inside small-animal-sized objects by detecting gold x-ray fluorescence (XRF) photons from GNPs. Especially, in our latest experimental study,⁷ we demonstrated the capability of performing benchtop XFCT of GNP-loaded objects using polychromatic cone-beams, paving the way to build a practical benchtop XFCT system. Additionally, other researchers have applied similar benchtop XFCT techniques to image various other metal probes (e.g., platinum) within small-animal-sized phantoms,^{9–11} suggesting the possibility of extending benchtop XFCT techniques beyond GNP applications.

Following up on the studies mentioned above, research efforts are currently underway to build a benchtop XFCT system for routine preclinical *in vivo* imaging with GNPs and/or other metal probes. These efforts require further development and optimization of the existing experimental setup, especially in terms of maximizing the production/detection of gold XRF photons under the given physical limitations. While it could be done entirely by an experimental approach, Monte Carlo (MC) methods are particularly well suited for spectroscopic XRF imaging,¹² capable of producing accurate results even with polychromatic x-ray spectra and heterogeneous geometries,¹³ and would be useful for streamlining further optimization efforts. For example, a well-validated MC model of our experimental XFCT setup would enable proper tailoring (or quasimonochromatization) of the incident polychromatic x-ray spectrum (one of the major challenges associated with benchtop XFCT) in a much more efficient manner. Also, it could be applied to various optimization tasks covering from source/detector collimator design to an overall benchtop XFCT system configuration.

Therefore, in this study, we developed a thorough MC model of our benchtop polychromatic cone-beam XFCT setup using the Monte Carlo N-Particle Version 5 (MCNP5) code.¹⁴ The model was validated with experimental measurements and, as one exemplary application of it, was subsequently used to investigate the effect of different incident x-ray energy spectra on the production/detection of XRF photons from GNPs. An optimized incident x-ray source spectrum, in the context of quasimonochromatization, would not only help lower the detection limit for GNPs, but it would also decrease XFCT scanning time and reduce unnecessary dose from low energy photons which do not contribute to XRF photon production.^{15,16} The current MC model can also be used to optimize other aspects of the benchtop XFCT system and will help facilitate further development of it.

2. METHODS AND MATERIALS

2.A. Monte Carlo modeling of experimental setup

The experimental polychromatic cone-beam XFCT system was comprised of several components, as described in our previous work.⁷ These included an x-ray source, filter, beam collimator, polymethyl methacrylate (PMMA) phantom, detector, and detector collimation. Briefly, a combination of phantom rotations and detector translations is utilized to acquire XRF signal data from multiple lines, which are then

FIG. 1. Components of MC model simulating the experimental setup. The PMMA phantom with GNP-loaded insert was irradiated by a virtual cone-beam source with configurable photon spectra. The XRF and scattered x-rays (at 90° with respect to the incident beam) from the GNP-loaded insert and phantom were collimated and detected by a shielded CdTe detector. Note that the incident beam collimator and filter were modeled by a virtual photon phase-space source. Inset: detail of detector element located inside the detector housing.

used for reconstructing an axial XFCT image of the phantom. The current MC model, created using the MCNP5 code and rendered in Fig. 1, was based on one specific, arbitrary, detector position, and phantom orientation of the experimental XFCT system, in order to facilitate direct comparison with experimental measurements taken under the same conditions.

2.A.1. X-ray source, collimation, and filtration

The x-ray source used for the current XFCT system was the Hamamatsu L9631 microfocus x-ray unit (Hamamatsu Photonics, Inc.), operated at 105 kVp and 450 μ A. The x-ray beam from the source was collimated using a lead (Pb) block, 20 cm in width/height and a thickness in the beam direction of 5 cm. The block featured a conical (11.4°) opening with diameters of 1 and 2 cm along the beam direction. The divergence of the beam after the collimator allowed it to cover the entire PMMA phantom, placed 8 cm away. Either a 1-mm-thick Pb filter or a 0.9-mm-thick tin (Sn) filter was placed after the collimator to attenuate low energy photons below the *K*-edge of gold (80.7 keV) which are not capable of generating gold *K*-shell XRF photons. Pb and Sn were chosen not only because of their high photoelectric absorption cross sections at lower energy but also because of their ubiquitous availability. Instead of a computationally inefficient direct modeling of the beam propagation from the x-ray source through the collimator and filter, the current MC model implemented a diverging 2-cm-diameter disk source (i.e., cone-beam source) located immediately after the location of the filter to represent the phase space of x-rays with the appropriately filtered energy spectrum, shown in Fig. 2. This virtual source approach, validated in a previous investigation,¹⁷ provided the two following advantages: first, it was possible to perform a straightforward experimental measurement of the x-ray spectra after collimation and filtration of the

