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Abstract. Spectral computed tomography (CT) using photon counting detectors (PCDs) can provide accurate tissue composition measurements by utilizing the energy dependence of x-ray attenuation in different materials. PCDs are especially suited for K-edge imaging, revealing the spatial distribution of select imaging probes through quantitative material decomposition. We report on a prototype spectral micro-CT system with a CZT-based PCD (DxRay, Inc.) that has 16×16 pixels of 0.5×0.5 mm², a thickness of 3 mm, and four energy thresholds. Due to the PCD's limited size (8×8 mm²), our system uses a translate-rotate projection acquisition strategy to cover a field of view relevant for preclinical imaging (~ 4.5 cm). Projection corrections were implemented to minimize artifacts associated with dead pixels and projection stitching. A sophisticated iterative algorithm was used to reconstruct both phantom and *ex vivo* mouse data. To achieve preclinically relevant spatial resolution, we trained a convolutional neural network to perform pan-sharpening between low-resolution PCD data (247- μ m voxels) and high-resolution energy-integrating detector data (82- μ m voxels), recovering a high-resolution estimate of the spectral contrast suitable for material decomposition. Long-term, preclinical spectral CT systems such as ours could serve in the developing field of theranostics (therapy and diagnostics) for cancer research. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.6.1.011004]

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1 Introduction

Computed tomography (CT) is a fast and powerful anatomical imaging modality, but it is limited by low contrast detectability. Contrast discrimination can be increased using dual-energy (DE)-CT. Due to the energy dependence of x-ray absorption, two materials with different atomic numbers can be differentiated based on their unique attenuation coefficients at two different x-ray energies. DE imaging is the first implementation of spectral CT and has risen to the forefront of CT technology.¹ We have demonstrated preclinical, functional imaging applications of DE micro-CT involving the separation of iodine and calcium or iodine and gold, including classification of atherosclerotic plaque composition,² noninvasive measurement of lung³ and myocardial perfusion,⁴ and the classification of tumor aggressiveness and therapy response both in the lungs⁵ and in primary sarcoma tumors.^{6,7} Unfortunately, DE-CT methods are limited by the energy-integrating detectors (EID) used by current CT systems. For EIDs, the output signal is proportional to the detected photon flux, weighted by the photon energy and integrated across the entire energy spectrum. Thus, EID spectral resolving power is limited when used with polychromatic x-ray sources. Much is to be gained by extending spectral CT from energy-integrating DE-CT to multienergy (>2) CT using photon counting x-ray detectors (PCDs).^{8,9} Ideally, photon counting improves spectral separation by binning incoming photons into two or more energy bins, improving energy and material discrimination with a single CT scan. The other potential

advantages of PCD-CT include reduced electronic noise, higher contrast-to-noise ratios, and improved dose efficiencies. For now, the use of PCDs in clinical CT systems is limited by spectral distortions which occur at high photon count rates.^{8,10}

We focus here on preclinical spectral CT and show how practical issues related to PCD-based micro-CT imaging can be addressed in a prototype system. Currently, there is one commercially available PCD-based micro-CT system, the Medipix All Resolution System (MARS Bioimaging Ltd.; Christchurch, New Zealand).¹¹ The MARS is based on the Medipix3 detector chip developed at CERN (Geneva, Switzerland). In addition to its $55 \mu\text{m} \times 55 \mu\text{m}$ pixel pitch, a unique feature of the Medipix3 detector is its charge-summing circuitry which can be used to compensate for charge sharing between neighboring detector pixels.¹² Several other custom-built, PCD-based micro-CT scanners have been demonstrated.^{13–17} In the absence of hardware-based correction, trade-offs between PCD pixel size and energy resolution typically limit spatial resolution for micro-CT imaging.⁸ In a previous paper, we proposed and demonstrated an iterative reconstruction algorithm for hybrid, spectral CT reconstruction which robustly combines the spectral contrast of a PCD with the spatial resolution of an EID, recovering a high-resolution estimate of the spectral contrast suitable for material decomposition.¹⁸ The fusion of spatial and spectral information is a signal processing problem known as pan-sharpening that is commonly employed for the resolution enhancement of satellite imagery¹⁹ and has been previously applied to spectral CT.²⁰ Relative to our previous reconstruction-based approach, here we propose a computationally cheaper

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image-domain approach to pan-sharpening using a convolutional neural network (CNN).

Recently, deep learning (DL) methods such as CNNs have generated enthusiasm in various imaging applications, such as image denoising, deblurring, super resolution, segmentation, detection, and recognition.²¹ For example, Chen et al.²² utilized a CNN-based framework for low dose CT imaging. An algorithm using a CNN was also applied to the wavelet transform coefficients of low-dose CT images to suppress CT-specific noise.²³ In the field of remote sensing, CNNs have been successfully applied to overcome spectral artifacts caused by traditional pan-sharpening applications.^{24,25}

The purpose of this study builds on our previous work²⁶ and presents new ways to overcome the resolution limits of PCD-based micro-CT using CNN-based pan-sharpening with complementary EID data.

