Toward human MARS scanning: improving spectral performance for soft tissue imaging

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Abstract

This thesis reports on improving the spectral performance of a MARS scanner to enhance soft tissue information within the human diagnostic energy range. The results presented in this thesis might lead to multiple clinical benefits such as tissue characterisation and monitoring the disease response to therapy non-invasively.

Clinical CT, equipped with scintillator detectors operating in energy-integrating mode, is unable to measure the spectral information of the transmitted x-ray photons. When using a polychromatic x-ray spectrum, CT data suffer from the beam hardening effects, which introduce inaccuracy in the measured x-ray attenuation values. In addition, different elements, such as calcium and iodine in an object, can have similar average x-ray attenuation values when using a polychromatic x-ray spectrum. Spectral information, acquired using a MARS scanner equipped with energy-resolving photon-counting detectors, has allowed myself and co-investigators to identify and measure the composition of tissues, and may allow demonstration of the effectiveness of the targeted drug against the diseases non-invasively.

This thesis reports on development of accurate and efficient techniques for calibrating the energy response of individual pixels of an energy-resolving detector using both x-ray fluorescence and γ-ray from a radioisotope. Several high-Z semiconductor sensors bump-bonded to either Medipix3.1 or Medipix3RX ASIC were evaluated in both Single Pixel Mode and Charge Summing Mode. This thesis also reports on development of a novel technique for calibrating the energy response of the detector using x-ray tube voltage. Similarly, the count rate capability of a CdTe-Medipix3RX using a polychromatic x-ray source was investigated.

This thesis also reports the evaluation of imaging performance of a MARS scanner. The potential of the MARS scanner in characterising the composition of ex-vivo human carotid atherosclerotic plaque was demonstrated by differentiating and visualising multiple intrinsic bio-markers including calcium, fat and water within firstly, pre-clinical small animal energy range (15 - 50 keV) and secondly, human diagnostic energy range (30 - 120 keV). Similarly, element-specific spectral x-ray imaging was performed to discriminate the K-edges of I, Gd and Au in a physical phantom simultaneously.

In conclusion, I have developed accurate and efficient techniques to characterise the energy response of detectors, and I have evaluated the imaging performance of the MARS scanner. The improvement of soft tissue information was demonstrated by characterising the composition of an ex-vivo human atherosclerotic plaque, and performing element-specific imaging of a multi-contrast phantom within the human diagnostic energy range. When translated to human imaging, this work could offer multiple clinical benefits such as in-vivo early detection of vulnerable plaque, and opens several possibilities of spectral molecular imaging.
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I thank to all MARS team members I have worked with over the past few years. Particularly, Dr. Stephen Bell for insightful discussions about all aspects of my research and his suggestions are enormous help to move forward in my research; Dr. Mike Walsh for his intellectual inputs to fix innumerable bugs within the MARS environment, fruitful discussion and some of the collaborations in research works during the course of this thesis. I would like to thank Dr. Robert Doesburg for sharing his deep insight about MARS camera and offering valuable advices. It was great fun and productive to work and collaborate with Dr. Raja Aamir, Joe Healy, Kishore Rajendran, Niels de Ruiter, Christopher Bateman, and Mahdeih Moghiseh. I can never forget Dr. Nagraj Huilgol from Mumbai, India whose inspiration and help are milestones for my progress.

Finally I would like to express my love and gratitude to my parents (Tank Nath Panta & Mahalaxmi Panta), brothers, sister, in-law family, friends who supported me during my studies, particularly Pabitra Panta and Aryana Panta, my lovely wife and newly born wonderful daughter, who showed endless patience and belief.

I am grateful to the many authors of published papers and private communications that have made this research possible.
Scientific contributions

The research reported in this thesis investigates and develops the techniques for improving spectral performance of a MARS scanner for soft tissue imaging within the human diagnostic energy range. The works reported in this thesis have contributed to a number of journals and conference publications, and presentations which are included as below.

Publications/Conference Proceedings

Lead author


This paper establishes a method for measuring the spectral response of each pixel in a spectral x-ray detector (energy-resolving photon-counting detector) using XRF and γ-ray from a radioisotope. This allows the improvement of spectral imaging performance which enhances the characterisation and quantification of tissues and contrast agents. This paper proposes a novel global energy calibration technique based on x-ray peak tube voltage (kVp) and compares its performance with existing techniques. I was involved in the development of energy calibration techniques, measurement of energy response of spectral x-ray detectors, cross-validation and interpretation of results, writing and revising the manuscript, and I was the corresponding author.


This work demonstrates the quantitative capability of spectral x-ray CT in discriminating multiple intrinsic bio-markers (such as lipid-like components, water-like components, calcium) as well as extrinsic bio-markers (AuNP) in human carotid plaque in the human diagnostic energy range of 30 keV - 120 keV. This technique can be used for quantifying the severity of inflammation in atherosclerotic plaque. I was involved in the study conception and design, co-ordination between different lab members and
Scientific contributions

faculties, formulation of scan protocols, acquisition of spectral CT data, analysis and interpretation of results, writing and submitting the abstract.


This work demonstrates the capability of spectral x-ray CT in discriminating multiple intrinsic bio-markers (such as lipid-like components, water-like components, calcium) in human carotid plaque within the human diagnostic energy range of 30 - 120 keV. This technique could be translated into human imaging for non-invasive characterisation of plaque and determination of plaque composition which has big role in determining the plaque vulnerability. Vulnerable plaque leads to cardio-vascular disease like stroke and heart attack. I was involved in study conception and design, formulation of scan protocols, acquisition of spectral CT data, analysis and interpretation of results, and writing and revising the proceeding.


This study evaluates the spectral x-ray CT performance in characterising soft tissues such as human carotid plaque and lamb-chop. It differentiates and visualises multiple intrinsic bio-markers (such as lipid-like components, water-like components, calcium) in those specimens within the diagnostic energy range of 30 keV - 120 keV. This study demonstrates the current imaging performance of the MARS scanner. I was involved in study conception and design, formulation of scan protocols, acquisition of spectral CT data, analysis and interpretation of results, preparing and submitting the abstract and delivering the talk which was received by more than 200 attendees.


This study demonstrates the feasibility of spectral imaging of multiple contrast agents with MARS-CT to discriminate their K-edges in a single scan. It demonstrates the proof of concept of simultaneous discrimination of all six different materials (gold nanoparticles (2, 4, 8 mg/ml), gadolinium (2, 4, 8 mg/ml), iodine (9, 18, 36 mg/ml), calcium chloride (140, 280 mg/ml), water and air) in a phantom within the human diagnostic energy range (27 - 118 keV). The ability to discriminate multiple K-edges simultaneously as reported in this abstract is likely to open up possibilities for new medical applications such as imaging of targeted bio-markers in atherosclerosis, cancer and metabolic syndromes. I was involved in designing the experiments, optimising
the energy thresholds for discriminating the K-edges of I, Gd and Au simultaneously, formulating the scan protocols, acquiring of spectral CT data, analysing and interpreting the results, preparing and submitting the abstract and delivering the talk.

[6] **RK. Panta**, ST. Bell, JL. Healy, R. Aamir, CJ. Bateman, D. Knight, K. Rajendran, NJA. de Ruiter, M. Moghiseh, SP. Gieseg, NG. Anderson, APH. Butler, and PH. Butler. Element-specific spectral imaging of multiple contrast agents in a single scan. This manuscript is under preparation and it is planned for submission to *European Radiology*.

This paper will establish a method to perform element-specific spectral x-ray imaging of multiple contrast agents. This methodology can be implemented to target multiple bio-markers in a disease such as atherosclerosis and cancer. I am involved in designing the experiments, optimising the energy thresholds for discriminating multiple K-edges of I, Gd and Au in a single acquisition, formulating the scan protocols, acquiring of spectral CT data, analysing and interpreting the results, preparing and submitting the article. I will be the corresponding author.


This work demonstrates the energy resolving performance of a spectral x-ray detector. We demonstrated the simultaneous discrimination of multiple K-edge features of iodine, gadolinium and gold based contrast agents. I am involved in designing the experiments, measuring the energy response of a detector, performing spectral imaging of a phantom containing various concentrations of I, Gd and Au based contrast agents in a single scan, formulating the scan protocols, analysing and interpreting the results, preparing and submitting the abstract. I am the corresponding author.

**Co-author**


This paper describes the spectral imaging of a multi-contrast phantom and gold nanoparticles in a mouse kidney using Medipix3.1. I contributed by performing detector’s energy calibration, spectral imaging, and reviewing the manuscript.

