Evaluation of a photon counting Medipix3RX cadmium zinc telluride spectral x-ray detector

Jeffrey F. Marsh
Steven M. Jorgensen
David S. Rundle
Andrew J. Vercnocke
Shuai Leng
Philip H. Butler
Cynthia H. McCollough
Erik L. Ritman

Evaluation of a photon counting Medipix3RX cadmium zinc telluride spectral x-ray detector

Jeffrey F. Marsh,^a Steven M. Jorgensen,^a David S. Rundle,^b Andrew J. Vercnocke,^a Shuai Leng,^a Philip H. Butler,^c Cynthia H. McCollough,^{a,*} and Erik L. Ritman^d

^aMayo Clinic, Department of Radiology, Rochester, Minnesota, United States

^bJairiNovus Technologies Ltd., Butler, Pennsylvania, United States

^cMARS Bioimaging Ltd., Christchurch, New Zealand

^dMayo Clinic, Department of Physiology and Biomedical Engineering, Rochester, Minnesota, United States

Abstract. We assess the performance of a cadmium zinc telluride (CZT)-based Medipix3RX energy-resolving and photon-counting x-ray detector as a candidate for spectral microcomputed tomography (micro-CT) imaging. It features an array of 128×128 , $110\text{-}\mu\text{m}^2$ pixels, each with four simultaneous threshold counters that utilize real-time charge summing. Each pixel's response is assessed by imaging with a range of incident x-ray intensities and detector integration times. Energy-related assessments are made by exposing the detector to the emission from an I-125 radioisotope brachytherapy seed. Long-term stability is assessed by repeating identical exposures over the course of 1 h. The high yield of properly functioning pixels (98.8%), long-term stability (linear regression of whole-chip response over 1 h of acquisitions: $y = -0.0038x + 2284$; standard deviation: 3.7 counts), and energy resolution [2.5 keV full-width half-maximum (FWHM) (single pixel), 3.7 keV FWHM (across the full image)] make this device suitable for spectral micro-CT. © 2018 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JMI.5.4.043503]

Keywords: cadmium zinc telluride-based spectral microcomputed tomography; x-ray microtomography; photon counting; Medipix; charge sharing.

Paper 18061RR received Mar. 26, 2018; accepted for publication Nov. 13, 2018; published online Dec. 4, 2018.

1 Introduction

The recent availability of functional cadmium zinc telluride (CZT)-based spectral x-ray detectors, with effective charge sharing correction capabilities, presents enhanced opportunities for spectral x-ray imaging.^{1,2} The transition from silicon to a CZT-based detection layer significantly extends the upper limit of the x-ray energy operating range.^{3,4} This extended energy range encompasses the K absorption edges of several contrast enhancement materials of interest, including: iodine, barium, gadolinium, and gold. There is work underway to explore these materials for improved contrast agents.^{5–11}

This work reports our evaluation of a CZT-based Medipix3RX photon counting detector (PCD).¹² Historically, the design of the Medipix3RX was similar to that of its predecessor, the Medipix3, and provided the users with the ability to operate in either of the two mutually exclusive “pixel matrix modes” [fine pitch mode (FM) and spectroscopic mode (SM)] and also to select between the two mutually exclusive “acquisition modes” [single-pixel mode (SPM) and charge summing mode (CSM)].^{5,11,13–17} The Medipix3RX device our group used throughout all evaluations presented in this work was specifically designed for use in the Medipix All Resolution System (MARS) spectral microcomputed tomography (micro-CT) scanner (MARS Bioimaging Ltd., Christchurch, New Zealand). Considering the detector's intended integration into the MARS scanner, the manufacturer elected to implement additional design features, including: a unique bump bonding scheme

(detector pixel array restricted to 128×128) and software imposed operational mode (CSM by default). These design constraints allowed each pixel's four charge summed counters to acquire simultaneous and noise correlated images. However, they also confine the detector to one functional setting: SM pixel matrix mode paired with CSM acquisition mode. The SPM acquisition mode (no CSM or option to disable CSM) and the FM pixel matrix mode (detector pixel array size 256×256) were beyond the scope of our investigation for that reason; however, information using these modes are detailed within evaluations, which used other Medipix3RX design modes.^{5,14}

The performance and application of spectral PCDs are generally limited by the negative effects incurred by charge sharing and pulse pileup.¹⁵ The application-specific integrated circuit (ASIC) of our group's Medipix3RX has charge summing circuitry, which is established across every 2×2 cluster of $110\text{-}\mu\text{m}$ pixels, and each of these clusters form a so-called “summing node.” All of the detector's summing nodes are designed to exhibit the same response to charge sharing events. First, each of the partial pulses detected by the node's four pixels are summed together. Second, the original incident photon's full pulse height is allocated to the single pixel (within that 2×2 cluster), which received the largest partial pulse.^{13,14,16} In CSM, each pixel has four photon counters which are charged summed, and these only tally incident photons with energies greater than their specific energy threshold settings.¹⁷ The pulse pileup phenomenon occurs when a single pixel on a PCD experiences the arrival of two incident photons with insufficient time between their depositions for individual processing.^{15,18}

*Address all correspondence to Cynthia H. McCollough, E-mail: mccollough.cynthia@mayo.edu

Content was presented in part at SPIE Optical Engineering and Applications, 2016, San Diego, California, United States.