2 Materials and Methods

2.1 System Description

The PCD used by our system is CZT-based and consists of 16×16 pixels, each with a size of $0.5 \times 0.5 \text{ mm}^2$, a thickness of 3 mm, and four configurable energy thresholds. The detector is thus only $8 \text{ mm} \times 8 \text{ mm}$ in size. Unfortunately, some pixels close to the center of the detector are not functional, and the outside edge of pixels contains high biases [Fig. 1(a)]. Due to the limited size of this tile, to acquire projections without truncation, we have positioned this PCD tile on a horizontal linear translator controlled with a LabVIEW application [Fig. 1(b)]. We linearly shifted the detector in steps of half its size to 14 different positions at each angle. Next, the projection data were stitched together [Fig. 1(c)]. Thus, we have

implemented a translate-rotate micro-CT system (i.e., a second-generation CT system).

2.2 Spectral Response Measurements

To characterize and calibrate the spectral response of the prototype PCD tile, we used a Ba-133 nuclear source positioned directly in front of the active region of the detector. Ba-133 has spectral lines around 31 and 81 keV, close to the K-edges of iodine (33.2 keV) and gold (80.7 keV). This makes Ba-133 ideally suited for calibrating the PCD's spectral response (recorded signal to keV conversion) when attempting to separate these two materials. In our experiment, all four thresholds of the PCD were swept every 1 keV, from below 20 keV to above 110 keV, to record the spectrum of the deposited energy. All thresholds of the detector were exposed for 50 s/keV, improving the signal-to-noise ratio of the resultant energy spectrum by summing counts over all detector pixels and then by averaging counts over detector thresholds. The energy spectrum was obtained from the thresholded counts by differentiating the counts recorded above each energy threshold.

2.3 Physical Phantom Experiments

We performed calibration phantom experiments using a three-dimensional (3-D)-printed phantom made from polylactic acid (PLA; diameter: $\sim 3.4 \text{ cm}$; Fig. 2). The phantom contained two calibration vials with iodine concentrations of 6 and 9 mg/mL in water and one calibration vial with only water. We acquired 72 projections of the phantom over a single 360-deg rotation; all translations of the detector tile were acquired prior to rotation to the next projection angle [Fig. 1(c)]. Prior to scanning, the four detector thresholds were set to 25, 33,

Fig. 1 (a) A projection image acquired with the PCD prototype shows dead pixels in the center as well as biased responses at the edges. (b) To increase the field of view and avoid truncation, we have mounted the PCD tile on a linear translator stage. (c) The tile is horizontally shifted by half its size to 14 different positions at each angle, and the resulting projections are stitched and normalized accordingly.

Fig. 2 Ring artifact correction. (a–d) We used a Fourier-based filtration method to remove vertical strips in the log-transformed sinograms, (e) correcting ring artifacts in the reconstructed CT images (yellow arrows). The sinograms are shown for each energy threshold (25, 33, 45, and 80 keV) poststitching and before and after ring artifact correction. Difference images (bottom row) demonstrate the effectiveness of the ring correction in both the sinograms and CT reconstructions. CT reconstructions are windowed as shown in Hounsfield units.

45, and 80 keV. To prevent pulse pileup at the PCD, the x-ray source (Thermo Scientific, PXS10 MicroFocus; tungsten anode) was filtered with 5.6 cm of PMMA, 0.1 cm of Al, and 0.15 mm of Cu. Each projection angle and translation position was exposed for 250 ms at 130 kVp and 0.98 mA. The source–object and source–detector distances were 375 and 489 mm, respectively, resulting in a geometric magnification of 1.3 at isocenter.

As shown in Fig. 1(c), prior to log-transformation, the air-only images and projections were synthesized from the data acquired at each translated position. To reduce reconstruction artifacts, dead detector pixels were filled in based on the overlapping and neighboring information from the translated data. Detector pixels with significantly biased responses [edges in Fig. 1(a)] were either masked from overlapping data (internal edges) or interpolated with a Gaussian kernel (exterior edges). Following log-transformation, additional ring-artifact suppression was performed in the frequency domain via notch filtering to remove vertical stripes from the resultant sinograms. As seen in Fig. 2, this ring artifact correction procedure did not significantly bias the sinogram data.

2.4 Small Animal Experiments

Following our phantom experiments, we proceeded with an animal study. Using our system, we performed PCD-based micro-CT imaging in a study of radiation injury of the gastrointestinal (GI) tract of a mouse model. The mouse (genotype *LSL-Kras^{G12D}; p53^{FL/FL}*) received radiation therapy to the lower abdomen (20 Gy). A day later, the mouse was injected with gold nanoparticles (AuNP). As a result of radiation damage to the endothelial cells in the GI wall, the AuNPs accumulated via the enhanced permeability and retention effect.²⁷ Near the mouse and within the field of view, we placed calibration vials containing aqueous gold (2 mg/mL) and iodine (8 mg/mL) nanoparticle solutions and water-only. The mouse was scanned *ex vivo*.

The acquisition parameters for the animal study were similar to those used for the phantom study; however, the number of projections was increased from 72 to 90 projections acquired

over a single 360-deg rotation. The total scan took 70 min to complete. The four thresholds of the PCD were placed as with the phantom study ($T_1 = 25$, $T_2 = 33$, $T_3 = 45$, and $T_4 = 80$ keV) and were chosen to separate iodine and gold based on their K-edges (i.e., 33.3 keV for iodine and 80.7 keV for gold). Reconstruction was performed via filtered backprojection and with iterative reconstruction (see Sec. 2.5). The lower-noise, iteratively reconstructed images were used to perform material sensitivity measurements and image-domain material decomposition (see Sec. 2.6).