This paper optimizes the scan protocol and target elements for maximum reconstructed signal in spectral K-edge imaging. I contributed by measuring the spectral response of individual pixels in an energy-resolving photon-counting detector, and reviewing the manuscript.
Scientific contributions


This paper demonstrates the radiation dosimetry techniques for monitoring the radiation dose in a spectral CT. I contributed by assisting Noemie Ganet to provide the basic familiarity of a MARS scanner and scanning protocols, formulating the radiation dosimetry techniques for monitoring the radiation dose and reviewing the manuscript.


This paper demonstrates the high resolution visualisation and differentiation of different intrinsic bio-markers in an advanced human carotid plaque using a spectral CT. I contributed by calibrating the detector, designing the experiments, imaging the samples and analysing the data.


This paper evaluates the use of spectral x-ray CT in differentiating and visualising different tissue components in a lamb-tissue specimen. I was involved in measuring the accurate and precise energy response of the x-ray detector, data processing and interpretation, and reviewing the manuscript.


This paper discusses methods for reducing beam hardening effects and metal artefacts using spectral x-ray information in biomaterial samples. I was involved in measuring the accurate and precise energy response of the x-ray detector, interpretation of results, and reviewing the manuscript.


This poster demonstrates material discrimination using a prototype algorithm on various MARS research applications. I was involved in measuring the energy response of the x-ray detector, interpretation of results, and reviewing the poster.


This poster demonstrates material discrimination using a prototype algorithm on various MARS research applications. I was involved in measuring the energy response of the x-ray detector, interpretation of results, and reviewing the poster.
**Scientific contributions**

**Book chapter**


**Presentations († presenter)**


[2] **RK. Panta**. Multiple K-edges imaging with MARS scanner and some of its practical aspects. *MARS research group seminar, Department of Physics and Astronomy, University of Canterbury, Christchurch, New Zealand*, 10th December, 2014. (Oral)

[3] **RK. Panta**. Using spectral x-ray CT in soft tissue imaging. Delivered a talk in a Continuing Medical Education (CME) at *Department of Radiology, Christchurch School of Medicine, Christchurch, New Zealand*, 20th March, 2014. (Oral)


[8] **RK. Panta**. Calibration of energy-resolving detector (Medipix) for spectral x-ray imaging. *Biomedical Imaging Division, School of Biomedical Engineering & Sciences, Virginia Tech, Blacksburg, & Wake Forest University, Winston-Salem, USA*, 2012. (Oral)
Scientific contributions

**Student supervision**

Malte Schmidt, a bachelor’s student from South Westphalia University of Applied Sciences (Fachhochschule Sudwestfalen) from Germany, visited the MARS research group to undertake his internship for six months (2013/2014). He investigated spatial resolution using CdTe-Medipix3RX. His project report was entitled “MTF-Analysis of an X-ray Detector via Slanted Edge Method”. I was involved with his day-to-day supervision, basic familiarity with his project, designing the slanted edge phantom for his project, cross checking his results and offering advice.

**Translation of my research into practice**

Automated global energy calibration technique based on x-ray kVp is routinely used as a part of standard workflow in pre-clinical spectral imaging chain used by MARS research group. Similarly, per-pixel energy calibration technique based on x-ray fluorescence generated from metallic targets is in the process of being automated. This allows enhancement of material characterisation using the MARS scanner.

**International collaborations**

[1] *Biomedical Imaging Division, School of Biomedical Engineering & Sciences, Virginia Tech, Blacksburg, & Wake Forest University, Winston-Salem, USA*: I visited there to strengthen the ongoing partnership between two institutions. I was involved in formulating the scan protocol and K-edge imaging with spectral CT. Once I returned to my home institution, I acquired and sent spectral CT data of a phantom for reconstruction and further data analysis for joint publication.

[2] *Deutsches Elektronen Synchrotron (DESY), Hamburg, Germany*: I have been using the detector simulation toolkit ‘HORUS’ as a part of mutual collaboration between two institutions. I would like to acknowledge David Pennicard and his group for sharing ‘HORUS’.

**Award/Grant**

[1] **Rutherford Award**: I won all three Rutherford prizes at ‘MedTech in Christchurch’ workshop (2013) for best poster presentation in Clinical, Technology and Discovery categories. The poster was entitled ‘Simultaneous discrimination of multiple intrinsic bio-markers in excised atheroma with spectral molecular imaging’.

[2] **PhD travel grant**: I received this grant from University of Otago for presenting at the 4th National Conference of Association of Medical Physicists (AMPICON), November
Scientific contributions

13 - 16, 2013, Kolkata, India. I delivered a talk on ‘Implementing spectral molecular imaging (spectral CT) in soft tissue’.

[3] **PhD travel grant:** I received this grant from University of Otago to cover my expenditures partially to visit Biomedical Imaging Division, School of Biomedical Engineering & Sciences, Virginia Tech, Blacksburg, & Wake Forest University, Winston-Salem, USA, to exchange of ideas between two institutions and to present my research work. I was also involved in formulating the scan protocol and performing K-edge imaging with spectral CT.

[4] **PhD scholarship:** I was awarded a University of Otago Doctoral Scholarship to carry out my PhD research since February, 2012.
Glossary

1. ADC: Analog-to-Digital Converter. An electrical device that turns an analog value into a digital number.

2. ART: Algebraic Reconstruction Technique. A technique for CT reconstruction.

3. Atherosclerosis. A process of progressive thickening and hardening of the walls of medium-sized and large arteries as a result of fat deposits on their inner lining.

4. ASIC: Application Specific Integrated Circuit. A circuit built for a specific purpose (such as Medipix for spectral imaging).


8. CCD: Charge-Coupled Device. A common image sensor technology that measure energy-integrated x-ray signal.


11. CERN: European Organization for Nuclear Research. A European research organization whose purpose is to operate the world’s largest particle physics laboratory.

12. CCE: Charge Collection Efficiency. The ratio of the charge induced on the collecting electrode to the total free charge created by the ionizing events in semiconductor x-ray detector.

13. CMOS: Complementary Metal Oxide Semiconductor. Technology for constructing integrated circuits.


15. Contrast. The ratio of the signal difference to the average signal.
16. **CSM**: *Charge Summing Mode*. Mode of detector operation in Medipix3 that reconstructs the charge by summing split charge across adjacent pixels in $2 \times 2$ cluster.

17. **CT**: *Computed Tomography*. An imaging modality that uses x-rays to reconstruct cross sections of body.

18. **CVD**: *Cardiovascular Disease*. Cardiovascular disease refers to any disease that affects the cardiovascular system, principally cardiac disease, vascular diseases of the brain and kidney, and peripheral arterial disease.

19. **DAC**: *Digital-to-Analog Converter*. An electrical device that turns a digital number into an analog value (usually voltage, sometimes current).

20. **FDK**: *Feldkamp-Davis-Kress*. A cone beam CT reconstruction algorithm.

21. **Fluorescence/Characteristic x-rays**. A mono-energetic photon emitted from an atom when it absorbs a high energy photon.

22. **Fill Factor**. A ratio of x-ray sensitive area and total detector area.

23. **FOV**: *Field of view*. The extent of the imaging region at each moment.

24. **FPM**: *Fine Pitch Mode*. Alternative to spectroscopic mode with only 2 energy counters available.

25. **FWHM**: *Full width at half maximum*. An expression of the extent of a function, given by the difference between the two extreme values of the independent variable at which the dependent variable is equal to half of its maximum value.

26. **GaAs**: *gallium arsenide*. A semiconductor sensor material.

27. **HU**: *Hounsfield Unit*. A linear transformation of the original linear attenuation coefficient measurement into one in which the radio-density of distilled water at standard pressure and temperature (STP) is defined as zero Hounsfield units (HU), while the radio-density of air at STP is defined as -1000 HU.

28. **K-edge**. A sudden increase in the x-ray attenuation coefficient occurring at an energy just above the binding energy of the K shell electron of the atoms interacting with the photons.

29. **kVp**: *Peak kilo-Voltage*. The maximum voltage across anode and cathode of the x-ray tube. It determines the maximum kinetic energy of the electrons accelerated in the x-ray tube and the peak energy of the x-ray emission spectrum.

30. **µ**: *Linear Attenuation Coefficient*. The fraction of an incident beam of photons that is absorbed or scattered per unit thickness of the target absorber.