The vendor of our Medipix3RX has expressed that operating the device in circumstances where pixels experience a photon count rate exceeding their recommended maximum count rate of 10 counts/ms/pixel will incite pulse pileup.

Earlier research performed with the Medipix3RX device has investigated topics that include: the use of a silicon sensor, CSM, and FM in the spectral x-ray imaging of material K-edges,¹⁴ the use of a gadolinium arsenide sensor, CSM, and FM in a spectral CT scanning scenario,⁵ and the application and effectiveness of CSM in comparison to SPM.^{14,17,19} Some recent work involving the MARS scanner has focused on the use of its spectral scan data for x-ray beam profile assessments²⁰ and also in material decomposition algorithms.⁹ However, a systematic evaluation of the Medipix3RX detector in terms of fundamental performance parameters such as linearity, pile up, uniformity, and stability has not been conducted. The main purpose of our study was to analyze the fundamental characteristics of a CZT-based Medipix3RX detector (operated using the SM and CSM modes), which was designed to be used in the MARS spectral micro-CT imaging system. We present six distinct evaluations of the Medipix3RX in this report, each of which was devised to examine a certain performance feature directly applicable to spectral micro-CT imaging. Based on the results of this study, we found that the performance of this device makes it an acceptable candidate for use in spectral micro-CT imaging equipment.¹²

2 Methods

Our group's Medipix3RX detector had the following characteristics: a 14.08×14.08 mm² active area, a 2-mm thick CZT semiconductor, and an ASIC containing an array of 128×128 pixels. The detector was operated in SM and CSM modes for all studies. Each of its square pixels had the following characteristics: a 110- μ m pixel pitch, a single bump bond connecting the CZT sensor to the ASIC, and four simultaneous 12-bit energy threshold counters that receive charge sharing corrected data. Although every pixel contained eight threshold counters, spatial and temporal limitations imposed by pairing SM and CSM only allowed for the accommodation of the charge summing circuitry on four of the counters.¹⁷

The six performance evaluations we conducted on the Medipix3RX each required a range of configurations and methods and are presented in detail within the remainder of this section.

2.1 Pixel Response Evaluation 1—Pulse Pileup Assessment

Avoiding pulse pileup during operation is imperative for PCDs such as the Medipix3RX, as its occurrence would yield inaccurate counts in the projection domain of all four of its CSM threshold counters, and any spectral CT applications would result in images containing erroneous attenuation values. In this evaluation, images were acquired by incrementally increasing the x-ray tube current setting while maintaining a fixed integration time (proportionally increasing photon flux per increment), where the maximum current setting yielded 10 counts/ms/pixel. This scenario challenged every pixel's ability to maintain an ideal linear response to increasing counting rates, as the aforementioned pulse pileup phenomenon would cause the response to deviate from linearity.¹⁸

2.1.1 Equipment and setup

The x-ray source for this set of measurements (MXR-160HP/11, COMET, Flamatt, Switzerland) was operated with a tungsten target at 120 kVp over a range from 0.1 to 0.9 mA with 15.4 mm of Al filtration at the exit port. The source-to-detector distance (SDD) was ~ 1200 mm. The detector was the MARS CZT-based Medipix3RX (MARS Bioimaging Ltd., Christchurch, New Zealand). All programmable detector energy thresholds were set to 15 keV. The images were acquired with no object in the beam.

2.1.2 Measurement technique

A 10-min camera warmup was performed after startup to allow the detector to stabilize. The maximum x-ray current, 0.9 mA, for this assessment was determined by increasing the x-ray current until the count rate approached 10 counts/ms/pixel. The detector integration time was set to 100 ms, resulting in counts per exposure of ~ 1000 counts per pixel for the maximum arrival rate condition. 400 images were acquired at each setting of x-ray current from 0.1 to 0.9 mA with 0.1-mA increments.

2.2 Pixel Response Evaluation 2—Linearity Assessment

A PCD composed of pixels that exhibit linear responsiveness to count measurements, ranging from zero to saturation, would be ideal for micro-CT applications. Correspondingly, the evaluation presented in this section explored the detector's response to a fixed intensity x-ray beam while the detector's integration time was varied. These variations spanned the 12-bit threshold counter's full range of usable values (0 to 4095). Plotting each pixel's response to the incident x-ray beam over the varying range of integration times revealed the pixel's signal behavior and range of linear operation. These findings provide insight into the number of linearly responding pixels, as well as the nonlinear and nonresponsive pixels.

2.2.1 Equipment and setup

The x-ray source for this set of measurements was the same x-ray tube as in Sec. 2.1, 120 kVp, 0.2 mA with 2.5 mm of Al filtration at the exit port. The detector and SDD were also the same as in 2.1. The detector's energy thresholds were set at 15, 25, 35, and 45 keV. The images were acquired with no object in the beam.

2.2.2 Measurement technique

A 10-min camera warmup was performed after startup to allow the detector to stabilize. The x-ray current was set to generate an average count rate of 3.9 counts/ms/pixel. Following the warmup, 400 frames were acquired at each integration time setting. Integration time settings were 1, 2, 4, 8, 16, 32, 64, 128, 256, 384, 512, 640, and 768 ms.