FIG. 2. X-ray spectra, experimentally measured using a CdTe detector, obtained by filtration of 105 kVp x-ray beam through (a) 1-mm Pb filter and (b) 0.9-mm Sn filter. Fluence has been normalized to aid visual comparison (see Fig. 4 for relative fluence comparison). These spectra were used as incident spectra in the MC model to generate XRF/scatter spectra, which in turn were compared with measured spectra for validating the model (see Fig. 3).

source x-ray beam, yielding more realistic spectra which could then be used for MC simulations; second, by not having to repeatedly simulate the transport of photons from the x-ray source through the collimator and filter, computational time was shortened dramatically.

2.A.2. Cylindrical PMMA phantom with GNP-loaded inserts

The PMMA phantom mimicking a small animal was also modeled accurately using the MCNP5 code. The irradiated portion of the cylindrical phantom had a diameter and height of 3 cm and was molded on top of a cylindrical base, 4.5 cm in diameter and 2 cm in height. The top portion had three equally spaced 1.5-cm-deep, 6-mm-diameter holes drilled with their centers located 1 cm from the center of the phantom. Tapered imaging inserts of slightly smaller diameter and height were accommodated by these holes. The phantom was oriented as shown in Fig. 1, and the insert closest to the x-ray source was filled with a solution of water and uniformly distributed GNPs at a concentration of 20 mg/cm³ (or 2% by weight); the other two inserts contained water only.

2.A.3. Cadmium-telluride x-ray detector and collimation

The detector model was based on a commercially available cadmium-telluride (CdTe) gamma and x-ray detector (XR-100T-CdTe, Amptek, Inc.), which had a beryllium window of 100 μ m thickness, 1.27 mm behind which was a 3 $\times$ 3 $\times$ 1 mm³ CdTe crystal serving as the active area of the detector. The detector housing, comprised of the head and base of the detector, was also modeled. These included the 0.25-mm-thick, 1.4-cm-diameter nickel cover and the 1.5-mm-thick base made of Kovar steel (a nickel-cobalt ferrous alloy). The detector was placed at 90° with respect to the beam direction and 0.75 cm behind a 4-cm-thick Pb pinhole collimator with

aperture diameter of 2.5 mm. The collimator opening and CdTe detector element were aligned with the center of the GNP-loaded imaging insert.

2.A.4. Monte Carlo simulation parameters

The MCNP5 input deck was configured to track photons, with an energy-specific flux (F4) tally over the CdTe detector element to score XRF and scattered photons reaching it (90° XRF/scatter spectrum). Default physics option was used for photon transport, including treatment of bremsstrahlung, coherent scattering, and Doppler broadening. No variance reduction methods, biasing, or forced transport were used. The energy-bin width was set to be 0.5 keV in order to discern spectral features such as the gold XRF peaks of interest (K_{α} peaks at ~67 and ~69 keV) while still approximating the typical energy resolution of the Amptek XR-100T-CdTe detector. While the less prominent K_{β} peak (~78 keV) was visible in some of the results, it was not considered for analysis. In addition, the average dose to the center of the phantom was obtained using an energy-deposition (F6) tally. For each set of simulation corresponding to the testing of one source spectrum, 80 $\times$ 10⁹ individual particle histories were run in order to obtain results with average statistical uncertainty below 5%.

