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Bio-medical X-ray imaging with spectroscopic pixel detectors

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Abstract

The aim of this study is to review the clinical potential of spectroscopic X-ray detectors and to undertake a feasibility study using a novel detector in a clinical hospital setting. Detectors currently in development, such as Medipix-3, will have multiple energy thresholds allowing for routine use of spectroscopic bio-medical imaging. We have coined the term MARS (Medipix All Resolution System) for bio-medical images that provide spatial, temporal, and energy information. The full clinical significance of spectroscopic X-ray imaging is difficult to predict but insights can be gained by examining both image reconstruction artifacts and the current uses of dual-energy techniques. This paper reviews the known uses of energy information in vascular imaging and mammography, clinically important fields. It then presents initial results from using Medipix-2, to image human tissues within a clinical radiology department. Detectors currently in development, such as Medipix-3, will have multiple energy thresholds allowing for routine use of spectroscopic bio-medical imaging in the future.

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1. Aim

The goal of this paper is to review the benefits of spectroscopic X-ray detectors for bio-medical imaging. Images obtained with the Medipix-2 detector are used to establish the practicality of using such detectors within clinical radiology departments.

Advances in detector technology are likely to make routine spectroscopic X-ray imaging possible. The growing use of dual-energy systems is hastening the identification of applications for spectroscopic systems.

2. Background

In recent years there has been a new breed of X-ray detectors in which the X-ray photons are processed and counted as individual quanta. This allows for low noise imaging, and extraction of energy information from the X-ray beam. Many names are used for this type of detector, but common terms include: direct detector, quantum detector, photon counting detector and photon processing detector. Many of these detectors, such as Medipix-2, allow thresholds to be selected so that only photons within a specified energy range are recorded [1,2]. New detectors in development, such as Medipix-3, have multiple thresholds and counters within each pixel and thus allows for full spectroscopic imaging [3,4].

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Previous work on the Medipix-2 detector has shown it has many of the necessary characteristics for bio-medical imaging, such as spatial and temporal resolution (frame rate for 2D imaging) [5,6]. The Medipix-2 detector is a 14 mm square detector with 55 μm square pixels [1,2]. It comprises a sensor layer, typically 300 μm of silicon, bump bonded onto the CMOS micro-electronics layer. Each photon interacting with the sensor layer produces several electron–hole pairs. This charge is collected and analyzed by the associated pixel's electronics with each pixel working independently.

The energy-resolving capability of the Medipix-2 detector is made possible by placing discriminators before the counting circuitry. That is, a pixel only counts an event if the energy of the incoming photon is between low and high thresholds. These thresholds are set by the user and can be calibrated to the energy of incident photons. Thus, it is possible to only count photons within a desired energy range, e.g. 15–20 keV. One issue with the Medipix-2 design is charge sharing. When charge from a single photon is collected by two neighboring pixels, each records separate events of lower energy. The Medipix-3 design corrects for this by summing the charge for neighboring pixels when co-incident events occur. The sum of the charges is then allocated to the pixel, which recorded the highest energy [3].

Medipix detectors are advanced because they allow for spectroscopic X-ray imaging, rather than simple gray scale imaging. Traditional spectrographs (i.e. multi-channels analyzers) for X-ray are a "single" large pixel of up to several centimeters with excellent energy resolution. However, in one proposed configuration Medipix-3 allows for 110 μm pixels with up to eight separate energy thresholds [4]. Thus, the traditional approach of describing radiographs (X-ray images) by their spatial resolution and temporal resolution is no longer adequate. Rather, images taken with spectroscopic imaging detectors provide energy resolution as well as spatial and temporal resolution. We have coined the term MARS (Medipix All Resolution System) image for such spectroscopic images.

3. Potential benefits of spectral imaging

The full clinical significance of spectroscopic X-ray detectors is difficult to predict but insights can be gained by examining both image reconstruction artifacts caused by beam hardening, and the current uses of dual-energy techniques in bio-medical imaging.