2.3 Long-Term Stability Evaluation

The historical issue with the implementation of CZT semiconductors in PCDs is related to the subtle defects, which can manifest in their crystalline structure (Te inclusions) during the fabrication process.²¹ During imaging applications, such defects can incur "charge trapping," a detrimental phenomenon that can

degrade a PCD's spectroscopic information by disrupting the count measurements in successive acquisitions (obtained over a period of time).²¹ In this assessment, the Medipix3RX's ability to acquire a series of images without significant differences from image-to-image was evaluated under a fixed exposure condition and over an extended period of time. Repeated image acquisitions (with the same source and detector configurations) were acquired over the course of 1 h. Ideally, the image-to-image difference throughout the sequence would be limited to the expected noise from the incident illumination (i.e., quantum noise), and there would be no distinguishable contribution from charge trapping.

2.3.1 Equipment and setup

The x-ray source for this set of measurements was the same x-ray tube as in Sec. 2.1, 120 kVp, 0.2 mA with 2.5 mm of Al filtration at the exit port. The detector and SDD were the same as in 2.1. The detector energy thresholds were set at 20, 30, 40, 50, 61, 71, and 81 keV. These setup conditions resulted in an average count rate of 4.56 counts/ms/pixel in energy threshold counter 1. The integration time for each image was 500 ms with the image-repeat period set to 3.6 s. The images were acquired with no object in the beam.

2.3.2 Measurement technique

No specific camera warmup was performed as this test was intended to explore changes in the camera response over time. The camera had been powered up for about 18 min before the first set of images were collected. The x-ray source was energized and allowed to stabilize. 1000 frames over the course of 1 h were acquired.

2.4 Photon Energy Resolution Evaluation

Spectral micro-CT applications are also reliant on the accuracy with which their PCDs can measure beam spectra information. It is, therefore, imperative that the energy threshold counters of these spectral PCDs be able to accurately count incident photons with energies exceeding their assigned threshold. In this evaluation, we used an Iodine-125 photon source to analyze the energy measurement accuracy of the Medipix3RX device. The four CSM counters of our Medipix3RX were also expected to demonstrate resilience to energy contamination related to charge sharing.

2.4.1 Equipment and setup

The photon source for the energy resolution assessment was an Iodine-125 brachytherapy seed. Iodine-125 sources produce photons primarily at 27.2, 27.5, 31.2, 31.8, and 35.5 keV.²² The majority of photons are produced at the narrowly separated 27.2 and 27.5 keV energies. A tin (K-edge 29.2 keV) foil, 0.4-mm thick, was placed between the source and detector to preferentially attenuate the 31.2-, 31.8-, and 35.5-keV emission components. The SDD was ~21 mm. The activity of the source was ~2.38 mCi. The detector integration time was set to 4 s. The energy thresholds set to 20 keV resulted in an average signal of 10.95 counts per pixel per image acquired.

2.4.2 Measurement technique

Measurements were made by stepping the energy threshold over the energy range of 20 to 36 keV to cover the expected emission from the Iodine-125. The increment between measurements was 1 keV. All globally programmable energy threshold counters were set to the same nominal value for each measurement. One hundred measurements were acquired at each energy threshold setting.

2.5 Threshold Comparison Evaluation

In the last section, we investigated the accuracy of the energy threshold assigned to CSM counters, however, it is also of interest to compare and contrast the performance of the counters which reside within the same pixel. This is especially important when generating energy bins during spectral CT imaging applications. The accuracy of a given energy bin is dependent on the accuracy of the specific energy threshold counters being used to make it. In this evaluation, we compared the measurements of the four charge summed counters among themselves in circumstances where their global energy threshold settings were nominally identical. The data acquired in methods Secs. 2.2 and 2.4 corresponded with this analysis, as the detector's CSM counters were all set to the same threshold, and so their data were reused in this evaluation. However, the data obtained in Secs. 2.1 and 2.3 were acquired using different threshold settings for the four CSM counters. As a result, we repeated their methodologies for this evaluation, with the subtle differences noted below.

2.5.1 Equipment and setup

The supplemental 2.1 dataset (used in this evaluation alone) was acquired using a source (SB-80-1k, Source-Ray, Inc., Ronkonkoma, New York) operated with a tungsten target at 80 kVp over a range of 5 to 77 μ A with 12.9-mm Al filtration at the exit port. The SDD was ~202 mm. The detector was the same as in 2.1. Here all detector thresholds were set to 15 keV, and the detector integration time was 250 ms.

The supplemental 2.3 dataset (also used in this evaluation) was acquired using the same tungsten tube noted above operated at 80 kVp, 29 μ A with 12.9 mm of Aluminum filtration at the exit port. The SDD was also 202 mm and the detector was the same as in 2.1. Here all detector thresholds were set to 15 keV, and the detector integration time was 700 ms.

For the varying integration time with fixed x-ray current assessment, the equipment and setup were the same as described in Sec. 2.2, using data where the thresholds were all set to 15 keV during acquisition.

For the energy resolution evaluation, the equipment and setup were the same as described in Sec. 2.4.

2.5.2 Measurement technique

During acquisition of the supplemental 2.1 dataset described above, it was determined that an x-ray current setting of 77 μ A produced a count rate in the detector of 9.05 counts/ms/pixel. Images were acquired in sets of 400 with a current setting ranging from: 5 to 77 μ A with 6- μ A increments. The detector integration time was set to 250 ms.

During acquisition of the supplemental 2.3 dataset described above, the detector integration time was set to 700 ms and the count rate was fixed at 2.95 counts/ms/pixel. A total of one thousand images were acquired over the course of 1 h.