2.B. Validation of Monte Carlo model with experimental data

The MC model needed to be validated as an accurate representation of the experimental setup so that it could be used as a tool for further purely computational investigation. Mirroring the experimental setup, the validation was done for both 1-mm Pb-filtered and 0.9-mm Sn-filtered spectra for the virtual cone-beam source, presented in Fig. 2. The XRF/scatter spectra from the MCNP5 simulations were compared with experimentally obtained data under the same conditions as described previously.⁷ The simulated results were validated with

experimental data by computing their similarity, given by the sample Pearson product-moment correlation coefficient (r)

$$r = \frac{1}{n-1} \sum_{i=1}^n \left(\frac{M_i - \bar{M}}{\sigma_M} \right) \left(\frac{S_i - \bar{S}}{\sigma_S} \right),$$

where n is the number of energy bins, M_i is the measured fluence in bin i , $\bar{M}$ is the sample mean of the measured fluence, and σ_M is the sample standard deviation of the measured fluence. The terms are defined equivalently for S , the simulated results.

2.C. Effects of incident x-ray spectra on XRF signal for a benchtop cone-beam XFCT system

The capability and usefulness of the current MC model were demonstrated by applying it to investigate the effects of incident x-ray spectra on the performance of our experimental benchtop XFCT system. This task also enabled further validation of the MC model via comparison between the MC results and additional experimental data.

2.C.1. Filtration of 105 kVp x-rays with lead and tin filters

The previously discussed 1-mm Pb-filtered and 0.9-mm Sn-filtered spectra (i.e., measured spectra as shown in Fig. 2) were used as input data for the MC model to computationally generate supplementary spectra with further filtration. For each case, a filter of appropriate thickness (Pb: 1 and 2 mm, Sn: 0.1, 1.1, and 2.1 mm) was placed in the model immediately after the virtual cone-beam source to obtain these spectra (Pb: 2 and 3 mm, Sn: 1, 2, and 3 mm of total filtration). With further filtration, it was important to consider not only the alteration of incident x-ray spectra but also the decrease in overall photon fluence in the incident beam. Thus, investigation was limited to the consideration of relatively thin filters. These spectra were then used for the virtual cone-beam source to generate XRF/scatter spectra for assessing the effects of filter material and thickness on the production/detection of gold XRF photons.

2.C.2. Quasimonochromatic source spectra

One of the major technical concerns regarding benchtop XFCT is that the detection of XRF photons could be obscured considerably by Compton-scattered photons. To best allow discrimination of XRF photons from scattered photons, the Compton scatter peak and XRF peaks appearing in the XRF/scatter spectra should be separated well and the XRF peaks should be located on a plateau region of the scatter background. Although not readily obtainable with conventional filtration of polychromatic x-rays, quasimonochromatic x-ray spectra with sufficient intensity could, in principle, be obtained using crystals such as highly oriented pyrolytic graphite (HOPG) as demonstrated previously.¹⁶ In our previous study,¹⁸ this possibility was also investigated specifically for the purpose of benchtop XFCT, resulting in a positive

preliminary outlook about the approach that warrants further research and development efforts despite a few technical issues (e.g., requirement of very shallow beam incident angles to produce x-rays with energy above the gold K -edge).

In the current study, therefore, quasimonochromatic x-ray spectra were also simulated for the phase-space source in order to determine the minimum energy needed to approximately discriminate the gold XRF peaks from the Compton scatter peak. The energy ranged from just above the gold K -edge to just below the maximum photon energy of our x-ray source (i.e., 81, 85, 90, 95, and 100 keV). Since measured spectra were not readily available at the time of this study, all quasimonochromatic incident beam spectra were assumed to have undefined, but identical, photon fluence. Considering our own experience in quasimonochromatization of polychromatic x-rays,¹⁸ the energy spectrum of each source was assumed to have a Gaussian spread of 10 keV full width at half maximum (FWHM).