3.1. Improved image quality

Beam hardening artifact is a computed tomography (CT) artifact where an area of low attenuation is falsely computed around a highly attenuating object. As the X-ray beam passes through a highly attenuating object the lower energy photons are preferentially absorbed hardening the X-ray beam. Adjacent to the object this hardened beam is more penetrating (less attenuated) and so this part of the CT image is displayed as if it was a less attenuating material. The artifact is normally corrected for by either filtering the beam at the source, or by advanced software algorithms [7]. Neither technique completely suppresses the artifact.

In clinical medicine beam-hardening artifact remains an important issue. The artifact is common around metal implants such as joint replacements, catheters, and vascular stents. Unfortunately, by the very nature of these implants, the artifact often obscures the areas of clinical concern making it difficult to confidently diagnose or exclude infections, tumors, or fractures close to implants [8,9].

3.2. K-edge imaging

Most CT studies use contrast agents such as chelated gadolinium or iodine [10–12]. These agents are used for vascular studies, tumor characterization studies, and variety of other applications. Both agents have K-edges within the diagnostic X-ray energy range, 33 and 50 keV, respectively.

The sharp edge in the attenuation profile has allowed development of dual-energy X-ray systems where two different images are acquired with different energy X-ray sources [13]. A difference image is then used to identify the contrast agent separate from background structures. That is, it would be possible to separate calcium in renal stones from iodinated contrast in the renal parenchyma. In addition K-edge imaging can be used to identify contrast agents, which have been injected with lower concentrations of iodine and gadolinium than current used. Thus, the same or better image quality could be achieved more safely and at a lower cost.

Using spectroscopic detectors (more than two energies), rather than dual sources, it is also possible to separate these contrast agents from background structures. Furthermore, with spectroscopic detectors it is possible to identify background structures, gadolinium, and iodine as three separate components. Simulations have confirmed that this is possible for both two-dimensional (2D) and three-dimensional (3D) (CT) images [14,15].

The availability of routine spectroscopic imaging will decrease patient examination time at substantially reduced radiation dose, allowing improved safety and greater productivity. This is particularly significant in multi-phase protocols where images are typically acquired before iodine contrast, immediately following injection, and 15 min after injection [11,12]. Fig. 1 contains an example of a conventional CT triple-phase renal protocol. With a MARS imaging system these three images can be obtained with a single scan. This could be achieved by giving iodine contrast intravenously 15 min before scanning, then gadolinium 30 s before scanning. The three different images could then be calculated by subtracting off the gadolinium, then iodine, then both agents without the need for additional scanning.