2.6 Spectral Micro-CT Application Evaluation

All factors investigated in previous sections affect the final images of spectral CT. In this final evaluation, we used the Medipix3RX in a spectral micro-CT application where individual effects are intrinsically combined and shown in the final performance of the spectral CT images. We scanned a micro-CT phantom containing different concentrations of various materials, analyzed the linear attenuation coefficients extracted from the reconstructed images, and then made conclusions about the materials imaged using this spectral information.

2.6.1 Equipment and setup

The micro-CT scanner used for this assessment was our prototype MARS scanner (MARS-1, MARS Bioimaging Ltd., Christchurch, New Zealand) equipped with this Medipix3RX device for the x-ray detector. The x-ray source in this scanner is the same as in Sec. 2.5. The test object was a 30.5-mm diameter cylindrical Plexiglas phantom that contained ports for nine sample materials. Centrifuge tubes (0.2 ml volume) containing deionized water, lipid, both 2 and 8 mg/ml concentrations of gold and gadolinium, 18 mg/ml of iodine, and 280 mg/ml of calcium were installed into the ports of the cylinder. This test object assembly is shown in Fig. 1.

2.6.2 Measurement technique

Prior to starting a micro-CT scan on the MARS system, the user must first define the scan parameters to be used, and often times these are specifically tailored to each specimen being scanned. During this phantom scan, the tungsten x-ray source was set to 80 kVp and 5 μ A. The source-to-object distance was 129 mm. The SDD was 202 mm. The integration time for each frame was 375 ms. With these settings, the average count rate (across many pixels) for the arbitration counter, with no object in the beam, was 5.1 counts/ms/pixel. The energy threshold settings used for this scan were: 23, 28, 35, and 44 keV. These settings were chosen because they provided approximately equal counts in each of the resulting energy bins (generated by subtracting

different thresholds from each other) in acquisitions with no object in the beam. The micro-CT scan was set to acquire 720 projection frames, 200 flat-field frames, and 10 dark-field frames during 360 deg of rotation around the phantom. Six tangential detector positions were required, at each acquisition step, in order to cover the projected size of the phantom at the image plane.

After completion of the scan, the raw projection data first received dark-field and flat-field correction, and then the corrected projections from all six tangential detector positions were stitched together (for each acquisition angle). The stitched and corrected projections and the detector's bad-pixel mask were then submitted to an iterative reconstruction algorithm (provided by the vendor) in order to generate tomographic images.²³ During reconstruction, inputs from "bad pixels" identified on the mask are simply ignored, and this is acceptable due to the iterative algorithm's ability to tolerate slightly sparse projection datasets without significant degradation.

3 Results

We refer to "properly functioning pixels" as those that responded linearly and consistently to the input signal. Pixels discovered to exhibit improper functionality were identified by an automated mask generating service script, available in the MARS software (provided by the vendor), and had their locations recorded in a bad-pixel mask (Fig. 2). This automated process included: source and detector warmup, images acquired with x-ray source off, images acquired with x-ray source on, and then bad-pixel mask generation. Bad pixels were classified as such by having one of the following characteristics: displaying nonzero counts when x-ray was off, displaying no counts when x-ray was on, displaying saturated counts when x-ray was on, or having "atypical counts" when x-ray was on. Atypical counts were defined as ones occurring beyond specified cutoffs of the anticipated Poisson distribution. In this case, a mean of 2000 counts was expected to be measured out of the 200 flat-field frames acquired, counts between 1750 and 2250 were accepted (Poisson cutoffs established by the vendor), and any pixels counting outside this range were considered atypical. Masks were generated either daily, to ensure that any new malfunctioning detector pixels were accounted for, or after a protocol change (magnification, scan diameter, etc.). For a complete and unbiased presentation of this detector's functionality, the figures presented within Secs. 3.1–3.5 show both properly functioning and nonfunctioning pixels.

Fig. 1 Plexiglas cylinder phantom with samples installed for scanning. Samples include water, lipid, 8 and 2 mg/ml gold and gadolinium, 18 mg/ml iodine, and 280 mg/ml calcium.

Fig. 2 (a) A typical flat-field image from this Medipix3RX detector (no object in the beam) and (b) a representative bad-pixel mask generated by the MARS masking service script.

However, the spectral micro-CT imaging application we evaluated in Sec. 3.6 utilized a bad-pixel mask to screen out contributions from the improperly functioning pixels during reconstruction. In the masks acquired during this evaluation, our Medipix3RX had 16193 out of 16384 (98.8%) pixels considered to be properly functioning (Fig. 2).

3.1 Pulse Pileup

In order to determine if pulse pileup was experienced by counters in our detector, during operation within the desired intensity range, we selected a representative counter (counter #1) and evaluated its count behavior across all detector pixels. By plotting the counts measured by counter #1 in all relevant pixels and over the range of intensities analyzed, we obtained a visual representation of its overall responsiveness [Fig 3(a)]. If pulse pileup were experienced, the counter's response would plateau after the intensity in which the phenomenon was encountered, as it would become unable to properly respond to additional events. A closer look at the line graph [Fig 3(a)] reveals a spread in the count measurements between the apparently linearly responsive detector pixels. There are two predominant factors contributing to this spread: inherent sensitivity differences among detector pixels and also slight differences in illumination across the detector due to the cone beam x-ray source. However, both of these issues would be addressed by the incorporation of a flat-field correction during actual micro-CT imaging applications. In order to gain further insight into counter #1's linear behavior, the plotted lines in Fig 3(a) were statistically analyzed on a per pixel basis using the coefficient of determination [Figs. 3(b) and 3(c)]. The mean R -squared value calculated from all functioning pixels was 0.9993. These findings support that, for count rates up to about 10 counts/ms/pixel, pulse pileup was not detected in the Medipix3RX.