31. **L-edge**. A sudden increase in the x-ray attenuation coefficient occurring at an energy just above the binding energy of the L shell electron of the atoms interacting with the photons.
32. **MARS**: Medipix All Resolution System. The Medipix detector based spectral imaging system that can provide spatial, temporal and spectral resolution.


34. **Medipix3RX**. Latest Medipix3 chip, essentially Medipix3.2.

35. **MTF**: Modulation Transfer Function. A figure of merit to measure spatial resolution of an imaging system.

36. **MXR**. A revised Medipix2 chip.

37. **Quantum Efficiency**. A fraction of incident photons detected in an x-ray detector.

38. **ρ**: Density. Mass per unit volume.

39. **Si**: silicon. A semiconductor material.

40. **spectral x-ray detector**: The energy-resolving photon counting detector.

41. **spectral imaging/CT**: The capability of providing energy-resolved information with more than two different measurements simultaneously using a spectral x-ray detector.

42. **Spectroscopic Mode**: An alternative to Fine Pitch Mode in Medipix3 in which 1 pixel in 4 is bump bonded that increases the sensor pixel pitch from 55 µm to 110 µm (super pixel) while having 8 counters per pixel.

43. **SPM**: Single Pixel Mode. Alternative to Charge Summing Mode in Medipix3 in which each pixel works independently.

44. **Sinogram**. 2-D array of data containing series of angular projections.

45. **spectral CT**. The capability of providing energy resolved information with more than two different measurements using an energy-resolving photon-counting detector in a single exposure.

46. **Spectral resolution**. The ability of the x-ray detector to accurately distinguish the energy of the incoming x-ray. It is usually calculated as $\frac{\Delta E}{E}$, where $\Delta E$ is FWHM at given photon energy, E.

47. **Threshold Equalisation**. The process of making each pixel in a pixel matrix respond to energy uniformly.

48. **V_{bi}**: Built-in Voltage. A potential difference formed across the p-n junction in an equilibrium condition, without applying external electric field.

49. **Z**: Atomic Number. A measure of number of electrons (or protons) in an atom.
Chapter 1

Introduction

1.1 Objective

The main objective of this study was to investigate the potential of a spectral (multi-energy) imaging system (MARS scanner) equipped with an energy-resolving detector to enhance soft tissue information within the human diagnostic energy range. Conventional clinical CT systems use a polychromatic x-ray source, and have scintillator detectors that operate in energy-integrating mode. As such they are unable to provide spectral information. They introduce inaccuracy in the x-ray attenuation value of a reconstructed volume due to beam hardening effects. Moreover, the contribution of each photon to the signal in conventional CT is weighted by a factor proportional to the energy of the photon. The spectral information of low energy photons is lost and this results in poor soft tissue contrast.

The ability of an energy-resolving detector to measure each detected photon’s energy and assign an equal contribution to all detected photons allows better identification and differentiation of multiple components of soft tissues. This enables a multitude of improved capabilities which should lead to better understanding the pathophysiology of a disease, increasing the accuracy of diagnosis in wide range of diseases, and provide monitoring of the therapeutic efficacy non-invasively.

This thesis presents the development and establishment of an accurate method for measuring the energy response of the energy-resolving x-ray detector. The results are used to maximise the difference in x-ray attenuation between multiple soft tissue components. In this
thesis, I will also demonstrate the improvement of spectral imaging performance of a MARS scanner by (1) characterising the composition of an ex-vivo human atherosclerotic plaque within pre-clinical small animal energy range (15 - 50 keV) and human energy range (30 - 120 keV) separately, and (2) performing element-specific spectral imaging of several high-Z contrast agents in a physical phantom by discriminating their K-edges in a single exposure. When translated to human imaging, this work promises multiple clinical benefits such as in-vivo early detection of vulnerable plaque before it disrupts, thus preventing life-threatening cardio-vascular events such as stroke and myocardial infarctions, and opens several possibilities of spectral molecular imaging such as simultaneous quantification of bio-markers of a disease.

1.2 Background

1.2.1 Conventional clinical CT and its limitation

X-ray transmission Computed Tomography (CT) introduced in 1972 [Hounsfield, 1973], revolutionised clinical practice by providing high quality 3D cross sectional images in a short imaging time. Good soft tissue contrast, spatial resolution of images and high throughput have enabled CT to enter widespread clinical uses such as cancer, cardiovascular diseases, interventional procedures (eg. angiography), radiotherapy and orthopaedics. Conventional clinical CT has evolved as an indispensable and integral imaging modality in modern clinical medicine and in pre-clinical bio-medical research. Conventional CT is now very mature and it is used in most areas of clinical medicine [Kalender, 2005].

Even though conventional CT using a single energy spectrum is one of the great innovations of modern medicine, it has the following limitations:

1. The intrinsic contrast between different components of soft tissue is often insufficient: Different components of soft tissue show very poor intrinsic contrast (differential x-ray attenuation) due to their small atomic number (Z < 20). The physical density between different components of soft tissue varies between 0.9 and 1.1 g.cm$^{-3}$. The density in healthy and pathological tissues usually differs by 1% to 2% [Bjorn et al., 2012]. This
causes low differential x-ray attenuation between different components of soft tissue and results in poor intrinsic contrast.

This intrinsic poor soft tissue contrast is made worse by using scintillator x-ray detectors operating in energy-integrating mode [Taguchi and Iwanczyk, 2013]. Integrating types of x-ray detectors integrate energy fluence and lose the spectral information of individual transmitted photons. For example, in energy-integrating mode, 3 photons at 30 keV produce the same signal strength as 1 photon at 90 keV. This results in poor soft tissue contrast due to loss of spectral information of lower energy photons which carry maximum information of soft tissue contrast.

2. CT images are not tissue-type specific: In conventional CT, different tissue types can appear with similar x-ray attenuation values. For example, multiple components of an object, such as calcified atherosclerotic plaques, iodine contrast agent in blood, and bone, can have similar x-ray attenuation values which cause them to be indistinguishable from each other.

3. CT scanning is a relatively high dose procedure: With the advent of helical, fluoroscopic, and multi-slice techniques the dose per procedure has increased. The number of CT examinations has increased by an even larger percentage. CT scans accounts for about two-thirds of the radiation dose in diagnostic radiology [Mettler et al., 2000].

4. Gray-scale pixel values of CT images are not quantitative but qualitative: Conventional CT measures relative x-ray attenuation in Hounsfield Unit (HU), which is proportional to the radio-density of tissues. HU value depends not only on the density and composition of tissues but also on CT scanner design and type, and image acquisition parameters (eg. kVp, mAs and filter). Moreover, conventional CT suffers from beam hardening effects due to the polychromatic nature of the x-ray photons and introduces an inaccuracy in the x-ray attenuation values of materials.

The attenuation of the x-ray photons while passing through the object depends on the photon’s energy and this energy dependent x-ray attenuation property is unique for each element. X-ray attenuation of an element depends on its atomic number (Z). The x-ray attenuation profile of an element is its spectral signature; it contains information about the elemental composition of the scanned object.
1.2. Background

Thus, imaging a volume of multi-component tissue at sufficient number of different energies provides detailed energy information (or spectral information) to allow one tissue component to be differentiated from another. In Hounsfield’s original paper on CT, he raised the possibility that materials could be identified via two CT scans performed at different x-ray tube voltages [Hounsfield, 1973]. This technique is referred to as ‘dual energy’ CT these days.

There are three different approaches to the technical implementation of dual energy CT commercially available or under investigation. These approaches are: (1) using dual x-ray tubes operating dual tube voltage [Johnson et al., 2006]; adopted by Siemens Healthcare (Forchheim, Germany) (2) fast voltage switching between low kVp and high kVp [Wu et al., 2009]; adopted by GE Healthcare (Milwaukee, WI) and (3) using two detector layers with different x-ray response to photon energies [Thorsten et al., 2011]; adopted by Philips Medical Systems (Cleveland, OH).

There are various clinical and pre-clinical applications of dual energy CT that offer relevant additional diagnostic information or make the interpretation easier and faster. Even though dual energy CT techniques were first explored in the late 1970s and 1980s [Alvarez and Macovski, 1976, Millner et al., 1979, Clasen et al., 1983], it took until 2005 to be clinically useful as they suffered from various technical problems such as image registration between two different scans, the lack of stability of HU values, higher radiation dose burden, cost of hardware, limited spatial resolution, difficulty in post-processing and other difficulties that delayed the development in this area [Dunscombe et al., 1984].