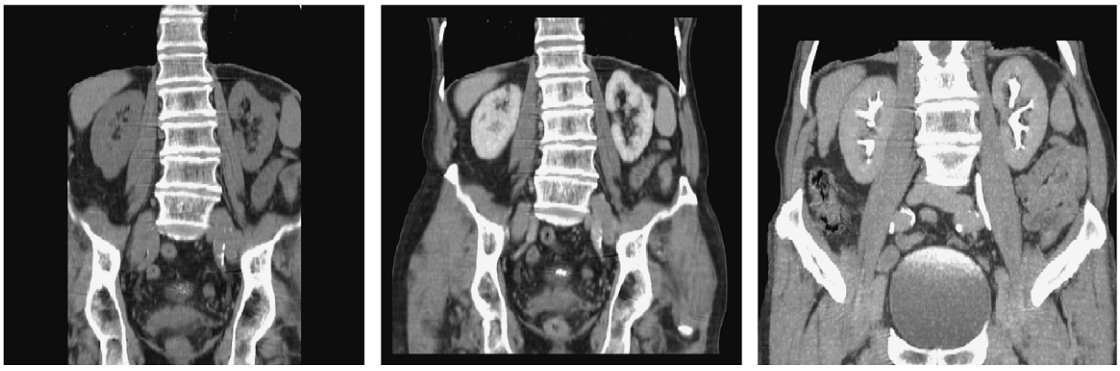

Fig. 1. A typical triple phase CT series of the kidneys. Using traditional techniques the left image is acquired before intravenous iodinated contrast is given, the middle image is acquired 30 s after administration of the contrast, and the right image 15 min later. Typically the patient goes back to the waiting room during this period and it is extremely difficult to get the patient to return to exactly the same position within the scanner. Thus a traditional scan requires three acquisitions, and two visits to the scanner. Using a spectroscopic detector with a combination of gadolinium and iodine contrast agents the three images could be obtained with a single scan, reducing the radiation dose and decreasing total imaging time.

Other advantages in using a single exposure with a spectroscopic detector, rather than dual-energy sources, include no patient movement between images, a single source of quantum (Poisson) noise, and no overlapping spectra.

3.3. Intrinsic tissue contrast

It is well known that many tissues have different attenuation profiles. Again, this is the basis of dual-energy X-ray absorption techniques such as bone densitometry and dual-energy chest radiography [11,12]. The underlying physical principle is that atoms within a mixture each have a different X-ray attenuation profile, which depends on the atom's proton number and electron configuration [16].

A short review of the literature shows there are many areas where energy information will be of clinical benefit. However, dose and other practical considerations limit routine use of dual-source systems.

To estimate the magnitude of the benefit from spectroscopic images, it is helpful to review the literature regarding mammography, an area of clinical significance and public interest. There are a number of studies that have examined the use of dual-energy systems at improving detection of cancerous and pre-cancerous lesions. Important benefits include:

- *Microcalcification detection*: Pre-malignant areas in a breast, such as ductal carcinoma in-situ, often contain micro-calcifications. These are an important feature used for mammographic screening of breast cancer. Unfortunately due to their extremely small size they can be difficult to identify. Several studies have shown that an energy-resolving system increases the ability of the radiologist to identify these microcalcifications [17].
- *Distinguishing tissues types*: Currently clinicians use morphological information to distinguish normal from abnormal tissues. For example, to distinguish fibrous tissue from malignant tissue a radiologist may use size and the presence of spicules radiating away from the lesion. However, it is known that fibrous tissue and malignant tissue have different attenuation profiles [18,19]. Clinical trials with dual-energy sources report that 62% of cancers and 81% of benign masses can be more accurately identified [20].
- Tumors retain intravenously injected iodinated contrast agents. This physiological characteristic is the basis for dual-energy contrast mammography and MRI breast imaging [11,12,21].

The spectroscopic detector with a MARS system will allow routine use of energy-resolving imaging. This is because there is no time or dose penalty to recording the energy response of the tissue, whereas dual-source systems require higher dosage, often more time in image acquisition, and they introduce movement problems between images.

4. Imaging of biological samples

In order to demonstrate that the Medipix-2 detector can produce clinical images we undertook a program of using the detector in a hospital to image human samples. Initially 2D and 3D images were obtained with the high- and low-energy thresholds as far apart as possible in order to produce images in which all energies contribute, similar to non-spectroscopic images. Subsequently 2D images were obtained where a series of different thresholds were used, producing a 2D spectroscopic image.

4.1. Two-dimensional images

Previous work has shown that the spatial resolution and contrast resolution of Medipix-2 is adequate to produce diagnostic mammography images [5,6]. However, most of this work was done with phantoms and little work has been published imaging real human breast disease.