3.2 Linearity

In order to assess the linearity of the detector's counters over their 12-bit operating range, we again began using a visual evaluation to distinguish each pixel's line profile behavior. Counter #1 was again used as a representative of the other counters, and its counting behavior in each pixel over the range of

integration times was plotted for all pixels [Fig. 4(a)]. As noted in Sec. 3.1, the different sensitivities of the pixels would be accommodated for using flat-field corrections during a scanning procedure. The statistical coefficient of determination was employed, and the resulting mean R -squared value of 0.9999 was calculated [Figs. 4(b) and 4(c)]. These findings support our conclusion that the counters of the Medipix3RX exhibit linear responses over their full operating range.

3.3 Long-Term Stability

The count behavior for all of the Medipix3RX's functional pixels was plotted Fig. 5 using the data obtained from 1 h of continuous acquisitions. In this figure, the functional pixels form the closely grouped horizontal band, which is modulated by the noise in the x-ray source. Close inspection reveals some vertical widening of the band at the beginning of the acquisitions. The width of the band stabilizes after 2 to 3 min. This can be attributed to expected drift during the detector warmup period. The slope of a linear fit to the average response of the whole detector over 60 min was -0.0038 . The standard deviation of that dataset was 3.7 counts; the average value was 2282 counts. As individual specimen scans in our MARS scanner typically last between 30 min to 1 h, we consider the Medipix3RX to demonstrate a level of pixel stability sufficient for use in spectral micro-CT applications.

3.4 Energy Resolution

The energy specific count measurements made using the charge summed counters were first used to generate 1 keV wide energy bins from 20 to 36 keV. The resulting energy bin information is presented in the line graph of Fig. 6(a), which includes the response from every detector pixel. In order to make more detailed conclusions about the Medipix3RX's energy resolution capabilities, the averaged response of all pixels was plotted in Fig. 6(b), and a single representative pixel was plotted in Fig. 6(c). In both cases, the full-width half-maximum (FWHM) was calculated using the measured Iodine-125 emission peak. The measurement of the 27.4-keV peak of the tin-filtered Iodine-125 radiation showed a spread of the detected energy peak of 3.7 keV (FWHM) when the responses of all pixels

Fig. 3 (a) A line graph displaying the count measurements with respect to increasing intensity as recorded by counter #1 in all pixels ($n = 16,384$). (b) A scatter plot of the coefficient of determination, where each R -squared value represents a single-detector pixel. The majority of the pixels R -squared values tended to form a line just beneath $R = 1$. (c) A histogram displaying the pixel distribution of the line formed near $R^2 = 1$ in panel (b). The use of a more narrowed R -squared region and presenting the log of the pixel numbers provided further insight into their distribution. As the pixels demonstrated a linear slope with respect to the intensities investigated, it can be concluded that the count "plateau" expected from the pulse pileup condition was not encountered.

Fig. 4 (a) A line graph displaying the count measurements with respect to detector integration time as recorded by counter #1 in all pixels ($n = 16,384$). (b) A scatter plot of the coefficient of determination, where each R -squared value represents a single detector pixel. The majority of the pixels R -squared values tended to form a line just beneath $R^2 = 1$. (c) A histogram displaying the pixel distribution of the line observed near $R^2 = 1$ in panel (b). The use of a more narrowed R -squared region and presenting the log of the pixel numbers provided further insight into their distribution. These results support that the Medipix3RX's detector pixels exhibit a desirable linear response as the integration time increased over a range from 1 to 768 ms.

Fig. 5 A line graph in which every detector pixel's behavior is represented by its own representative line ($n = 16,384$). The properly functioning pixels show a narrow band, 2000 to 2500 counts, of stable measurements over the course of 1 h, indicating satisfactory long-term stability performance. The traces outside the narrow band represent pixels that would be eliminated from most imaging applications by applying the bad-pixel mask.

were averaged [Fig. 6(b)]. The spread of the detected energy peak of a representative pixel is 2.5 keV (FWHM) [Fig. 6(c)]. While some pixels still showed counts on the lower energy side of their peaks, no evidence of charge sharing contamination was observed. The energy resolution measurements yielded from both the single and averaged pixels' responses are considered to be acceptable for spectral micro-CT.

3.5 Threshold Counter Comparison

This assessment consisted of comparing the counts measured by each pixel's four available charge summed counters, while their four energy thresholds were set to the same nominal value, creating a condition where the counts registered in each counter should be identical. For all pixels, the coefficient of variation of the four counters' values was calculated over a reasonable portion of the operating range and plotted in Figs. 7–9.

Histograms were included to provide insight into the distribution of the coefficient of variation. The exposure conditions assessed included: varying integration time with fixed x-ray current (Fig. 7), varying x-ray current with fixed integration time (Fig. 8) and repeated exposures of fixed x-ray current and fixed integration time over an operating period of 1 h (Fig. 9). A typical average coefficient of variation across the detector was 0.00127 with a standard deviation of 0.00320. This average variation equates to a difference of ~ 2.5 counts out of 2000 total counts, which is an acceptable performance. The consistent values observed over the range of the operating conditions and times tested indicate that these four thresholds are sufficiently stable under the varying conditions assessed in this study.