2.C.3. Analysis of results

The net signal from the gold K_α XRF peaks (~67 and ~69 keV) was first extracted for each XRF/scatter spectrum, after necessary corrections, using a background subtraction algorithm.⁶ Subsequently, the ratio of the net XRF signal to the dose to the center of the phantom was calculated for each result; this ratio, for both the results from the Pb- and Sn-filtered incident spectra and the quasimonochromatic incident spectra, was then normalized relative to a reference case (1-mm Pb filter results, which had the lowest signal-to-dose ratio) to obtain a unitless quantity, the fluorescence signal-to-dose ratio (FSDR). The FSDR, as defined and reported here, is a quantity that is independent of incident beam fluence. Computing the reciprocal of the FSDR provides a comparative measure of the dose required to obtain a certain amount of XRF signal with each filter.

In general, an incident beam spectrum with additional filtration would have lower overall photon fluence and would presumably require an increased scan time to obtain the same net XRF signal. However, spectral differences could partially offset this expected increase in scan time. Therefore, in order to take this factor into account, a quantity must be defined with respect to the net XRF signal attained, and not just by considering the overall fluence of the incident spectra. Therefore, a fluorescence-normalized scan time (FNST) was defined for the results from the Pb- and Sn-filtered incident spectra as the ratio of the net XRF signal from a reference case (0.9-mm Sn filter results, which had the shortest scan time) to that obtained from each simulation. In other words, the FNST value computed for each spectrum represents the time needed to obtain a set amount of net XRF signal, relative to the time needed using the 0.9-mm Sn filter. As described previously, the quasimonochromatic incident beam spectra had undefined, but identical, fluence and thus, the FNST for these spectra could not be defined with respect to the 0.9-mm Sn filter and instead were defined relative to a different reference case (quasimonochromatic 90-keV results, which had the shortest scan time).

FIG. 3. Comparison between measured and simulated XRF/scatter spectra used for validating the MC model (normalized to aid qualitative assessment; linear scale), obtained from the following incident x-ray spectra: (a) 1-mm Pb-filtered spectrum and (b) 0.9-mm Sn-filtered spectrum. The gold XRF peaks of interest (K_{α}) are located at ~ 67 and ~ 69 keV (vertical dotted lines).

3. RESULTS

3.A. Comparison of Monte Carlo calculated XRF/scatter spectra with measured data

The measured and simulated XRF/scatter spectra used for validation of the MC model are shown in Fig. 3. The Pearson product-moment correlation coefficient (r) between the simulated and measured results showed excellent agreement for both cases (1-mm Pb-filtered: $r = 0.997$; 0.9-mm Sn-filtered: $r = 0.996$).

3.B. Generation of filtered incident x-ray spectra

Figure 4 displays, in addition to the measured spectra (1-mm Pb-filtered and 0.9-mm Sn-filtered), the computationally generated spectra from additional filtration: three Sn-filtered spectra (1, 2, and 3 mm) and two Pb-filtered spectra (2 and 3 mm). The overall incident x-ray photon fluence for each case, relative to the 0.9 mm Sn filter, is also shown. Clearly, increasing filtration hardened the source spectra and also exponentially decreased the photon fluence available for irradiation.

3.C. XRF/scatter spectra due to filtered incident x-ray spectra

Figure 5 shows the corresponding XRF/scatter spectra for the Pb-filtered and Sn-filtered spectra. Qualitatively, the latter had generally higher overall fluence as well as more prominent gold XRF peaks than the former. Using Sn for filtration also favorably shifted the Compton scatter peak to higher energy, further away from the XRF peaks.

For the tested thicknesses of both filter materials, Fig. 6(a) shows the FSDR (relative to the 1-mm Pb filter; linear scale), while Fig. 6(b) shows the FNST (relative to the 0.9-mm Sn filter; log scale); the results are also tabulated in Table I. Quantitatively, the FSDR values increased with increasing filter thicknesses for both filter materials. The 0.9-mm Sn filter and 1-mm Pb filter, as used experimentally, had comparable

FSDR values. However, the FNST for the 1-mm Pb filter was almost three times as much as that for the 0.9-mm Sn filter, a fact that matched our experimental observations,⁷ providing another strong support for the validity of the current MC model. For thicknesses above 2 mm, both the Sn and Pb filters resulted in similar FSDR values. However, filtration using Pb required considerably longer FNST compared to that using Sn. In general, for both filter materials, the FNST increased at a much higher rate for a given increase in FSDR. Using Sn for filtration, instead of Pb, is consistently advantageous in terms of both FSDR as well as FNST.