2.5 Image Reconstruction

Iterative reconstruction of both the phantom and mouse PCD data was performed using the spectral CT reconstruction framework we have previously described.¹⁸ Specifically, we applied the split Bregman method with the add-residual-back strategy²⁸ to solve the following optimization problem:

$$X = \underset{X}{\operatorname{argmin}} \frac{1}{2} \sum_e \|RX_e - Y_e\|_2^2 + \lambda \|X\|_{\text{BTV}}, \quad (1)$$

$$\|X\|_{\text{BTV}} := \sum_e \frac{\sum_{i,j} D(i)K(i,j)|W(i)X_e(i,j)|}{\sum_{i,j} D(i)K(i,j)}, \quad (2)$$

$$K(i,j) = \prod_e \exp \left\{ -\frac{[W(i)X_e(i,j)]^2}{2m_e^2\sigma_e^2} \right\}. \quad (3)$$

This algebraic reconstruction problem solves for the vectorized, reconstructed data (the columns of X) for each sampled threshold simultaneously (indexed by e). The reconstruction for each threshold minimizes the reprojection error (R , system projection matrix) relative to the log-transformed projection data acquired at each threshold (the columns of Y). To reduce noise in the reconstructed results, this data fidelity term is minimized subject to the bilateral total variation (BTV) measured within and between energy thresholds. Specifically, as shown above,

BTV is calculated as the weighted sum of image gradients (intensity gradient operator W), where the weights are computed over a local neighborhood (D domain, index i) and summed over the entire image (index j) and energies. To handle varying noise levels and contrast with energy, range weights (kernel K) are determined by intensity gradient magnitudes relative to the noise level (σ_e) and smoothing parameter (m_e) set for each energy. During iterative reconstruction, BTV is reduced by the application of bilateral filtration (BF). To maximize redundancy between the reconstructed thresholds and, therefore, minimize noise in the material decomposition results, we employed a specific extension of joint BF known as rank-sparse kernel regression (RSKR), which is similar to the equations above, except that a weighted singular value decomposition is performed across the energy dimension prior to filtration to improve performance and to simplify parameter selection. RSKR and our regularization strength scaling strategy compensate for different noise levels between thresholds, as detailed in previous work.¹⁸ All PCD-based phantom and mouse data were reconstructed with an isotropic voxel size of 247 μm .

2.6 Material Decomposition

To decompose spectral CT data containing a mixture of materials into quantitative, 3-D maps showing the concentrations of each element, we use a postreconstruction decomposition method. Extending the approach of Alvarez and Macovski,^{29,30} we perform a basis material decomposition³¹

$$\mu(e) = a_{\text{PE}}\mu_{\text{PE}}(e) + a_{\text{CS}}\mu_{\text{CS}}(e) + a_{\text{I}}\mu_{\text{I}}(e) + a_{\text{Au}}\mu_{\text{Au}}(e). \quad (4)$$

Given reconstructions for each energy bin, the first two terms describe the energy-dependent attenuation, $\mu(e)$, owing to the photoelectric effect (PE) and Compton scattering (CS) in water. The next two terms are basis functions for K-edge

materials, in this case iodine (I) or gold (Au). Given a set of linear equations for the attenuation measured in each voxel across energy bins, image-domain material decomposition can be performed by inversion of the material-sensitivity matrix. For the decompositions presented in this work, we combined the PE and CS components into water images.¹⁵ Decomposing water directly improved the fidelity of the material decompositions but had the side-effect of representing calcium (bones) within the decomposed iodine or gold maps.

2.7 Hybrid Spectral CT with CNN-Based Pan-Sharpening

The spatial resolution of the PCD (500- μm pixel size) is low compared to that of the EID (75- μm pixel size). However, we can harness the spatial resolution of EID data and the spectral resolution of the PCD data using pan-sharpening. The objective of this hybrid spectral CT imaging approach is to combine the higher resolution of the EID data with the spectral contrast of the PCD data, enabling high-resolution material decomposition.

Our EID-based micro-CT system is comprised of a flat-panel CsI-based detector (Dexela 1512CL) with a pitch of 75 μm and a pulsed x-ray source (G-297, Varian Medical Systems) with a 0.3-mm focal spot size. Acquisitions with this system were reconstructed with a voxel size of 82.3 μm . For these studies, the EID- and PCD-based micro-CT scans were performed sequentially; however, a hybrid system with simultaneous scanning capabilities is currently under development.

2.7.1 CNN architecture

Pan-sharpening has been performed through a variety of methods.³² We have elected to use DL methods in our work as it has shown gains in computational efficiency and increased accuracy.²⁴ The structure of the CNN used to pan-sharpen the PCD reconstructions is shown in Fig. 3. This network was

Fig. 3 CNN used for pan-sharpening as adapted from Ref. 25. Input pairs of registered PCD and EID reconstructions are passed into the network. The network consists of a deep and a shallow network. The output of the network is a single, pan-sharpened image. In each layer, the number of feature maps (top) and the convolution kernel size (bottom) are given.

adapted from Ref. 25 and takes a single high-resolution and low-resolution spectral image, combined into a two-channel image, as inputs. The images are passed into the two branches of the CNN, a deep network and a shallow network. The outputs from these networks are summed together to create a pan-sharpened image.