As the number of resolvable basis functions for material decomposition is limited (usually two), dual energy CT is being used for only a few clinical applications. Moreover, the energy spectra in dual energy CT overlap significantly. This produces similar x-ray attenuation in both images. There has been much effort to invent a photon-counting spectral CT. The aim of photon-counting spectral CT equipped with an energy-resolving detector is to provide multiple distinct energy information (more than two) of a scanned object in a single exposure by measuring the energy of each photon. This enables the detection and quantification of several distinct energy signals. MARS scanner is an example of a photon-counting spectral CT.
1.2.2 Medipix based spectral imaging system: MARS scanner

The Medipix All Resolution System (MARS) group is a multi-disciplinary research group of physicists, clinicians, biochemists, mathematicians and engineers associated with the Universities of Otago and Canterbury, Christchurch, New Zealand. The MARS research project is developing an innovative spectral imaging system and testing it to advance personalised medicine. As a proof of concept, the MARS group has developed several MARS scanners which are pre-clinical spectral imaging systems. They use the Medipix based energy-resolving photon-counting detector developed by an international collaboration led by designers at the European Organisation for Nuclear Research (CERN) [Campbell et al., 1998, Llopart et al., 2001, Ballabriga et al., 2007, Ballabriga et al., 2013a].

The Medipix family of detectors are energy-resolving photon-counting detectors so they enable spectral x-ray imaging. They acquire spectral information by recording the energy of individual x-ray photons and assigning them into their respective energy ranges simultaneously. A Medipix detector comprises two parts: an Application Specific Integrated Circuit (ASIC) and a sensor. Both are flip chip bump bonded together.

The Medipix ASIC is a Complementary Metal Oxide Semiconductor (CMOS) detector readout that is designed to be connected to a segmented direct conversion semiconductor sensor. The Medipix ASIC uses small pixels (55 or 110 µm) to acquire images with excellent spatial resolution. When a photon interacts with a segmented direct-conversion semiconductor sensor, the energy of the photon is deposited by creating a charge cloud (electron-hole pairs) within a tiny volume of the sensor. Under the influence of an external electric field (the bias voltage) the electrons and holes drift towards the collection electrodes. At the same time as the charge drifts under the electric field it also diffuses isotropically. This means that while most of the charge is collected in the pixel where the initial hit took place, some charge is also collected by adjacent pixels. This process, known as charge sharing, distorts the energy spectrum measured by a single pixel.

The Medipix3 ASIC seeks to mitigate the effect of charge sharing by implementing an advanced charge summing architecture between adjacent pixels (2 × 2). The ASIC sums the charges (voltage pulse) to each pixel corner, and separately, decides which pixel should count if it is above the energy threshold. This preserves both spatial and spectral information of individual photons in an image.
1.2. Background

By performing pulse height analysis of individual charge pulses generated by incident photons in the direct-conversion material, the ASIC assigns each x-ray photon to one of several different energy ranges, registering its arrival by incrementing the counter of the corresponding energy. Reading out the counters at the end of each acquisition period reveals the number of x-ray photons arriving in each energy range during the period, allowing the derivation of a spectrum of absorbed photon energies.

Direct conversion sensor materials are characterised by the fact that the absorption of each incident x-ray photon generates a near-instantaneous electron-hole cloud which is proportional to the number and energy of photons. The common examples of room temperature high-Z direct-conversion semiconductor materials are cadmium telluride (CdTe), cadmium zinc telluride (CdZnTe or CZT) and gallium arsenide (GaAs). Si is the most widely used low-Z direct conversion semiconductor material for photon counting detectors since it is available in large sizes, is relatively low in cost and is nearly defect-free which results in high image uniformity.

However, due to its relatively low stopping power, the quantum detection efficiency of Si (in typical sensor thicknesses of several hundred microns) is poor for photons with energy greater than 30 keV. High-Z sensors are desirable within the human diagnostic energy range (30 - 120 keV) as their higher stopping power allows dose efficient imaging without compromising the image quality. Since the MARS team aims to build up a photon-counting spectral CT for human imaging, the search for suitable high-Z semiconductor sensors has become an important task alongside the development and improvement of the readout ASIC itself.

The high-Z sensors require a relatively small amount of energy to generate electron-hole pairs so that even low energy photons generate a sufficient amount of charge. This improves the statistics of photon counts, spectral resolution (energy resolution) and noise performance. Moreover, high-Z sensors such as CdTe, CZT and GaAs can be operated at room temperature, unlike some semiconductors (eg. germanium) which must be cooled to operate effectively. Room temperature operation reduces both cost and size of the detector, there is no need for a bulky cooling system.

However, some of the limitations in the material properties (such as inclusions or crystal impurities) prevent reliable imaging with the high-Z sensor. Due to small pixel size in Medipix based detectors, the probability of inclusions per pixel is reduced. This makes the Medipix chip suitable for imaging with high-Z sensors allowing for the best spectral imaging currently
possible.

My works reported in this thesis investigate the spectral imaging performance of high-Z sensors (GaAs and CdTe) based energy-resolving photon-counting detectors (Medipix based detectors) within the human diagnostic energy range.

1.3 Research overview

One key research question of this study was whether low-Z soft tissue components have sufficient distinct energy information to be measured using a high-Z sensor based energy-resolving detector within the human diagnostic energy range (30 keV - 120 keV). Unlike energy-integrating types of x-ray detectors, Medipix based energy-resolving detectors exploit the potential advantages of reduced electronic noise and the ability to discriminate the energy of detected x-ray photons, each providing the potential for improved contrast-to-noise ratio in soft tissue imaging. The other research question was whether an energy-resolving detector allows element-specific spectral imaging by discriminating the K-edges of multiple high-Z contrast agents such as iodine, gadolinium and gold. Exogenous high-Z contrast agents are used to increase the contrast-to-noise ratio of multiple components of soft tissue.

To fully exploit the advantages of the energy-resolving detectors, a thorough knowledge of many technical parameters including energy response, count rate capability, and other imaging performances of the imaging system need to be characterised and optimised. When I joined the MARS group, I found that energy calibration was crude and inaccurate. Furthermore, spectral imaging used to be performed within the pre-clinical imaging energy range (10 - 50 keV) using low-Z sensors (Si) bump bonded to either MXR or Medipix3.0 ASIC.

In the first phase of my research, I aimed to develop a reliable and accurate method to measure the energy response of individual pixels in Medipix based energy-resolving detectors. This allows imaging of an object within an intended energy range to maximise the differential x-ray attenuation (contrast) of multiple components in an object. Choice of energy width is important in spectral imaging which is constrained by the energy (spectral) information, quantum signal-to-noise ratio (SNR) and spectral resolution of the x-ray detector. Moreover, the ability to accurately select the energy thresholds allows element-specific spectral imaging by exploiting the K-edge feature of an element.
1.4 Thesis organisation

In the second phase, I aimed to optimise the count rate capability of an energy-resolving photon-counting detector to maximise the signal-to-noise ratio (or number of photons) and reduce the image acquisition time, and yet to avoid the saturation of the detector at high x-ray flux.

In the third phase of my research, I aimed to evaluate the overall performance of the MARS scanner. As the MARS group is now funded to develop photon-counting spectral CT for human imaging, my final aim was to study the imaging performance of a MARS scanner for soft tissues within the human diagnostic energy range using high-Z sensor (including GaAs and CdTe) bump-bonded to both Medipix3.1 or Medipix3RX ASIC. As an illustrative example of soft tissue, I used an excised human carotid atherosclerotic plaque for characterising and determining its composition. Similarly, element-specific spectral imaging was performed by discriminating the K-edges of several high-Z contrast agents iodine, gadolinium and gold in a physical phantom.

1.4 Thesis organisation

This thesis is organised as follows: Chapter 1 introduces the objective of the research work and rationale for using spectral x-ray imaging in soft tissue. Chapter 2 reviews the physical basis of photon-counting spectral (multi-energy) CT, material decomposition, potential benefits of spectral CT in soft tissue imaging and finally provide an overview of hybrid pixel detectors with special focus on Medipix based hybrid pixel detectors.

Chapter 3 reports on the development of a new energy calibration method based on x-ray tube voltage to measure the global (pixel matrix or chip) energy response of an energy-resolving detector (eg. CdTe-Medipix3RX) and cross-validates its accuracy by comparing with an existing energy calibration technique based on x-ray fluorescence and γ-ray from a radioisotope.