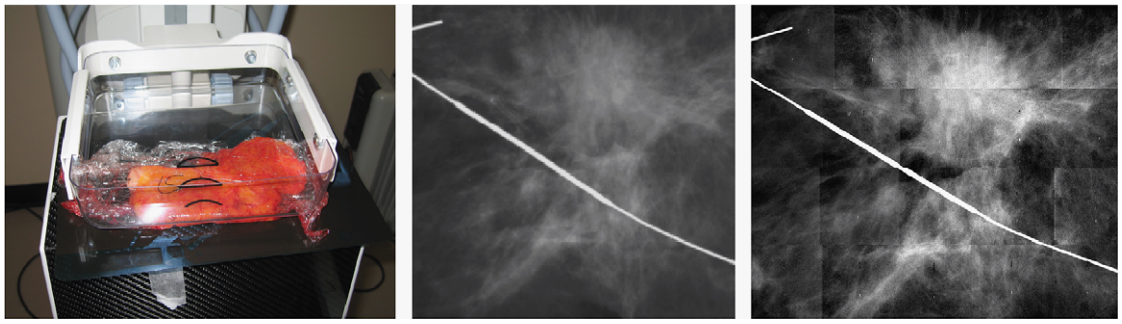

Fig. 2. The left image is a photograph of an excised breast lesion containing normal tissue and a ductal carcinoma. The middle image is a radiograph of the specimen taken using conventional mammographic film. The right radiograph is taken by tiling images from a Medipix-2 detector. In both the film and Medipix images the typical features of the cancer are clearly seen. Namely, a central density with radiating spicules. A hook-wire from the surgical procedure is seen running from the top left to the bottom right of the image.

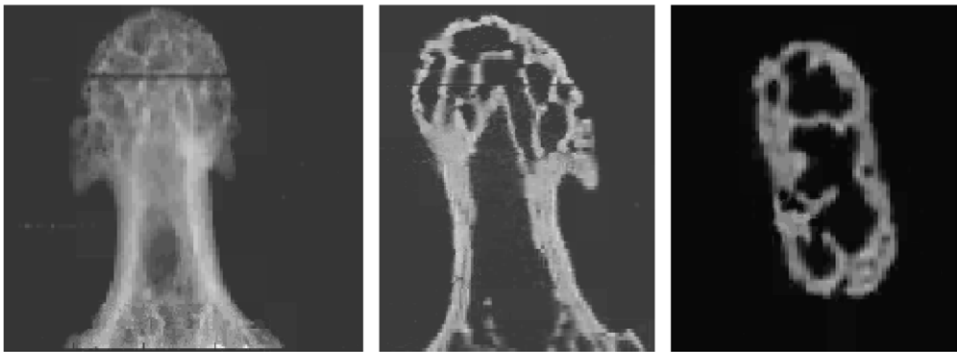

Fig. 3. Images of a 12 mm finger bone from a dried human skeleton. The left image is one of the 180 projection images used to reconstruct the volume data. The hole in the shaft is where a wire articulated the bone with the remainder of the dried skeleton. The middle and right images are sections through the reconstructed volume. Fine internal structure, such as trabeculae, is clearly visible.

We imaged a series of seven excised breast specimens using both a Medipix-2 detector and traditional mammographic film. Each specimen contained a known breast lesion, typically a cancer that had been identified during routine clinical work and then removed by a surgeon. Sub-images from the Medipix-2 detector were tiled together in software to produce a single larger image that covered the entire lesion. Each image was reviewed by a clinical radiologist to ensure that the Medipix image contained all radiologically important details that were present in the plain film image.

An example of a ductal carcinoma (sub-type NOS) is shown in Fig. 2. This work confirmed the pre-clinical studies that showed Medipix-2 produces similar image quality to mammographic film.

4.2. Three-dimensional images

Any imaging system that can produce 2D images can be adapted to produce projection images for CT. Our goal was to use a Medipix-2 detector to produce CT images of human tissue. Again, the thresholds were wide in order to produce data similar to non-spectroscopic detectors.

For the experiment, the distal phalynx from the 5th finger of a dried human skeleton was attached to the end of a stepper motor. One hundred and eighty projection images were obtained at 1° angles. The geometry was with a source-detector distance of 1 m, and the center of rotation to detector of 1 cm. This setup provided parallel beam geometry, with the maximum irradiation angle 0.3°. Reconstruction was performed using a filtered back projection algorithm. Fig. 3 shows one of the projection images and two cross-sectional images after reconstructing the projections into a volume data set.