One notable anomaly, from the otherwise low variation observed in the threshold counter performance, occurred in the long-term stability dataset. Here a single threshold counter from two different pixels (and two different times) each reported a value, which deviated greatly from those provided by the other three counters their pixels, and from their own previous and following frame measurements. In the case of pixel (80, 70), the errant value was 3000 while the expected value would have been nearer to the mean value of the series for this pixel, 2146 (std. dev. 56). In the case of the other errant observation, pixel (33, 65), the errant value was 2799 while the expected value would have been nearer to the mean value of 2194 (std. dev. 49).

We also assessed the behavior of the threshold counters' as their threshold settings were swept across the emission peak of I-125 (~ 27.4 keV). Several times during this assessment we observed instances where there were significant differences between threshold counters within the same pixel. These differences were initially detected when the threshold settings approached and passed the energy peak of I-125. As counts in the properly performing counters started to decline to zero, some counters exhibited nonzero values for several threshold steps beyond the energy peak. Affected counters tended to manifest simultaneously in 2×2 clusters of neighboring pixels. If one counter in a given pixel was errant, it was not uncommon for one or more of the remaining counters to be properly functioning. Also, when comparing images from counter-to-counter, the position of these affected pixel clusters was not fixed. Plots

Fig. 6 (a) Line graph representing the binned responses of all detector pixels ($n = 16,384$) over the energy range from 20 to 35 keV plotted in 1 keV bins. The detector was being exposed to the radiation from the Iodine-125 seed, filtered with 0.4 mm of tin (27.4-keV peak). (b) All pixel responses were averaged and then plotted. The FWHM was calculated using the peak measurement from the averaged data, and then used to determine the measured energy spread (3.7 keV) from the I-125 seed. (c) Line graph conveying the behavior recorded by a single representative detector pixel. The FWHM was calculated using the peak measurement from the pixel's data and determined the measured energy spread (2.5 keV) from the I-125 seed. Projecting a vertical line from the midpoint of the FWHM in (b) and (c) to the x-axis corresponded well in both cases to the expected I-125 emission spectrum.

Fig. 7 (a) The coefficient of variation was calculated to compare the count measurements yielded among the four charge summed counters during the linearity evaluation (outlined in Secs. 2.2 and 2.5). The results are plotted in this line graph, where each line represents the coefficient of variation between the four counters within a given detector pixel ($n = 16,384$ pixels). (b) Histogram of identically set threshold counters for all pixels under fixed tube voltage and current settings over a range of integration times from 1 to 768 ms. The slight modulation in the variation at the very low integration times is due to the noise resulting from low photon counts. Here, the average coefficient of variation of 0.0009 corresponds to ~ 2 counts out of 2000.

of the response of properly performing counters and affected counters from two representative pixels are compared in Fig. 10. All counters begin experiencing a decrease in counts around the same point. The slopes of the errant counters are less steep and their responses approach zero at significantly higher energy threshold settings. Figure 11 shows images of the four threshold counters from the energy threshold setting at 31 keV. Note the spatial distribution and frequency of the nonzero errant counters, the curious 2×2 pixel clustering, and the dynamic spatial distribution from counter-to-counter.

3.6 Spectral Micro-CT Application

An image of the micro-CT phantom is shown in Fig. 12 and provides labels denoting the type and concentration of the materials contained therein. Figure 13 shows a plot of each materials linear attenuation values as a function of increasing energy. As expected, the lipid, water, calcium, and gold show continuously decreasing attenuation as the photon energy increases; these materials do not have absorption edges in the energy range from 20 to 80 keV. The iodine attenuation flattens as its

Fig. 8 (a) The coefficient of variation was calculated to compare the count measurements yielded among the four charge summed counters during the pulse pileup evaluation (outlined in Secs. 2.1 and 2.5). The results are plotted in this line graph, where each line represents the coefficient of variation between the four counters within a given detector pixel ($n = 16,384$ pixels). (b) Histogram of identically set threshold counters for all pixels under fixed tube voltage and detector integration time over a range of tube current settings from 5 to 77 μA . Here the average coefficient of variation of 0.0014 corresponds to ~ 3 counts out of 2000.

Fig. 9 (a) The coefficient of variation was calculated to compare the count measurements yielded among the four charge summed counters during the long-term stability evaluation (outlined in Secs. 2.3 and 2.5). The results are plotted in a line graph, where each line represents the coefficient of variation between the four counters within a given detector pixel ($n = 16,384$ pixels). (b) Histogram with identically set threshold counters for all pixels with fixed tube voltage, fixed tube current, and fixed detector integration time from a series of repeated images over the course of 1 h. The two impulse-like outliers are from a single abnormal response in two different threshold counters in two different pixels at two different times during the acquisition. Here the average coefficient of variation of 0.0016 corresponds to ~ 3 counts out of 2000.

Fig. 10 Threshold counter response curves of the four threshold counters in two different pixels: (a) one pixel with four properly operating counters and (b) another pixel with two normal responses and two responses that deviate from normal. These curves were generated by incrementing the identically set thresholds in 1-keV steps across the 27.4-keV peak of I-125 irradiation.