Chapter 4 reports on measuring the energy response of individual pixels in an energy-resolving detector using x-ray fluorescence and γ-ray from a radioisotope. This chapter also reports the variation of energy response (gain variation) and spectral resolution across the pixel matrix of a CdTe-Medipix3RX operated in Charge Summing Mode.

Chapter 5 describes the count rate capability of an energy-resolving detector in different
modes (Single Pixel Mode and Charge Summing Mode) of detector operation and it also investigates the effect of ‘Ikrum’ Digital-to-Analog Converter (DAC) and applied bias voltage on count rate capability of the detector.

Chapter 6 presents the overall imaging performance of the MARS scanner including the temporal stability of the x-ray source, operational characteristics of tube current and tube voltage, spatial resolution, noise performance, spectral resolution, linearity of the detector, contrast-to-noise-ratio of the contrast agent; it also investigates the effectiveness of flat field correction in reducing the residual inter-pixel variation of counts.

Chapter 7 presents the potential of the MARS scanner to characterise the composition of an atherosclerotic plaque firstly within the pre-clinical small animal imaging energy range (15 - 50 keV), then secondly within the human diagnostic energy range (30 - 120 keV). Similarly, Chapter 8 demonstrates the element-specific spectral imaging of multi-contrast agents (I, Gd and Au) in a physical phantom using a MARS scanner.

Chapter 9 confirms the potential of spectral x-ray imaging using MARS scanner to enhance soft tissue spectral imaging performance and opens several possibilities of spectral molecular imaging to investigate underlying cellular or molecular processes non-invasively. The existing limitations of the energy-resolving photon-counting detector are highlighted, and finally proposals are made about how spectral imaging should evolve to cope with the unmet needs of human imaging.
Chapter 2

Photon-counting spectral CT

2.1 Introduction

In this chapter, I will review the physical basis of photon-counting spectral (multi-energy) CT, material decomposition, potential benefits of spectral CT in soft tissue imaging and finally provide an overview of hybrid pixel detectors with special focus on Medipix based hybrid pixel detectors.

While conventional CT is an indispensable clinical tool, researchers are pursuing innovations to access more diagnostic information of a scanned object. Potential clinical benefits of using energy information in diagnosis have sparked renewed interest in the invention of spectral CT using energy-resolving photon-counting detectors. By measuring the energy of individual x-ray photons with energy-resolving photon-counting detectors, spectral CT will be able to identify and characterise chemical elements within the human body non-invasively. This could allow targeted contrast agents to reveal functional as well as structural information within the body. Maturation of spectral CT technology could allow investigators to exploit the ubiquity and cost-effectiveness of CT scanners in the diagnosis of a much wider range of diseases.
2.2 Physical basis of spectral CT

Figure 2.1(a) shows the relative contributions of each of the interaction mechanisms to the total attenuation coefficient for iodine, a common contrast agent used in x-ray CT. The total attenuation coefficient of iodine is compared to some other common contrast agents and soft tissue in Figure 2.1(b).

It can be seen in Figure 2.1(b) that the x-ray attenuation profile for each material is unique and the measurement of the attenuation properties of a tissue comprising these components may yield information about the partial densities of each component. Figure 2.1(b) shows an abrupt discontinuity in the attenuation coefficient of each contrast agent (I, Ba, Gd & Au) which is called the K-edge. The K-edge energy is specific to the element. K-edge imaging in spectral CT utilises the presence of a K-edge to specifically identify high-Z contrast materials such as iodine, gadolinium or gold. Spectral CT aims to exploit the unique x-ray attenuation profile of materials to distinguish them with high sensitivity and specificity. In this way, non-invasive tissue characterisation and identification of bio-markers of diseases becomes possible.

However, the ability to identify and quantify the material components will depend upon the energy range and spectral resolution of the detector. Where the mass attenuation coefficient profiles for two given components are parallel, their partial densities cannot be determined from attenuation data if both materials are present, as each component profile is arithmetically related. Thus, over the human diagnostic energy range (30 - 120 keV), iodine, barium, gadolinium, gold and soft tissue are distinguishable by their measured mass attenuation coefficient. However, if a limited energy range is used, or data is measured with the spectral detector having poor intrinsic spectral resolution (energy resolution), then the quality of material decomposition will be heavily compromised.
Figure 2.1: (a) A logarithmic plot of photon interaction cross section for iodine, a common contrast agent in medical imaging. The photo-electric effect is dominant in the low energy x-ray region. Compton scattering is dominant in the mid-energy region. Pair production is not significant below a few MeV (b) A logarithmic plot of the total attenuation coefficients for soft tissue (International Commission on Radiation Units and Measurements (ICRU)), iodine, barium, gadolinium, and gold. The cross sections converge in the region where the Compton effect dominates, and diverge in the regions where photo-electric and pair production dominate.
2.3 Material decomposition

The fundamental principle of using spectral CT is that different materials have different x-ray attenuation coefficients when using a sufficiently narrow energy range. In spectral CT images, different materials may be represented with either different or similar attenuation values depending on physical characteristics (e.g. density, thickness, atomic number and electron density) and energy of photons. For a compound or mixture with two or more constituent elements, the mass attenuation coefficient is the sum of weighted mass attenuation coefficients of each constituent.

Material decomposition aims to transform spectral CT images into material representation based on energy information. Broadly, material decomposition (MD) methods are based on functions describing either physical interaction mechanisms or material properties. MD based on physical interaction mechanisms such as photo-electric effect or Compton effect determines the mass fraction of the compound or mixture of interest directly, as well as the effective atomic number ($Z$) and density ($\rho$). MD based on the material properties determines only the effective atomic number ($Z$) and density ($\rho$). So, MD based on physical interaction mechanisms is more practical clinically [Liu et al., 2009]. However, both methods are fundamentally equivalent as demonstrated by Lehmann et al. [Lehmann et al., 1981].

Alternatively, instead of decomposing the mixture or compound of interest into individual physical interaction mechanisms, the mixture or compound of interest can be decomposed based on the function describing material properties such as effective atomic number and mass density of materials by modeling the photo-electric effect and Compton effect [Liu et al., 2009]. Depending on how the x-ray spectral information is extracted, MD approaches for material characterisation can be classified broadly into projection-based (pre-reconstruction) methods, image based methods (post-reconstruction) and simultaneous material decomposition with CT image reconstruction. Projection-based MD pre-processes the projection data to extract energy independent information before the reconstruction, while image-based MD utilises the energy information based on separately-reconstructed images in each energy range. Simultaneous material decomposition with CT image reconstruction directly reconstructs material basis coefficients.

The advantage of implementing MD in pre-reconstruction space is that beam hardening effects can be accounted for in the raw data. This is because, already having determined the
mass density of each basis material at each point in the image, the attenuation coefficient is
calculated using only the attenuation coefficients of the multiple basis materials at the desired
photon energy and therefore can lead to improvements in quantitative accuracy. But MD
performed in pre-reconstruction space does not take account of x-ray scattering. The advan-
tage of MD performed on post-reconstruction data is that it is fast, easy, and computationally
less intensive to implement. An advantage of directly reconstructing material basis coeffi-
cients is that they are invariant for every measurement (ignoring object motion), unlike linear
attenuation coefficients which have a functional relationship with x-ray energy [Bateman,
2014].

Alvarez and Mackovski’s spectral basis material decomposition [Alvarez and Macov-
ski, 1976] and Lehmann and Kalender’s material basis decomposition [Lehmann et al.,
1981, Kalender et al., 1986] were implemented in pre-reconstruction space. Heismann
et al. implemented their spectral basis decomposition in post-reconstruction space [Heismann
et al., 2003]. Unfortunately, none of these methods consider the K-edge discontinuity in
photo-electric absorption.

In 2008, Schlomka et al. successfully demonstrated the MD of photo-electric, Compton
and iodine component images using a micro CT system incorporating a commercially avail-
able energy discriminating CdTe line array detector [Schlomka et al., 2008]. In another study,
Firsching et al. completely replaced the photo-electric and Compton components in favour of
a set of material specific basis functions [Firsching et al., 2008]. Both of these methods are
applied in the projection space and require a detailed detector response function that is diffi-
cult to measure accurately. Both of these techniques were implemented in pre-reconstruction
space. Schioppa et al implemented simultaneous material decomposition with CT image
reconstruction [Schioppa, 2014].