The deep network contains two residual multiscale convolutional blocks, modeled after the inception blocks proposed in Ref. 33. These blocks are comprised of a single convolutional layer followed by three parallel convolutional layers. The parallel layers employ filters of different sizes (3×3 , 5×5 , and 7×7) which are suited to detect features at multiple scales, including fine textures and coarser image features. While a bank of the largest filters in the network (7×7) is capable of detecting the full range of features found by the multiscale block, the computational cost of large convolution filters quickly blows up. Each convolutional layer is paired with a rectilinear activation function (ReLU), which introduces nonlinearities into the network's processing and allows it to learn complex mappings. The outputs of the parallel layers are concatenated into a single layer. The input features to the multiscale blocks are added to the output in what has been called a skip connection, making these blocks residual. In a residual configuration, the parallel layers learn to extract relevant sparse features from the input feature maps rather than having to form a complete output image. This residual strategy addresses the problem of vanishing gradients in deep networks and greatly decreases the time required to train a deep network.³⁴

The shallow network has been adapted from single-image super resolution work.³⁵ This network contains three convolutional layers with different filter sizes, each followed by a ReLU. The first convolutional layer (9×9 filter size) encodes the input images. The second layer (1×1) applies a nonlinear mapping by filtering each element of the features maps of the first layer. The final layer (5×5) decodes the features maps into an output image. It has been found that a shallow network can produce better super-resolution results than a deep network and with less training time work.³⁵ One of the purposes of the shallow network is to make the deep network residual with more degrees of freedom than a simple skip connection would provide.

2.7.2 Training data

Training data were acquired both experimentally and through simulations. Experimental data were acquired using the EID micro-CT system. A phantom comprised of vials with various concentrations of iodine, gadolinium, and gold contrast agents was scanned with six kVp settings (40, 45, 60, 65, 80, and 120 kVp) to obtain registered reconstructions with six spectral contrasts. Reconstruction was performed from 720 projections using the FDK algorithm.³⁶ The difference in resolution between the EID and PCD reconstructions (82.3 versus 247 μm) was a factor of 3. To simulate low-resolution spectral images, EID sets were also reconstructed with 247- μm voxel sizes.

Simulated PCD training data using the MOBY digital phantom³⁷ were generated for a tungsten x-ray spectra as modeled using Spektr.³⁸ Detector energy thresholds were simulated at 25, 34, 80, and 81 keV. The MOBY phantom was modified to include calibration vials and iodine and gold contrast agents in the blood. A perfect spectral response for the PCD was used. These sets were reconstructed with the same voxel sizes as the experimental EID (82.3) and PCD (247 μm) data. Noise

was added to the reconstructions by simulating Poisson noise in the projection domain for 40 k photons/pixel.

The network was trained on a shuffled mix of EID micro-CT and simulated data sets. Pairs of high-resolution and spectral slices were randomly selected, concatenated, and passed into the network. Training labels were the full-resolution images with spectral contrast corresponding to the low-resolution, spectral input images.

2.7.3 Training the network

The network was implemented in Tensorflow³⁹ and trained on 1680 sets of the experimental and 520 simulated image pairs. Network weights were updated using stochastic gradient descent, which was employed via the Adam optimization algorithm. The learning rate was set to 3×10^{-5} . Training was performed with a batch size of 128 over 2500 epochs and took about 36 h to complete. Computations were performed on a stand-alone workstation using four NVIDIA TITAN Xp graphics cards.

To validate the CNN pan-sharpening method, a phantom containing vials of gold (8 mg/mL) and iodine (12 mg/mL) nanoparticles and water was scanned on both the PCD- and EID-based micro-CT systems. The phantom was reconstructed with 247- and 82.3- μm voxel sizes, respectively. The PCD acquisition was upsampled by a factor of 3 via cubic interpolation to have the same size as the EID reconstructions. The PCD volume was affine registered to the EID data using ANTs.⁴⁰ Registered pairs of EID and PCD images, one energy and two-dimensional slice at a time, were run through the network to generate a pan-sharpened phantom reconstruction.

2.8 Alternative Pan-Sharpening Method

To provide a comparison for the resolution enhancement achieved with CNN-based pan-sharpening, we also performed a computationally inexpensive form of pan-sharpening that we previously proposed for spectral CT.¹⁵ Specifically, we performed material-based component substitution, substituting the EID data into the low-resolution PCD data via image-domain material decomposition. Numerically, material-based component substitution was performed as follows:

$$U_{\text{PCD}} = DX_{\text{PCD}}, \quad (5)$$

$$C_{\text{PCD}} = U_{\text{PCD}}M^+, \quad (6)$$

$$C_{\text{EID}} = C_{\text{PCD}}(\mathbf{m}_{\text{EID}} \mathbf{1}^T), \quad (7)$$

$$X_{\text{PCD,sharp}} = U_{\text{PCD}} + X_{\text{EID}} - C_{\text{EID}}. \quad (8)$$

The reconstructions of the PCD thresholds are arranged as columns of the matrices X_{PCD} (low-resolution PCD data) and $X_{\text{PCD,sharp}}$ (high-resolution estimate). The reconstruction of the EID data is replicated across the columns of the matrix X_{EID} , one column for each PCD threshold. A low-resolution estimate of the EID data is obtained by upsampling and rescaling X_{PCD} (D matrix), to create U_{PCD} [Eq. (5)]. Next, we perform an image-domain material decomposition to get C_{PCD} by multiplying the upsampled estimate, U_{PCD} , by the pseudoinverse material sensitivity matrix, M^+ [Eq. (6)]. C_{PCD} is multiplied with the EID material-sensitivity vector expanded to a matrix with redundant columns, $\mathbf{m}_{\text{EID}}$ [Eq. (7)] to obtain a low-resolution

EID estimate, C_{EID} . Component substitution is finally performed by subtracting C_{EID} from U_{PCD} , and then by adding the high-resolution EID data (X_{EID}) [Eq. (8)].