4.3. Spectroscopic images

The final step was to image human tissues with a range of narrow energy thresholds in order to produce spectroscopic images. Using this technique images of the hand from a miscarried 20-week human fetus were obtained.

Seven energy windows were chosen, evenly spaced between 4 keV (the detector's noise floor) and 27 keV (the X-ray tube voltage). Principal components analysis (PCA) was then applied to the spectral data to identify patterns of independent variance [22]. The first three components identified and are shown in Fig. 4. Three dead columns in the detector were filled using bi-cubic interpolation.

Using this method the bone and soft tissues could be identified, despite the semi-ossified nature of early fetal bone development. This is in keeping with results from dual-source radiography where the energy information is

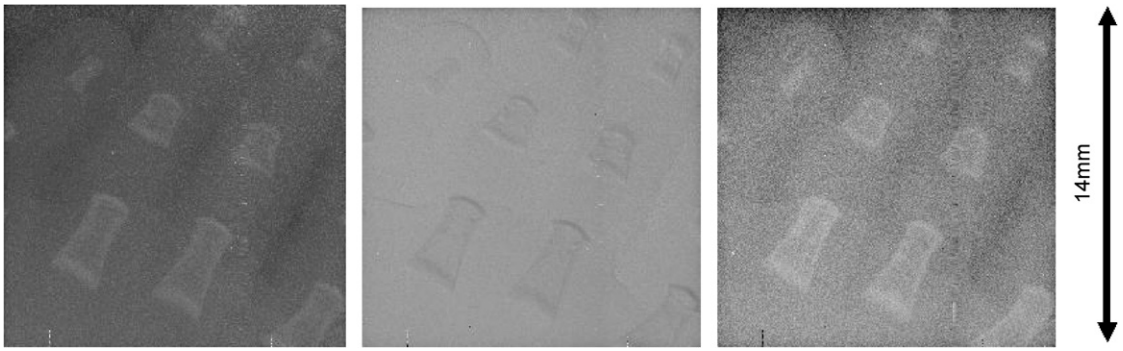

Fig. 4. A spectroscopic image of a 20 week miscarried fetus' hand. Principal components analysis was applied to identify areas in which the image changed with varying energy. In the left and middle image, it is seen that the calcified bones have a different energy response than the background soft tissue. This is most pronounced at the bone edges where the cortical layer is more calcified. A vertical line in the right $\frac{1}{3}$ of the image is the dead columns that were interpolated. The right image shows that along the dead column and top of the detector there is variation in spectroscopic performance of the detector.

used to calculate bone density [11,12]. In addition the PCA process identified a line along the dead column and the bottom of the detector in which the detector energy response varied from the rest of the detector.

5. Conclusion

The anticipated benefits from using spectroscopic pixel detectors for bio-medical imaging include reduction of image artifacts, better contrast imaging, and improved soft tissue contrast.

Initial work with the Medipix-2 detector found that is a reliable and easy to use device. Importantly it is robust enough for further clinical work. Our experiments using human tissues have confirmed other groups' work with phantoms that Medipix-2 can produce images of at least the quality of conventional radiographic films.

6. Future work

An important future development will be the availability of Medipix-3 detectors. These detectors will be able to be configured to have eight energy thresholds per pixel, thus allowing a single exposure to record eight different energy ranges.

The design of both the Medipix-2 and Medipix-3 detectors allow for materials other than silicon to be used as the sensor layer. Use of other materials, such as gallium arsenide, will give a detector with excellent quantum efficiency at the X-ray energies typically used in clinical medicine [23].

While a brief literature review has allowed identification of several pathologies where energy information is useful, it will be necessary to explore a wider range of diseases to assess the full clinical benefit of this new technology.

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