3.D. XRF/scatter spectra due to quasimonochromatic incident x-ray spectra

From the MC simulations using quasimonochromatic spectra, the XRF/scatter spectra, displayed in Fig. 7, qualitatively show that increasing the source energy shifted the scatter peak to higher energy, as expected, which allowed the XRF peaks to be more easily discerned (i.e., have a higher signal-to-background ratio). For the modeled configuration, quasimonochromatic energy of at least 90 keV was required to clearly distinguish the gold XRF x-rays from the Compton scatter background. In theory, higher beam energy would be preferable since the scatter peak would not overshadow the gold XRF peaks. However, the unique geometry of the current XFCT configuration would determine the actual shape of the scatter spectra and its effect on the signal-to-background ratio of the XRF peaks.

Figure 8(a) shows the FSDR (relative to the 1-mm Pb filter, linear scale), while Fig. 8(b) shows the FNST (relative to the 90 keV results, linear scale) for these quasimonochromatic spectra; the results are also tabulated in Table II. The FSDR increased linearly with increasing source energy in the range between 81 and 100 keV, with an expected improvement of up to a factor of almost 20 (relative to 1-mm Pb filter) with a 100 keV incident beam. Although FNST could not be compared with the filtered incident spectra, for reasons explained previously, a comparison can be made within the

FIG. 4. Computationally generated spectra (solid lines) after additional filtration of experimentally measured 1-mm Pb-filtered and 0.9-mm Sn-filtered incident spectra (cross markers and dotted lines). The overall fluence available for irradiation (%), relative to the 0.9-mm Sn filter (set to 100%), is displayed within each subplot. Fluence is defined in arbitrary units, but can be compared directly between subplots and with Fig. 5.

quasimonochromatic spectra results. While the higher energies resulted in improved FSDR, this came at the expense of an increase in FNST. Note that the FNST was a minimum for the 90-keV quasimonochromatic incident spectrum. For example, comparing the results from the 90- and 100-keV beams, the FSDR increased by 13% while the FNST increased by 35%.

4. DISCUSSION

The significance and usefulness of the current MC model are especially highlighted when considering the fact that each component of the experimental benchtop XFCT system has been modeled in detail. If created based on valid assumptions/approximations, a simplified MC model could still provide meaningful results in a computationally efficient manner. For example, our own simplified MC models,^{8,19} which were developed prior to experimental investigations, enabled computational investigations of many critical issues including the effect of detection geometry on acquired XRF/scatter spectra, feasibility of cone-beam XFCT, and development of an effective reconstruction algorithm for XFCT images. Nevertheless, there had been an unmet need to develop a

more comprehensive and robust MC model such as the current one, because simplified MC models might not always yield results accurate enough to guide further optimization efforts after the initial experimental investigations, due to their inability to properly predict subtle influences of various hardware components within the experimental setup on the production/detection of XRF and scattered photons. Thus, a successful experimental validation of the MC model as shown in this study could be attributed, at least in part, to the effort put into creating a model that is as detailed and realistic as possible. Once rigorously validated, a realistic MC model should also have predicting power. For example, besides the XRF/scatter spectra used for initial experimental validation, the FSDR and FNST results from the current MC simulations for additional thicknesses of Sn also matched experimental data available from the study⁷ in which we demonstrated remarkable improvements (e.g., reduction of scan time by a factor of 3) in the performance of our benchtop XFCT system by implementing a 0.9-mm Sn filter instead of a 1-mm Pb filter.

The results from the exemplary application of the current MC model provide valuable insight into further modification/optimization strategies of our experimental benchtop

FIG. 5. Corresponding XRF/scatter spectra (at 90°), obtained from MC simulations, for Pb-filtered and Sn-filtered incident spectra of various thicknesses. The gold XRF peaks of interest (K_{α}) are located at ~67 and ~69 keV (vertical dotted lines). Fluence can be compared directly between subplots and with Fig. 4.