Recently, least square based MD algorithms have been tested using a constraint, such as
volume conservation [Yu et al., 2009, Ronaldson et al., 2012] or mass conservation [Liu et al.,
2009] or both [Mendonca et al., 2014]. Volume (or mass) conservation assumes the sum of
the volumes (or masses) of individual constituent materials is equivalent to the volume (mass)
of the mixture or compound of interest. These methods first measure the spectral response
of a phantom containing known materials and perform spectral calibration of pixel values
to the known materials. Then they match the spectral calibration against the measured pixel
values of the unknown material using a least squares approach. The disadvantage of these
2.4. Soft tissue imaging using spectral CT

methods is that they need a priori knowledge of the materials to be decomposed for spectral calibration. Ronaldson et al has implemented this method only in low-Z materials like water and lipid [Ronaldson et al., 2012].

Statistical methods such as Principle Component Analysis (PCA) or statistical image reconstruction [Long and Fessler, 2014], requiring no priori knowledge, may also be used for MD. These methods do not need to model the detector response function and they analyse multi-dimensional data directly for significant patterns or correlations. PCA has been successfully applied to spectral data acquired using the Medipix detector [Butzer et al., 2008, Butler et al., 2009]. The method assumes that the spectral data is linear with reference to some unknown basis functions. PCA then determines the most significant subset of these directly from the measurement data. As a consequence, PCA and other statistical methods may be used to classify structures within an image by considering the spectral properties of materials, but statistical methods cannot identify specific materials nor determine their concentrations or mass fraction.

![Figure 2.2: A logarithmic plot of x-ray attenuation for different human tissues (soft tissues and bone) as a function of x-ray energy. It illustrates that x-ray attenuation difference between different tissues is maximal at the lower energy end.](image)
2.4 Soft tissue imaging using spectral CT

In conventional CT using energy integrating detectors, the contribution of each photon to the signal is weighted in proportion to the energy of photon. However, spectral CT using photon-counting detector assigns the same weighting factor (1) to all detected photons. This means that when the photon-counting detector is used, true spectral information of each photon beam is adequately registered. Therefore, the energy integrating detector underestimates the contribution of the lower energy photons to the signal as compared to the photon-counting detector. However, lower energy photons carry the important diagnostic information of soft tissues.

The significance of lower energy photons in providing soft tissue contrast is demonstrated in Figure 2.2. It shows that within the human diagnostic energy range, maximum differential x-ray attenuation (which controls the contrast) between different soft tissue types is achieved at the lower energy end of the spectrum. Spectral CT using photon-counting detectors utilises the information from these lower photons to measure the subtle difference in intrinsic x-ray attenuation and enhance the soft tissue contrast information compared to conventional CT. The other advantage of using photon-counting detectors in soft tissue imaging is that the energy threshold can be selected just above the electronic noise and thus increases the contrast-to-noise ratio, and improves the soft tissue contrast.

The intrinsic contrast of soft tissue can be enhanced (amplified) by introducing an exogenous high-Z contrast agent which increases the x-ray attenuation coefficient of a voxel. If the measured energy range is sufficiently small, the K-edge feature of the contrast agent can be discriminated as the K-edge is element-specific.

The MARS research team has identified several preclinical research projects for which spectral CT may offer promising outcomes. Among them, soft tissue imaging such as atherosclerosis imaging and K-edge imaging within the human diagnostic energy range are at the forefront. The ability to perform spectral molecular imaging in atherosclerosis would allow characterisation of the composition of an atherosclerotic plaque and monitoring of its treatment. This would enable a multitude of improved capabilities and new applications such as depicting functional characteristics of formation and progression of atherosclerotic processes. The research reported in this thesis utilises not only intrinsic differences in attenuation between various soft tissue components in a human atherosclerotic plaque but also involves the
use of multiple exogenous contrast agents to perform element-specific spectral imaging by discriminating their K-edges in a single scan.

**Potential of spectral CT in atherosclerosis and K-edge imaging**

Atherosclerosis is a chronic inflammatory disease of an artery [Libby, 2002]. The prevalence of atherosclerosis is increasing, owing to the ageing population, the improved survival of patients with atherosclerotic cardiovascular disease and, above all, the widespread under-recognition and under-treatment of individuals with risk factors for atherosclerosis [Libby, 2002, Sanz and Fayad, 2008]. Atherosclerosis involves thickening of the arterial wall to form a plaque, a process in which cholesterol deposition, inflammation, extracellular-matrix formation and thrombosis play major roles. Investigations in atherosclerosis pathology have led to characterisation of two main types of atherosclerotic plaque or lesion: stable plaque and unstable plaque.

Stable plaque is characterised by the presence of a thick fibrous cap, a modest lipid core, and few inflammatory cells. Unstable plaque, which is more dangerous, is characterised by a thin fibrous cap, low collagen content, large lipid core, many inflammatory cells, and angiogenesis [Finn et al., 2010]. Symptoms in atherosclerosis occur late in the course of disease and are usually caused by sudden rupture of an unstable atherosclerotic plaque. The resultant decrease in blood supply can affect almost any organ, although myocardial infarction, stroke and peripheral vascular diseases are the most common and severe consequences.

The major goal of atherosclerosis imaging is to detect, treat and monitor vulnerable plaque to prevent strokes and cardiac events which are caused by acute thrombotic or embolic events occurring after rupture of the fibrous cap [Cormode et al., 2010, Falk et al., 2011]. In order to influence clinical outcome, imaging needs to determine the composition of the plaque rather than plaque burden or luminal stenosis [Zhao et al., 2011]. Current imaging modalities align treatment to disease burden (narrowing or stenosis of the vessel by atheroma plaque, often inactive), whereas most strokes and myocardial infarcts are related to the composition of the plaque [Davies and Thomas, 1985]. If a patient presents with a transient ischemic attack, current imaging methods are used to measure plaque size in the carotid artery and this blunt tool is used to decide if the patient requires endarterectomy or medical management.
With the advancement of imaging technology, not only has the ability to image anatomy and physiology on a macroscopic scale improved, it has also become increasingly possible to detect biological phenomena at the cellular or molecular level. Spectral CT has the potential to identify tissue-type and quantify disease activity in individual plaques at cellular level. This could be achieved by identifying intrinsic bio-markers of the disease and using them as imaging targets. Potential imaging targets within the plaque include haemorrhage, activated platelets, inflammatory cells (monocytes/macrophages), cytokines and oxLDL, amongst others [Baturin et al., 2012, Saam et al., 2007, Canet-Soulas and Letourneur, 2007]. Spectral CT, by processing the individual photons of given energy, can measure the intrinsic attenuation difference between various soft tissue components such as water-like and lipid-like components. Higher amounts of lipid component make plaque vulnerable to rupture [Falk et al., 2011].

High-Z material based exogenous contrast agent (such as gold nano-particles) can be introduced to tag particular bio-markers of an atherosclerotic plaque. K-edge imaging of nanoparticles has emerged as a very promising method for imaging bio-markers in-situ [Roessl and Proksa, 2007, Anderson et al., 2010, Wang et al., 2011, Baturin et al., 2012, Anderson and Butler, 2014], because of its high specificity, excellent spatial resolution and ability to image multiple bio-markers simultaneously. Spectral CT along with targeted high-Z contrast agent makes spectral molecular CT feasible [Cormode et al., 2010].

Most K-edge imaging involves relatively high energy x-ray photons and consequently requires high-Z detector materials such as CdTe, CZT and GaAs. The research reported in this thesis uses GaAs and CdTe sensor material for spectral imaging within the human diagnostic energy range, so that the results can be translated to clinical use in future.

In atherosclerosis, spectral molecular CT (spectral CT integrated with functionalised targeted nano-particles) can characterise the disease activity, such as endothelial dysfunction, plaque inflammation, platelet activation and neo-vascularization, which are important factors to determine the progression and complications of the human atherosclerotic plaque [Eraso et al., 2011]. This imaging capability could lead to a personalised treatment of atherosclerosis by enabling novel non-invasive strategies for individualized risk assessment, and facilitate monitoring the efficacy of targeted therapies, in order to reduce the risk of death and disability from atherosclerosis.
2.5 Hybrid pixel detectors

The hybrid pixel detectors in spectral CT are energy-resolving photon-counting detectors which are used to measure the energy of each individual transmitted photons. The hybrid pixel detector consists of a direct conversion semiconductor sensor to detect the radiation and frontend readout electronics to transform the charge into a digitisable signal. The two parts are distinct and can therefore be partially optimized separately, depending on the application. This is the major advantage of the hybrid detector. Both the sensor and readout electronics are segmented into many small units which are referred to as detector elements (pixels). Each pixel (on both the sensor and readout electronics) has an electrode to which the bump bond forms an electrical connection. The segmented sensor is electrically connected to the readout electronics.