Fig. 11 (a)–(d) The images generated from the four threshold counters within each pixel. The threshold setting for each counter was 31 keV. The illumination energy was 27.4 keV. Properly operating counters, the majority in these images, are zero (black) under these conditions. Counters with nonzero values have an abnormal response. The magnified region of threshold 1 (inset e) shows the curious 2×2 pixel clustering associated with nonzero counters. Note also that the position of the affected counters within the image changes from counter to counter, indicating that this behavior is not pixel specific across the counters.

Fig. 12 Micro-CT image of the 30-mm diameter Plexiglas cylinder containing centrifuge tubes with water, lipid, 2 and 8 mg/ml gold and gadolinium, 18 mg/ml iodine, and 280 mg/ml calcium.

33-keV K-edge impacts the energy bin ranges 29 to 35 keV and 35 to 44 keV; beyond those it continues to decrease as expected. The gadolinium attenuation increases as the 44- to 80-keV photon bin is influenced by its 50 keV K-edge, also as expected.

4 Discussion and Conclusions

The performance of this Medipix3RX detector was satisfactory in all but the energy threshold counter comparison performed in Sec. 3.5. In an evaluation such as this, any threshold dispersion existing between the different counter's threshold settings could lead to count differences, if not properly accounted for. However, to address these inherent differences the vendor already employs correction procedures, threshold equalization and kVp-based energy calibration, in order to adjust the thresholds of the Medipix3RX so to mitigate threshold dispersion.^{24,25} In Figs. 7–9, we observed differences between threshold counters of about 2 counts out of 2000 counts or more, and while perfect performance would have yielded coefficients of variation of zero, we consider these differences to be acceptable. In reference to the errant pixel measurements also noted in this section, this occurrence rate is also considered acceptable, as their occurrence can be reasonably detected in many imaging scenarios and compensated for.

In regards to the pulse pileup evaluation presented in Secs. 2.1 and 3.1, we did not pursue operation above

Fig. 13 Plot of the linear attenuation coefficients of the materials indicated, as calculated within energy bins made from the four charge-summed counter's energy threshold measurements (and in one case the 7-keV arbitration counter). Materials with K-edges in the measured energy range, iodine (33 keV), and gadolinium (50 keV) show attenuation plateaus compared to other materials' continuously downward-trending slopes.

10 counts/ms/pixel, as count rates above this value will not be encountered during scanning applications within the MARS scanner system. The manufacturer has established a prescan criterion, in which the user obtains flat-field acquisitions using their intended scan parameters (voltage and current), and using the MARS software the user can ensure the measured count rates are less than or equal to this maximum value. As a result of this precautionary step, it is ensured that at no time during the scan will the count rate exceed 10 counts/ms/pixel.

The results of the energy sweep study performed in Sec. 3.4 were satisfactory, with some degradation in the energy threshold resolution in some threshold counters of some pixels. This could be compensated for in cases where enhanced energy separation is desired by providing counter specific corrections or masking. If not corrected for in a given pixel, then generating an energy bin by subtracting an errant high-energy counter (with erroneously high counts) from a normal low-energy counter could result in a negative number of counts.

With 98.8% of the pixels operating properly, this Medipix3RX device provided adequate spatial coverage for many applications, including micro-CT. During our evaluations, this device's pixels demonstrated linear behavior across the functioning pixels. The energy resolution on both the pixel level (2.5-keV FWHM) and across the whole device (3.7-keV FWHM) is considered acceptable for spectral micro-CT applications. The device's counters maintained stability over the time required for a typical micro-CT scanning application in the MARS system. We plan to use this device in future spectral micro-CT applications and explore the opportunities that spectral imaging provides.

Disclosures

Dr. McCollough receives industry support from Siemens Healthcare. Dr. Phillip Butler is affiliated with the MARS Bioimaging Company. David Rundle is affiliated with JairiNovus, the United States representative for the MARS Bioimaging Company.

Acknowledgments

Research reported in this article was supported by the National Institutes of Health under Award No. R01 EB016966. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

1. J. S. Iwanczyk et al., "Photon counting energy dispersive detector arrays for X-ray imaging," *IEEE Trans. Nucl. Sci.* **56**(3), 535–542 (2009).
2. E. Fredenberg et al., "Contrast-enhanced spectral mammography with photon-counting detector," *Med. Phys.* **37**(5), 2017–2029 (2010).
3. N. G. Anderson et al., "Spectroscopic (multi-energy) CT distinguishes iodine and barium contrast material in MICE," *Eur. Radiol.* **20**(9), 2126–2134 (2010).
4. G. Mettievier, M. C. Montesi, and P. Russo, "First images of a digital autoradiography system based on Medipix2 hybrid silicon pixel detector," *Phys. Med. Biol.* **48**(12), N173–N181 (2003).
5. E. Hamann et al., "Performance of a Medipix3RX spectroscopic pixel detector with a high resistivity gallium arsenide sensor," *IEEE Trans. Med. Imaging* **34**(3), 707–715 (2015).
6. T. E. Curtis and R. K. Roeder, "Effects of calibration methods on quantitative material decomposition in photon-counting spectral computed