XFCT setup. Most notably, the current study quantified the degree of interplay between FSDR and FNST, dependent on the thickness of Sn and Pb filters. As a result, an optimum filter thickness can be determined, in consideration of this interplay

as well as other constraints such as available x-ray tube power, acceptable scan time, and desired GNP detection limit. For example, according to Table I, the FSDR, closely related to the detection limit, can be further improved by almost

FIG. 6. Metrics for analysis of XRF/scatter spectra from Pb-filtered (closed circle) and Sn-filtered (open circle) incident spectra as a function of filter thickness. (a) Fluorescence signal-to-dose ratio (FSDR, relative to 1-mm Pb filter results; linear scale). (b) Fluorescence-normalized scan time (FNST, relative to 0.9-mm Sn filter results; log scale).

TABLE I. Tabulated values for fluorescence signal-to-dose ratio (FSDR, relative to 1-mm Pb filter results) and fluorescence-normalized scan time (FNST, relative to 0.9-mm Sn filter results) computed from XRF/scatter spectra for all Pb-filtered and Sn-filtered incident spectra.

Incident spectrum (mm)	Fluorescence signal-to-dose ratio ^a	Fluorescence-normalized scan time ^b
105 kVp, lead (Pb) filter		
1.0	1.00	2.94
2.0	1.74	22.1
3.0	2.06	211
105 kVp, tin (Sn) filter		
0.9	1.11	1.00
1.0	1.20	1.10
2.0	1.76	4.51
3.0	2.13	20.4

^aRelative to 1-mm Pb filter results.
^bRelative to 0.9-mm Sn-filter results.

100% (factor of 2) by adopting a 3-mm Sn filter instead of a 0.9-mm Sn filter. In the reconstructed XFCT images obtained in the aforementioned experimental study with a 0.9-mm Sn filter,⁷ delivering 3.4 mGy of x-ray dose per projection was sufficient to visualize a GNP-loaded (at 0.5% by weight) imaging insert within a small-animal-sized PMMA phantom. Thus, an imaging insert containing GNPs at 0.26% by weight could, in theory, be imaged if the same dose was delivered with the beam filtered by 3 mm of Sn. However, in order to realize this predicted improvement, the scan time needs to be increased by about a factor of 20. Alternatively, the x-ray

source power, inversely proportional to the scan time, can be increased by a factor of 20 to achieve the same improvement in FSDR, all other parameters being constant. Considering our previous experimental work conducted with a low power (50 W maximum) microfocus source, such an increase in FSDR could have been realized if an x-ray source with about 1 kW (i.e., a factor of 20 increase in x-ray source power) or more power, commonly available from various vendors, had been adopted instead. Similarly, using such a high power x-ray source, the scan time could, in theory, have been reduced by a factor of 20 or more during our original experiment conducted

FIG. 7. XRF/scatter spectra from quasimonochromatic (10 keV FWHM) incident spectra. The gold XRF peaks of interest (K_{α}) are located at ~67 and ~69 keV (vertical dotted lines). Qualitatively, as incident energy was increased and the 90° scatter became more energetic, the gold KRF peaks can be more easily discerned from background. Fluence is relative to this figure only and under the condition that all quasimonochromatic incident spectra were assumed to have identical overall fluence.

FIG. 8. Metrics for analysis of XRF/scatter spectra from quasimonochromatic incident spectra (81, 85, 90, 95, and 100 keV with 10-keV FWHM). (a) Fluorescence signal-to-dose ratio (FSDR, relative to 1-mm Pb filter results; linear scale). (b) Fluorescence-normalized scan time (FNST, relative to 90 keV results; linear scale). Note that the FSDR can be compared with the filtered incident spectra results in Fig. 6, but the FNST reported here is for comparison within this figure only.

with a 0.9-mm Sn filter while maintaining the same FSDR. Noting the reliability and predictive power of our MC model as demonstrated in this study, the aforementioned possibilities are deemed realistic and, in fact, have prompted an upgrade of our benchtop XFCT setup that is currently underway.