2.9 Spatial Resolution Measurements

Modulation transfer function (MTF) measurements were performed to compare spatial resolution between the EID data and the PCD data (25-keV threshold) before and after pansharpening. The MTFs were measured experimentally using the slanted edge of the PLA cradle and the “Slanted Edge MTF” plugin available for ImageJ.⁴¹ Cubic-spline interpolation was used to obtain smooth curves from discretely sampled spatial frequencies.

3 Results

3.1 Spectral Calibration

Figure 4 shows the results of the spectral response measurements acquired using a Ba-133 nuclear source. This plot

Fig. 4 The response of the 8 × 8 mm PCD prototype tile (0.5 × 0.5 × 3 mm) to a Ba-133 source. Ba-133 is characterized by spectral lines at 31 and 81 keV. A peak near 81 keV was distinguishable in the plot (dashed line, blue arrow).

demonstrates that the PCD poorly resolves the 31-keV spectral line, suggesting that K-edge imaging of iodine (K-edge at 33 keV) would be difficult to resolve with this detector. The poor performance of the PCD at low keV may be due to charge sharing. A small and relatively blurred peak is distinguishable around 81 keV, suggesting that Au (K-edge at 80.7 keV) will likely be suitable for K-edge imaging.

3.2 Phantom and Small Animal Results

Figure 5 shows the reconstructions of the physical calibration phantom. A comparison of Figs. 5(a) and 5(b) shows the merits of reconstruction of all four energy thresholds simultaneously with a joint, iterative reconstruction scheme. For threshold 4 ($T4$, 80 keV), the noise in the phantom by iterative reconstruction is less than one-third that by analytical reconstruction. Despite the general difficulty in separating iodine based on its K-edge contrast with the tile PCD, Fig. 5(c) shows that iodine at concentrations of 6 and 9 mg/mL is differentiated from water.

The results of our animal experiment are shown in Fig. 6. Clearly, iterative reconstruction is necessary to reduce noise in the threshold $T4$ CT image, where the number of photons counted above the K-edge of gold is very limited. The iterative reconstruction results were used for spectral sensitivity measurement [Fig. 6(b)] and image-domain material decomposition [Fig. 6(c)] into overlaid iodine (red), gold (green), and water (gray) maps. Images in both axial and coronal orientations are shown. The decomposition confirms the separation of gold accumulated in the GI tract (green arrows). Due to the low fidelity of iodine K-edge imaging and the choice of basis materials (water versus PE and CS), there was no distinct separation between iodine and bone (red). The low concentration of Au (2 mg/mL) in the included vial was not detected, presumably due to spectral distortions from the detector. The output count rate for the detector during these scans was measured to be 3.52×10^5 counts/mm². This rate is well below the rate given by the manufacturer to avoid pulse pileup (1×10^6 counts/mm²).

Fig. 5 Reconstruction results for the PLA physical calibration phantom. (a) FDK reconstruction results using a ramp filter ($T1 = 25$, $T2 = 33$, $T3 = 45$, $T4 = 80$ keV). Noise standard deviation is measured within a region of interest (yellow box, text). (b) Corresponding iterative reconstruction results showing a more homogeneous noise level between energies achieved through RSKR and data-adaptive regularization strength scaling. (c) Overlaid iodine (red) and water (gray) material maps, including calibration vial labels.

Fig. 6 Reconstruction results for the mouse data. Tomographic reconstruction results are shown using (a) the FDK algorithm and (b) our iterative algorithm. Iterative reconstruction significantly reduces the noise standard deviation, particularly for the fourth threshold ($T4 = 80$ keV) where the number of recorded photons counts is very low (yellow box, text). After reconstruction, (c) the four energy images were used for spectral decomposition into overlaid iodine (red), gold (green), and water (gray) maps. Both axial and coronal decomposed slices are shown.

Fig. 7 Comparison of pan-sharpening methods in the MOBY phantom. (a) Tomographic reconstructions from simulated PCD and EID data display the effectiveness of both component substitution and CNN pan-sharpening methods to restore high frequencies. (b) Material decompositions performed using images from the low-resolution spectral data only, component substitution pan-sharpening, and our CNN-based method. These material maps are compared with the reference image. Orange represents a combination of iodine and gold material maps. A blow-up of a simulated calcification in the aorta is shown for comparison of material recovery; calcium is represented in the gold material map. The RMSE has been measured inside the blue region of interest for each material map. These values are shown at the bottom of each decomposition.