The semiconductor material of the sensor can be chosen independently from the ASIC. Different types of semiconductor material such as Si, GaAs, CdTe, CdZnTe can be used as sensor materials. Modern deep sub-micron technologies offer the opportunity to achieve high functional density, thereby permitting complex photon processing to be realised within small pixel areas [Wong, 2012].

The hybrid pixel detector with small pixel pitch provides excellent spatial resolution. Semiconductor crystals may be arranged as single-sided (1D) strips or two-dimensional pixel arrays (2D) [Sellin, 2003]. Strip detectors may integrate only the analog electronics directly within the readout circuitry whereas hybrid pixel detectors include both the analog and digital processing in the readout ASIC. Another major advantage of using a hybrid pixel detector is that the fill factor of the detector is almost 100%, since there are no electronic circuit components occupying the radiation sensitive area. Another advantage of using hybrid technology is that by omitting a proportion of the bump bonds it is possible to assemble a detector with pixels that are a multiple of the standard pixel pitch in size, so called super pixels.

2.5.1 Sensors

Sensors are characterised by the fact that the absorption of each incident x-ray photon generates a near-instantaneous electron-hole cloud that is proportional to the photon’s energy. A reversed biased p-n junction semiconductor diode functions as a sensor in a hybrid pixel
Chapter 2. Photon-counting spectral CT

detector. If an external electric field with the same polarity as the built-in potential ($V_{bi}$) is applied to electrodes at the two surfaces, then the augmented electric field creates the depletion region across the sensor volume. Some basic criteria should be fulfilled to use crystalline semiconductor material as a sensor material in a hybrid pixel detector.

The thickness, atomic number and density of the sensor determine the quantum detection efficiency. Within the human diagnostic energy range, high-Z sensor materials (such as GaAs, CdTe, CdZnTe etc) yield better quantum detection efficiency compared to low-Z sensor materials such as Si. The wide band gaps of these compound semiconductors mean that they have high resistivity (> $10^9$ Ω cm) and are capable of room temperature operation, removing the need for cooling systems [Veale et al., 2014]. It has been shown in Figure 2.3(b) that the quantum efficiency can be enhanced by using thicker sensor materials.

The search for higher stopping power and quantum efficiency in the human diagnostic energy range (30 - 120 keV) has led to study of high-Z compound semiconductor materials such as GaAs, CdTe, and CdZnTe. All of these materials have already been incorporated into hybrid pixel detectors. However, it is difficult to manufacture a large-area sensor and yet maintain adequate charge collection efficiency. These sensors need further development to increase the wafer size, to reduce the charge loss due to trapping and recombination, and minimise the charge sharing between neighbouring pixels [Sellin, 2003]. The life-time mobility product of a hole is much smaller than that of an electron (10$^{-4}$ cm$^2$/V vs 10$^{-3}$ cm$^2$/V) in CdTe. Furthermore, the life-time of holes in CdTe or CZT is low due to charge trapping and holes may recombine with the defects before they are collected.

The ability of an x-ray detection system to resolve energies depends greatly on the probability and mechanism of x-ray interaction between the incident photon and the sensor material. Linear attenuation coefficient, $\mu$, is the probability that a photon interacts with the sensor materials per unit thickness by photo-electric absorption and Compton scattering.

X-ray interaction with the sensor generates the charge clouds which move to their respective contact electrodes. The mobility of the charge carriers (electrons and holes) induces electrical charges in the electrodes which are the transmitted via the bump bond to the low impedance input of the associated pixel in the readout electronics. The amplifier is usually charge-sensitive and integrates the signal current [Wong, 2012].
2.5. Hybrid pixel detectors

Figure 2.3: (a) Quantum detection efficiency for common semiconductor materials as a function of photon energy. Quantum detection efficiency decreases exponentially with photon energy. Similarly, quantum efficiency is higher for higher atomic number materials. (b) Quantum detection efficiency for CdTe as function of sensor thickness at various photon energies. Quantum detection efficiency increases exponentially with thickness for a given photon energy.

**Quantum detection efficiency**

Typically the operation of a semiconductor as an x-ray detector is based on collection of the charge carrier (either electrons or holes), generated by photon interactions, through the application of an external applied electric field. When an x-ray or γ-ray photon undergoes photo-electric absorption or Compton scattering in the semiconductor material, clouds of electron-hole pairs are created. Figure 2.3(a) shows the quantum efficiency for various semiconductor materials at 2 mm thickness (the thickness of CdTe that I have used for my research works) as a function of photon energy. The semiconductors with higher Z and physical density have higher quantum efficiencies due to higher probability of photo-electric absorption. 2 mm of CdTe thickness is characterised by ≈ 87 % of quantum efficiency for 100 keV photon energy as shown in Figure 2.3(b). Figure 2.3(b) illustrates that the quantum efficiency of CdTe increases exponentially with the sensor thickness.

These calculated quantum detection efficiencies as reported in Figures 2.3(a) and 2.3(b), however, assume that x-ray or γ-ray photons deposit all their energies in the detector volume and that we can collect all electron-hole pairs generated in the detector. The calculation of
quantum detection efficiencies is based on NIST database [Berger et al., 2010]. It has been pointed out that the considerable amount of charge loss in CdTe and CdZnTe used to limit their capability as high resolution spectrometers [Siffert, 1994]. This problem is raised due to the poor charge transport properties, especially for holes, charge trapping, recombination and material defects in the crystals. Incomplete charge collection could limit the thickness and, thus, the volume of detectors which in turn limits the usefulness of the detector.

Spectral resolution of x-ray semiconductor detector

One major advantage of using a semiconductor detector over a gas-filled detector is that the ionisation energy in a semiconductor is much lower that in a gas-filled detector (3 eV vs 30 eV). Ten times more charge carriers are generated in a semiconductor than in a gas-filled detector. This has two beneficial consequences on the attainable spectral resolution of the detector. The statistical fluctuation in the number of carriers per pulse becomes a smaller fraction of the total as the number is increased. This factor often is predominant in determining the limiting energy resolution of a detector for medium to high radiation energy. At low energies, the spectral resolution may be limited by electronic noise in the preamplifier, and the greater amount of charge per pulse leads to a better signal-to-noise ratio [Knoll, 2000].

Spectral measurement of a semiconductor x-ray detector is based on registration of the total number of electron-hole pairs produced by a single x-ray photon after a cascade of various processes. These include Compton scattering events, photo-electric absorption, deep core level excitation, core vacancy relaxation, emission of plasmons by the secondary electrons (holes), plasmon decay into electron-hole (e-h) pairs and impact ionizations. At each stage the cascade is accompanied by sequential energy branching between secondary particles, which results in almost random energy distribution in a cloud of secondary electrons and holes in the final state. The branching is terminated when the energy of a secondary electron or hole is below the impact ionization threshold. Due to the almost random nature of the cascade energy branching, the pair number, N, fluctuates from one event to the other. Therefore, the theoretical limit for the x-ray detector spectral resolution depends on the variance of the registered energy, E.

The observed statistical fluctuations in semiconductors are smaller than expected if the formation of the charge carriers were a Poisson process. The Poisson model would hold if all
events along the track of the ionizing particle were independent and would predict that the variance in the total number of electron-hole pairs should be equal to the total pair number, N, produced, or E/ε. The Fano factor, F, is introduced as an adjustment factor to relate the observed variance to the Poisson predicted variance as below:

\[
F \text{ano factor (F)} \equiv \frac{\text{Observed statistical variance}}{E/\epsilon}
\]  

(2.1)

For good spectral resolution, one would like the Fano factor to be as small as possible. For CdTe and Si, the fano factor is smaller than unity (≈ 0.1).

**Charge sharing**

When photon energy is absorbed by the sensor, electron-hole pairs are generated which form a three-dimensional charge cloud in the pixel volume. Ideally, the charge cloud is contained within the pixel and an external applied electric field collects all the charge carriers directly to its electrode. However, charge sharing may occur when the charge cloud is collected across several adjacent pixels.