In addition to the exemplary application presented in this work, there are many other applications of the current MC model for further development of a benchtop XFCT system. For example, the model can be used to thoroughly study the effects of higher x-ray tube potentials and different filtration options. It can also be used to optimize other parameters such as beam collimation, detector collimation, and detection/imaging geometry. Especially, the current MC model can be an indispensable tool for investigating the approaches that cannot immediately be tested experimentally, due to technical and/or financial difficulties (e.g., quasimonochromatization using HOPG crystals). Overall, it can serve as a reliable surrogate of time-consuming and potentially expensive experimentation, while producing accurate and realistic results that can be translated to tangible improvements in our experimental benchtop XFCT system.

5. CONCLUSIONS

In this work, an MC model of experimental benchtop XFCT system was created using the MCNP5 code. MC simulations were performed to obtain XRF/scatter spectra generated from the irradiation of a GNP-loaded phantom using 105 kVp cone-beam x-rays filtered by 1 mm Pb and 0.9 mm Sn. MC data agreed ($r \geq 0.996$) with experimentally measured XRF/scatter spectra under the same irradiation conditions, and the model was used for further investigation of XRF/scatter spectra from various filter thicknesses and quasimonochromatic incident spectra. As demonstrated by exemplary calculations using the current MC model, dramatic improvements of almost 100% increase in FSDR, compared to the latest experimental work, can be attained by judicious choice of filter material and thickness to shape the incident x-ray spectrum, while considering the interplay between FSDR and FNST. The current MC results also suggest that, using quasimonochromatic x-ray beams, far more drastic improvements up to a factor of 20 could be achievable, although the feasibility of creating such beams on a benchtop setting

TABLE II. Tabulated values for fluorescence signal-to-dose ratio (FSDR, relative to 1-mm Pb filter results) and fluorescence-normalized scan time (FNST, relative to 90 keV results) computed from XRF/scatter spectra for quasimonochromatic incident spectra. Note that the FSDR can be compared with the filtered incident spectra results in Table I, but the FNST reported here is for comparison within this table only.

Incident spectrum (keV)	Fluorescence signal-to-dose ratio ^a	Fluorescence-normalized scan time ^b
Quasimonochromatic		
81	16.0	1.49
85	16.8	1.19
90	17.8	1.00
95	18.9	1.15
100	20.1	1.35

^aRelative to 1-mm Pb filter results.

^bRelative to 90 keV results.

needs further investigation. Overall, the current MC model, which is realistic and well validated, will greatly facilitate the further development of a benchtop XFCT system for routine preclinical molecular imaging applications.

ACKNOWLEDGMENTS

This investigation was supported in part by NIH/NCI Grant No. R01CA155446. The authors acknowledge Dr. Andrew Karellas at University of Massachusetts Medical School, Dr. Chris Wang at Georgia Tech, and Dr. Eric Elder at Emory University for helpful comments on the current investigation.

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¹T. Takeda, K. Ito, K. Kishi, T. Maeda, T. Yuasa, J. Wu, M. Kazama, K. Hyodo, T. Akatsuka, and Y. Itai, "Preliminary experiment of the fluorescent x-ray computed tomography with synchrotron radiation," *Med. Imag. Tech.* **12**, 537–538 (1994).

²P. Boisseau, "Determination of three dimensional trace element distributions by the use of monochromatic x-ray microbeams," Ph.D. thesis, Massachusetts Institute of Technology, 1986.

³R. Cesario and S. Mascarenhas, "A new tomographic device based on the detection of fluorescent x-rays," *Nucl. Instrum. Methods Phys. Res., Sect. A* **277**, 669–672 (1989).

⁴P. J. La Rivière, "Approximate analytic reconstruction in x-ray fluorescence computed tomography," *Phys. Med. Biol.* **49**, 2391–2405 (2004).

⁵G. F. Rust and J. Weigelt, "X-ray fluorescent computer tomography with synchrotron radiation," *IEEE Trans. Nucl. Sci.* **45**, 75–88 (2005).