3.3 Pan-Sharpening Results

As shown by Figs. 5 and 6, the spatial resolution of our PCD-based spectral CT is limited. Therefore, we have used pan-sharpening based on a CNN to increase the resolution. We have assessed the performance of pan-sharpening using a MOBY mouse phantom constructed with different contrast concentrations compared to what was used to train the CNN. The results are shown by Fig. 7 as tomographic reconstructions, material decompositions, and residual images compared to the absolute truth (reference image). Note that the alternative method for pan-sharpening based on component substitution recovers high-frequency information in the reconstruction, but produces a decomposition similar to the low-resolution PCD decomposition. Residual decomposition images [Fig 7(b)] show that the CNN method produces decompositions with lower error than either the PCD alone or component substitution methods can provide. Moreover, the root mean square error (RMSE) values for each material in a region of interest around the aorta [Fig 7(b), blue box] are significantly lower for the CNN results.

Pan-sharpening results for a physical phantom scanned on both the PCD and EID-based micro-CT systems are shown in Figs. 8–10. Line profiles through both the vials and PLA cradle show that the contrast in the pan-sharpened PCD reconstruction is preserved while the resolution is comparable to the EID image. The resolution increase in the pan-sharpened image is confirmed by MTF plots (Fig. 9). Using 10% modulation as a point of comparison, CNN-based pan-sharpening increased the spatial resolution of the PCD data from 1.4 line pairs (lp)/mm to 3.6 lp/mm. This resolution enhancement compares favorably with the EID measurement of 3.4 lp/mm.

Fig. 9 MTF measurements obtained from the slanted edge of the PLA cradle used for imaging (see Fig. 8). Compared with the low-resolution data (red), CNN-based pan-sharpening significantly improves spatial resolution, closely matching the high-resolution EID data.

The decomposition of the pan-sharpened phantom reconstruction demonstrates the utility of this process (Fig. 10). Along with the high-frequency information that has been recovered, the spectral contrast has been preserved. The accuracy of material maps has been verified in the original PCD decomposition (I: 11.1 ± 2.7 mg/mL, Au: 6.7 ± 2.1 mg/mL) and in the pan-sharpened image (I: 11.6 ± 2.5 mg/mL, Au: 6.9 ± 2.2 mg/mL) against the physical values (I: 12 mg/mL, Au: 8 mg/mL).

Fig. 8 Results of pan-sharpening performed via a CNN. Features found in (a) the high-resolution EID image are used to enhance the resolution of (b) the lower-resolution PCD reconstruction to create (c) a high-resolution image with the contrast of the PCD. (d) Line profiles through both the vials and the PLA cradle demonstrate that the contrast of the PCD reconstruction is preserved in the pan-sharpened image (green arrow). High-frequency information is reintroduced in the vials and in the phantom structure (orange arrows).

Fig. 10 Decompositions of (a) the original PCD reconstruction and (b) the pan-sharpened result. The vials containing iodine and gold have been segmented from the high-resolution EID reconstruction and histograms of their material values are shown. These plots share a unitless y-axis. The actual concentrations are as labeled in the decompositions. The histograms demonstrate the effect on material values due to CNN-based pan-sharpening in the experimental data. Prior to pan-sharpening there are more low values in the spectrum which lower the mean value. Many of these values are filled in after pan-sharpening, yielding mean material concentrations nearer to those found in the physical vials.

Both before and after pan-sharpening, the differences between the decomposed mean gold concentrations and the true values could be explained by gold nanoparticle precipitation in the vial prior to imaging (see Fig. 10).

4 Discussion and Conclusion

Our results prove our capability to perform spectral micro-CT using our prototype PCD detector, despite some serious technical challenges associated with data acquisition and reconstruction. We managed to integrate this small-sized PCD into a translate-rotate geometry micro-CT system, and we successfully performed tomographic imaging in a physical calibration phantom and in an animal study. We acknowledge that the translate-rotate geometry configuration requires relatively long scan times (70 min) and potentially high radiation doses which are impractical for *in vivo* studies. It is understood that this limitation can be avoided with a larger-sized PCD.

Although a PCD-based spectral micro-CT system should be able to separate a wide variety of potential probes based on high-Z materials, we focused here on iodinated liposomes and gold nanoparticles due to their high potential for translation. Unfortunately, our PCD showed limited K-edge separation capabilities for iodine and somewhat limited sensitivity to low concentrations of gold (Figs. 4 and 6). In part, this may be due the thickness of the CZT detector (3 mm), which may cause more charge sharing effects than would a thinner detector. This in turn reduces the spectral resolution of the

detector. Given a larger and thinner PCD, it is however, quite feasible to perform K-edge micro-CT imaging. Spectral corrections exist which may serve to address the issue of charge sharing.⁴² Recently, we have designed a spectral correction method based on neural networks⁴³ using another CdTe PCD with $1.0 \times 1.4 \text{ mm}^2$ pixel size. However, due to the relatively large number of defective pixels, as well as the small size of the PCD used in this work, we have not applied spectral corrections here. The absence of spectral correction is a limitation of this work, and with a larger and higher quality PCD these corrections would have been applied. Recently, using a commercially available PCD (PILATUS3 CdTe 300K, Dectris AG of Baden-Dättwil, Switzerland), we have shown separation for iodine and barium, K-edge materials separated by only $\sim 5 \text{ keV}$.¹⁸

The results for the CNN pan-sharpening indicate that resolution is “transferred” from the EID-CT to the PCD-CT and, based on four energy bins, we can separate gold and iodine contrast agents. Our pan-sharpening based on CNNs illustrates that we can increase the resolution while maintaining the spectral contrast. Since we have performed CNN training using a large set of pairs of EID acquired images (at multiple kVps), the network learns to preserve the spectral contrast of the PCD data, independent of the chosen energy thresholds. More tests might be needed to validate this generalization. We believe that this approach has potential not only in increasing the resolution, but in correcting some of the imaging

problems such as ring artifacts in the PCD images based on the EID-CT data. A prerequisite of our method is a good registration between the EID and PCD data, which may be a problem with sequential scanning for *in vivo* studies. In further work, we will explore these aspects of hybrid spectral imaging using a larger-sized PCD and an integrated setup allowing simultaneous, and therefore well-registered, acquisitions of the EID and PCD data. Another direction for our future explorations could be in changing our CNN pan-sharpening to simultaneously process all low-resolution PCD images together with the high-resolution EID image, potentially improving spectral consistency and robustness.