- tomography using maximum a posteriori estimator," *Med. Phys.* **44**(10), 5187–5197 (2017).
7. S. Si-Mohamed et al., "Evaluation of spectral photon counting computed tomography K-edge imaging for determination of gold nanoparticle biodistribution in vivo," *Nanoscale* **9**(46), 18246–18257 (2017).
8. R. Symons et al., "Photon-counting CT for simultaneous imaging of multiple contrast agents in the abdomen: an in vivo study," *Med. Phys.* **44**(10), 5120–5127 (2017).
9. R. K. Roeder et al., "Nanoparticle imaging probes for molecular imaging with computed tomography and application to cancer imaging," *Proc. SPIE* **10132**, 101320X (2017).
10. R. Roeder, "A spectral of library nanoparticle contrast agents for spectral (Color) X-ray imaging," NSF Award Abstract #1309587 (2013).
11. M. F. Walsh et al., "Spectral CT data acquisition with Medipix3.1," *J. Instr.* **8**, P10012 (2013).
12. S. M. Jorgensen et al., "Evaluation of a photon counting Medipix3RX CZT spectral x-ray detector," *Proc. SPIE* **9969**, 99690J (2016).
13. R. Ballabriga, "The design and implementation in 0.13- μ m CMOS of an algorithm permitting spectroscopic imaging with high spatial resolution for hybrid pixel detectors," PhD Thesis, Universitat Ramon Llull, Barcelona, Spain (2010).
14. R. Ballabriga et al., "The Medipix3RX: a high resolution, zero dead-time pixel detector readout chip allowing spectroscopic imaging," *J. Instr.* **8**, C02016 (2013).
15. K. Taguchi and J. S. Iwanczyk, "Vision 20/20: single photon counting x-ray detectors in medical imaging," *Med. Phys.* **40**(10), 100901 (2013).
16. D. Pennicard et al., "Simulations of charge summing and threshold dispersion effects in Medipix3," *Nucl. Instrum. Methods Phys. Res. A* **636**(1), 74–81 (2011).
17. T. Koenig et al., "How spectroscopic x-ray imaging benefits from inter-pixel communication," *Phys. Med. Biol.* **59**(2014), 6195–6213 (2014).
18. H. Ding and S. Molloy, "Image-based spectral distortion correction for photon-counting x-ray detectors," *Med. Phys.* **39**(4), 1864–1876 (2012).
19. T. Koenig et al., "Charge summing in spectroscopic X-ray detectors with high-Z sensors," *IEEE Trans. Nucl. Sci.* **60**(6), 4713–4718 (2013).
20. M. Anjomrouz et al., "Beam profile assessment in spectral CT scanners," *J. Appl. Clin. Med. Phys.* **19**(2), 287–297 (2018).
21. R. Redus, "Charge trapping in XR-100T-CdTe and -CZT detectors," Application Note ANCZT-2 Rev. 3, <https://amptek.com/pdf/anczt2.pdf> (2007).
22. V. Chisté and M. M. Be, "Table of radionuclides," Laboratoire National Henri Becquerel (2010) http://www.nucleide.org/DDEP_WG/Nuclides/I-125_tables.pdf (22 December 2016).
23. N. Tang et al., "Using algebraic reconstruction in computed tomography," in *ACM Int. Conf. Proc. Series* (2012).
24. R. K. Panta et al., "Energy calibration of the pixels of spectral X-ray detectors," *IEEE Trans. Med. Imaging* **34**(3), 697–706 (2015).
25. A. Atharifarid et al., "Per-pixel energy calibration of photon counting detectors," *J. Instr.* **12**, C03085 (2017).

Jeffrey F. Marsh received his BS degree in bioengineering from the University of Illinois at Chicago in 2016. He is now a biomedical engineer working in the Department of Radiology at Mayo Clinic College of Medicine and Biomedical Sciences. His current research interests include investigating the translation of analytical methods established in anatomical models, using high-resolution microcomputed tomographic imaging into the clinical domain of computed tomographic diagnostic procedures.

Steven M. Jorgensen received his BSEE degree from South Dakota School of Mines and Technology in 1979. He is an associate in research and the micro-CT system lead engineer in the Physiological Image Research Lab of the x-ray imaging core at Mayo Clinic College of Medicine, Rochester, Minnesota, USA. Current projects include working with whole-body spectral x-ray imaging with the Mayo's Computed Tomography Clinical Innovation Center and spectral micro-CT x-ray imaging in the x-ray imaging core.

Andrew J. Vercnocke received his BS degree in computer science from Winona State University in 2004. He is currently a medical imaging analyst at Mayo Clinic, Rochester, Minnesota, USA. His research interests lie in the development of micro-CT imaging for clinical research applications and he has helped researchers to gather data by the way of this modality for numerous studies.

Shuai Leng received his BS and MS degrees in engineering physics from Tsinghua University in 2001 and 2003, respectively, and his PhD in medical physics in 2008 from the University of Wisconsin Madison. He is an associate professor of medical physics at Mayo Clinic, Rochester, Minnesota, USA. He has authored over 100 peer-reviewed articles. His research interest is in technical development and clinical application of x-ray and CT imaging.

Cynthia H. McCollough received her doctorate degree from the University of Wisconsin in 1991. She is a professor of radiological physics and biomedical engineering at Mayo Clinic, where she directs the CT Clinical Innovation Center. Her research interests include CT dosimetry, advanced CT technology, and new clinical applications, such as dual-energy and multispectral CT. She is an NIH-funded investigator and is active in numerous professional organizations. She is a fellow of the AAPM and ACR.

Erik L. Ritman is a physiologist who used CT to explore pathophysiological processes *in vivo*. In the 70's and 80's, he developed and used high-speed volume scanning CT and in the 90's and 00's on micro-CT. Currently, he is involved in evaluation of a whole-body spectral CT scanner.

Biographies of the other authors are not available.