⁶S. K. Cheong, B. L. Jones, A. K. Siddiqi, F. Liu, N. Manohar, and S. H. Cho, "X-ray fluorescence computed tomography (XFCT) imaging of gold nanoparticle-loaded objects using 110 kVp x-rays," *Phys. Med. Biol.* **55**, 647–662 (2010).

⁷B. L. Jones, N. Manohar, F. Reynoso, A. Karellas, and S. H. Cho, "Experimental demonstration of benchtop x-ray fluorescence computed tomography (XFCT) of gold nanoparticle-loaded objects using lead- and tin-filtered polychromatic cone-beams," *Phys. Med. Biol.* **57**, N457–N467 (2012).

⁸B. L. Jones and S. H. Cho, "The feasibility of polychromatic cone-beam x-ray fluorescence computed tomography (XFCT) imaging of gold nanoparticle-loaded objects: A Monte Carlo study," *Phys. Med. Biol.* **56**, 3719–3730 (2011).

⁹Y. Kuang, G. Pratz, M. Bazalova, B. Meng, J. Qian, and L. Xing, "First demonstration of multiplexed x-ray fluorescence computed tomography (XFCT) imaging," *IEEE Trans. Med. Imaging* **32**, 262–267 (2013).

¹⁰Y. Kuang, G. Pratz, M. Bazalova, J. Qian, B. Meng, and L. Xing, "Development of XFCT imaging strategy for monitoring the spatial distribution of platinum-based chemodrugs: Instrumentation and phantom validation," *Med. Phys.* **40**, 030701 (7pp.) (2013).

¹¹M. Bazalova, Y. Kuang, G. Pratz, and L. Xing, "Investigation of x-ray fluorescence computed tomography (XFCT) and K-edge imaging," *IEEE Trans. Med. Imaging* **31**, 1620–1627 (2012).

¹²L. Vincze, K. Janssen, and F. Adams, "A general Monte Carlo simulation of energy-dispersive x-ray fluorescence spectrometers—I: Unpolarized radiation, homogeneous samples," *Spectrochim. Acta, Part B* **48**, 553–573 (1993).

¹³T. Schoonjans, L. Vincze, V. A. Solé, M. Sanchez del Rio, P. Brondeel, G. Silversmit, K. Appel, and C. Ferrero, "A general Monte Carlo simulation of energy dispersive x-ray fluorescence spectrometers—Part 5: Polarized radiation, stratified samples, cascade effects, M-lines," *Spectrochim. Acta, Part B* **70**, 10–23 (2012).

¹⁴X-5 Monte Carlo Team, "MCNP—A General Purpose Monte Carlo N-Particle Transport Code, Version 5," LA-UR-03-1987, 2003.

¹⁵G. Jost, S. Golfier, R. Lawaczek, H. J. Weinmann, M. Gerlach, L. Cibik, M. Krumrey, D. Fratzscher, J. Rabe, and V. Arkadiev, "Imaging-therapy computed tomography with quasi-monochromatic x-rays," *Eur. J. Radiol.* **68**, S63–S68 (2008).

¹⁶G. Jost, T. Mensing, S. Golfier, R. Lawaczek, H. Pietsch, J. Hütter, L. Cibik, M. Gerlach, M. Krumrey, and D. Fratzscher, "Photoelectric-enhanced radiation therapy with quasi-monochromatic computed tomography," *Med. Phys.* **36**, 2107–2117 (2009).

¹⁷N. Manohar, "Effect of source x-ray energy spectra on the detection of fluorescence photons from gold nanoparticles," M.S. thesis, Georgia Institute of Technology, 2011.

¹⁸B. L. Jones, "Development of dosimetry and imaging techniques for pre-clinical studies of gold nanoparticle-aided radiation therapy," Ph.D. dissertation, Georgia Institute of Technology, 2011.

¹⁹F. Liu, "Monte Carlo modeling of an x-ray fluorescence detection system by the MCNP code," M.S. thesis, Georgia Institute of Technology, 2009.