Finally, in future work, we plan to explore statistical iterative reconstruction algorithms known to provide material selective images with improved tradeoffs between noise and resolution.^{44,45} Such algorithms incorporate a forward polyenergetic spectral CT model which links the (expected) spectral projection measurements and the material selective images.

In conclusion, we have presented methods for overcoming limitations associated with a PCD micro-CT system by showing how we can extend the FoV beyond the small size of a PCD using a translate-rotate geometry, performing corrections to improve image quality, and even increasing resolution via CNN pan-sharpening to achieve preclinically relevant spatial resolution. Long-term, preclinical spectral CT systems such as ours could serve for developing nanoparticles that show promise in the developing field of theranostics (therapy and diagnostics) of cancer. For example, gold nanoparticles can be used to augment radiation therapy⁴⁶ or to treat tumors via photo thermal therapy,⁴⁷ while also serving as K-edge contrast agents for PCD CT. Similarly, liposomes are used to deliver chemotherapy (e.g., Doxil, Janssen), but can also incorporate iodine to provide CT imaging contrast. By being fast, cost-effective, and wide-spread, spectral CT offers the ideal imaging method for theranostics probes based on high-Z materials.

Disclosures

The authors declare no conflicts of interest, financial or otherwise, in this work. This research was performed under an institutionally approved animal care and use committee protocol for animals.

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References

1. J. Fornaro et al., "Dual- and multi-energy CT: approach to functional imaging," *Insights Imaging* **2**(2), 149–159 (2011).
2. R. Bhavane et al., "Dual-energy computed tomography imaging of atherosclerotic plaques in a mouse model using a liposomal-iodine nanoparticle contrast agent," *Circ. Cardiovasc. Imaging* **6**(2), 285–294 (2013).
3. C. T. Badea et al., "Dual-energy micro-CT of the rodent lung," *Am. J. Physiol. Lung Cell. Mol. Physiol.* **302**(10), L1088–L1097 (2012).
4. J. R. Ashton et al., "Anatomical and functional imaging of myocardial infarction in mice using micro-CT and eXIA 160 contrast agent," *Contrast Media Mol. Imaging* **9**(2), 161–168 (2014).
5. J. R. Ashton et al., "Dual-energy micro-CT functional imaging of primary lung cancer in mice using gold and iodine nanoparticle contrast agents: a validation study," *PLoS One* **9**(2), e88129 (2014).
6. D. P. Clark et al., "In vivo characterization of tumor vasculature using iodine and gold nanoparticles and dual energy micro-CT," *Phys. Med. Biol.* **58**(6), 1683–1704 (2013).
7. E. J. Moding et al., "Dual-energy micro-computed tomography imaging of radiation-induced vascular changes in primary mouse sarcomas," *Int. J. Radiat. Oncol. Biol. Phys.* **85**(5), 1353–1359 (2013).
8. K. Taguchi and J. S. Iwanczyk, "Vision 20/20: single photon counting x-ray detectors in medical imaging," *Med. Phys.* **40**(10), 100901 (2013).
9. P. M. Shikhaliev, "Energy-resolved computed tomography: first experimental results," *Phys. Med. Biol.* **53**(20), 5595–5613 (2008).
10. K. Taguchi et al., "Interior region-of-interest reconstruction using a small, nearly piecewise constant subregion," *Med. Phys.* **38**(3), 1307–1312 (2011).
11. N. Anderson et al., "Spectroscopic (multi-energy) CT distinguishes iodine and barium contrast material in MICE," *Eur. Radiol.* **20**(9), 2126–2134 (2010).
12. R. Ballabriga et al., "The Medipix3 prototype, a pixel readout chip working in single photon counting mode with improved spectrometric performance," in *IEEE Nuclear Science Symp. Conf. Record*, pp. 3557–3561 (2006).
13. Q. Xu et al., "Image reconstruction for hybrid true-color micro-CT," *IEEE Trans. Biomed. Eng.* **59**(6), 1711–1719 (2012).
14. J. R. Bennett et al., "Hybrid spectral micro-CT: system design, implementation, and preliminary results," *IEEE Trans. Biomed. Eng.* **61**(2), 246–253 (2014).
15. D. P. Clark and C. T. Badea, "Spectral deblurring: an algorithm for high-resolution, hybrid spectral CT," *Proc. SPIE* **9412**, 941223 (2015).
16. D. P. Cormode et al., "Atherosclerotic plaque composition: analysis with multicolor CT and targeted gold nanoparticles," *Radiology* **256**(3), 774–782 (2010).
17. J. P. Schlomka et al., "Experimental feasibility of multi-energy photon-counting K-edge imaging in pre-clinical computed tomography," *Phys. Med. Biol.* **53**(15), 4031–4047 (2008).
18. D. P. Clark and C. T. Badea, "Hybrid spectral CT reconstruction," *PLoS One* **12**(7), e0180324 (2017).
19. H. Aly and G. Sharma, "A regularized model-based optimization framework for pan-sharpening," *IEEE Trans. Image Process.* **23**(6), 2596–2608 (2014).
20. D. Rigue and P. J. La Riviere, "Fast model-based restoration of noisy and undersampled spectral CT data," *Proc. SPIE* **9033**, 90333F (2014).
21. I. Goodfellow, Y. Bengio, and A. Courville, *Deep Learning*, MIT Press, Cambridge (2016).
22. H. Chen et al., "Low-dose CT via convolutional neural network," *Biomed. Opt. Express* **8**(2), 679–694 (2017).
23. E. Kang, J. Min, and J. C. Ye, "A deep convolutional neural network using directional wavelets for low-dose x-ray CT reconstruction," *Med. Phys.* **44**(10), e360–e375 (2017).
24. G. Masi et al., "Pansharpening by convolutional neural networks," *Remote Sens.* **8**(7), 594 (2016).
25. Q. Yuan et al., "A multiscale and multidepth convolutional neural network for remote sensing imagery pan-sharpening," *IEEE J. Sel. Topics Appl. Earth Obs. Remote Sens.* **11**(3), 978–989, (2018).
26. M. Holbrook et al., "Development of a spectral photon-counting micro-CT system with a translate-rotate geometry," *Proc. SPIE* **10573**, 105731D (2018).
27. H. Maeda, "The enhanced permeability and retention (EPR) effect in tumor vasculature: the key role of tumor-selective macromolecular drug targeting," *Adv. Enzyme Regul.* **41**, 189–207 (2001).
28. H. Gao et al., "Multi-energy CT based on a prior rank, intensity and sparsity model (PRISM)," *Inverse Prob.* **27**(11), 115012 (2011).
29. R. E. Alvarez and A. Macovski, "Energy-selective reconstructions in x-ray computerized tomography," *Phys. Med. Biol.* **21**(5), 733–744 (1976).
30. L. A. Lehmann et al., "Generalized image combinations in dual KVP digital radiography," *Med. Phys.* **8**(5), 659–667 (1981).

31. E. Roessl et al., "Sensitivity of photon-counting based K-edge imaging in x-ray computed tomography," *IEEE Trans. Med. Imaging* **30**(9), 1678–1690 (2011).
32. G. Vivone et al., "A critical comparison among pansharpening algorithms," *IEEE Trans. Geosci. Remote Sens.* **53**(5), 2565–2586 (2015).
33. C. Szegedy et al., "Going deeper with convolutions," in *IEEE Conf. on Computer Vision and Pattern Recognition (CVPR)*, pp. 1–9 (2015).
34. K. M. He et al., "Deep residual learning for image recognition," in *IEEE Conf. on Computer Vision and Pattern Recognition (CVPR)*, pp. 770–778 (2016).
35. C. Dong et al., "Image super-resolution using deep convolutional networks," *IEEE Trans. Pattern Anal. Mach. Intell.* **38**(2), 295–307 (2016).
36. L. A. Feldkamp, L. C. Davis, and J. W. Kress, "Practical cone-beam algorithm," *J. Opt. Soc. Am.* **1**(6), 612–619 (1984).
37. W. P. Segars et al., "Development of a 4-D digital mouse phantom for molecular imaging research," *Mol. Imaging Biol.* **6**(3), 149–159 (2004).
38. J. H. Siewerdsen et al., "Spektr: a computational tool for x-ray spectral analysis and imaging system optimization," *Med. Phys.* **31**(11), 3057–3067 (2004).
39. M. Abadi, "TensorFlow: learning functions at scale," *ACM SIGPLAN Notices* **51**(9), 1 (2016).
40. B. B. Avants et al., "A reproducible evaluation of ANTs similarity metric performance in brain image registration," *NeuroImage* **54**(3), 2033–2044 (2011).
41. W. S. Rasband, "ImageJ," U. S. National Institutes of Health, Bethesda, Maryland, USA, <https://imagej.nih.gov/ij/> (1997–2018).
42. M. Yaffe, K. W. Taylor, and H. E. Johns, "Spectroscopy of diagnostic x rays by a Compton-scatter method," *Med. Phys.* **3**(5), 328–334 (1976).
43. M. Touch et al., "A neural network-based method for spectral distortion correction in photon counting x-ray CT," *Phys. Med. Biol.* **61**(16), 6132–6153 (2016).
44. S. Ehn et al., "Basis material decomposition in spectral CT using a semi-empirical, polychromatic adaption of the Beer–Lambert model," *Phys. Med. Biol.* **62**(1), N1–N17 (2017).
45. T. Weidinger et al., "Polychromatic iterative statistical material image reconstruction for photon-counting computed tomography," *IEEE Trans. Biomed. Eng.* **2016**, 5871604 (2016).
46. J. R. Ashton et al., "A dual energy CT study on vascular effects of gold nanoparticles in radiation therapy," *Proc. SPIE* **9788**, 97880W (2016).
47. Y. Liu et al., "Plasmonic gold nanostar theranostic probe for in vivo tumor imaging and photothermal therapy," *Theranostics* **6**(5), 946–960 (2015).

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