When electrons and holes drift towards the positive and negative electrodes under the influence of an external electric field, they also undergo diffusion laterally. Without diffusion, all charge carriers would travel to the collecting electrodes following exactly the electric field lines that connect their point of origin to their collection point. The effect of diffusion introduces some spread in the arrival position of charge carriers that can be characterised as a Gaussian distribution whose standard deviation as given by following relationship [Spieler and Haller, 1985]:

\[
\sigma_x = \sqrt{D t} = \sqrt{\frac{2kT_x}{eE}}
\]  

(2.2)

where D is the diffusion coefficient for hole or electron, t is the respective drift time, K is the Boltzman constant, T is the temperature in K, e is the electric charge of an electron, x
is the drift distance, and $E$ is the electric field strength. Equation 2.2 assumes that the electric field strength is uniform across the sensor thickness. This diffusion of the charge limits the precision to which position measurements can be made using the location at which charges are collected at the electrodes in semiconductor detectors. The width of the distribution after drifting for a given distance is the same for electrons and holes and is, in fact, the same for any material.

Figure 2.4(a) illustrates the cross section of a typical pixel detector. Each dash of the electrode segments at the bottom represents different pixels. As a photon traverses the sensor, a charge cloud of electrons or holes is formed around the track. The lateral spread (diffusion) of charge cloud can be calculated using equation 2.2. Figure 2.4(b) shows the lateral spread of a charge cloud as a function of drift distance for 2 mm thick sensor (this is the thickness I have used for this thesis work) at different bias voltages (100 - 900 V). It is assumed that the electric field strength is uniform across the sensor thickness. The diameter of the charge cloud increases with the thickness of sensor and applied external electric field strength but it is independent of material properties such as mobility of charge carriers.

The physical phenomena that may cause charge sharing in a pixel detector are listed below:

1. lateral diffusion of charge carriers even in the presence of an external electric field
2. photo-electron crossing the pixel volume
3. generation of x-ray fluorescence (XRF) from the high-Z sensor itself and crossing the pixel volume

Charge sharing not only degrades the spatial information, but it also degrades the spectral information in the original pixel as well as in adjacent pixels. In pixel detectors, the severity of charge sharing increases with decreasing the ratio of pixel pitch over sensor thickness. The probability of charge sharing increases in high-Z sensor materials whose XRF photons have a mean free path length comparable to the pixel pitch. The significance of this effect depends on the sensor material (which governs the mobility of the charge carriers), the pixel size, the applied bias voltage, and the depth of interaction in the sensor [Myronakis and Darambara, 2010].
2.5. Hybrid pixel detectors

![Diagram of particle track and drift](image)

Figure 2.4: (a) Illustration of lateral diffusion ($\sigma_x$) of charge carriers in the sensor during charge collection. The Gaussian spread is shown for just one type of charge carrier [Spieler and Haller, 1985]. (b) Lateral diffusion of the charge cloud as a function of drift distance for 2 mm thick sensor layer at different bias voltages (100 - 900 V). The lower the applied bias voltage, the higher the lateral diffusion of charge cloud. It is assumed that the electric field strength is uniform across the sensor thickness.

2.5.2 ASIC

Modern deep sub-micron Complementary Metal Oxide Semiconductor (CMOS) technology offers the opportunity to achieve high functional density, thereby permitting complex photon processing, such as photon-counting. In a photon-counting detector, it is the Application Specific Integrated Circuit (ASIC) which allows the photon to be counted. ASIC is a sophisticated electronic chip designed for specific tasks. The ASIC component of a hybrid pixel detector forms the readout chip as it provides the means to acquire an amplified electrical signal from the sensor. Modern hybrid pixel detectors however, perform many complex processing functions in addition to readout capability [Wong, 2012].

Several energy-resolving proprietary photon-counting ASICs have been designed to meet the high count rate requirements of spectral CT while offering energy discrimination. There are a number of ASICs in development which aim to count the number of photons of the transmitted x-ray spectrum. Some examples of ASIC are: DXMCT-1 [Iwanczyk et al., 2009],
Barber et al., 2009] and DXMCT-2 [Barber et al., 2012], Siemens 2010 [Kappler et al., 2010, Kappler et al., 2012], ChromAIX [Steadman et al., 2011], Hamamatsu [Tomita et al., 2004], GMI CA3 [Schlomka et al., 2008, Feuerlein et al., 2008], Pilatus [Henrich et al., 2009], XPAD [Delpierre et al., 2007], CIX [Kraft et al., 2007], Nexis Detector [Cajipe et al., 2004, Rupcich and Gilat-Schmidt, 2013], MicroDose SI (Silicon strip) [Fredenberg et al., 2010a, Fredenberg et al., 2010b], KTH Silicon strip [Xu et al., 2011] and Medipix [Campbell et al., 1998, Llopart et al., 2001, Ballabriga et al., 2007, Ballabriga et al., 2013a]. The pixel pitch in those ASICs varies from 50 - 1000 µm, and the number of available energy thresholds range from 2 to 8. Each ASIC was typically developed with a specific application in mind. The Medipix ASIC has a small pixel pitch (55 - 110 µm) and provides higher spatial resolution with spectral information than other ASICs, suited for imaging of small animals in preclinical applications. The experiments reported in this thesis were carried out using Medipix ASIC which is described below.

**Medipix2**

Following the successful demonstration of Medipix1 [Campbell et al., 1998] as a prototype photon-counting pixel detector in x-ray imaging applications, the Medpix2 collaboration at CERN was formed to develop a new ASIC with many more and much smaller pixels. The first Medipix2 ASIC [Llopart et al., 2001] was designed in 2000 for a 0.25 µm standard CMOS process, with 256 × 256 square pixels originally targeted to occupy an area of 50 µm × 50 µm but later increased to a 55 µm side-length to accommodate an overflow prevention circuit. Each pixel had its own leakage compensation circuit. Each pixel contains a preamplifier (which can be programmed to accept either positive or negative charge input), two threshold discriminators, and a single 13-bit counter which increments for every preamplifier output pulse whose amplitude lies within the energy window defined by the two discriminators. The versatility, along with the ability to tile multiple chips for larger area arrays, has permitted many evaluation studies of new sensor materials and detector configurations. However, poor spectral performance due to occurrence of charge sharing limited the success of Medipix2.
2.5. Hybrid pixel detectors

**Medipix3**

Medipix3.0 ASIC [Ballabriga et al., 2007] was designed to overcome the charge sharing problem that was encountered in Medipix2.0. It uses analog summing circuits and coincidence detection to implement a ‘winner takes all’ algorithm for pixels in groups of four. Like its predecessors, Medipix3.0 contains 256 × 256 pixels of 55 µm pixel pitch. In order to accommodate the many new features and modes, Medipix3.0 was implemented in a standard CMOS 0.13 µm process, which permits much higher transistor densities than the 0.250 µm CMOS technology used by the previous Medipix chips. It has two comparators and two counters per pixel. The counters can be varied in depth from two 1-bit, 4-bit, 12-bit counters, to one 24-bit counter. The comparators and counters of the four pixels can be switched to operate in parallel to provide eight simultaneous thresholds. Spectroscopic mode allows pixels to be combined into groups of four ‘super pixels’ of 110 µm on a side by omitting three of the four bump bonds between sensor and ASIC. Spectroscopic Mode allows to have 8 counters per pixel. The charge summing logic can be extended to work with the super pixels.

**Medipix3.1**

Medipix3.1 is a slightly modified version of Medipix3.0, with the changes to three mask layers to disconnect a leaky electrostatic discharge protection diode and to raise the threshold voltage of transistors in analog multiplexors in order to reduce leakage current. These modifications affect the analog frontend but the digital counters are identical in both versions (Medipix3.0 and Medipix3.1) [Wong, 2012]. Medipix3.1 had better threshold equalisation and improved spectral data acquisition compared to Medipix3.0 in pre-clinical x-ray imaging [Walsh et al., 2013]. However, it suffered from a poor hit allocation mechanism in Charge Summing Mode due to high pixel-to-pixel threshold mismatch.

**Medipix3RX**

Medipix3RX was designed to improve the charge summing allocation algorithm and to remove the effects of preferential summing that were encountered with its predecessors. Medipix3RX implements a new charge summing architecture for the hit allocation and it is
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less prone to pixel-to-pixel threshold mismatch [Ballabriga et al., 2013a]. The Medipix3RX has removed the random telegraph signalling (RTS) noise that was present in Medipix3.0.

**Pixel architecture and photon processing**

The art and challenge of pixel design in a hybrid pixel detector is to find the means to physically accommodate many complex charge-processing components within an extremely compact area, and at the same time balance the design tradeoffs between the analog and digital circuits. For MedipixRX, the pixel is implemented in a 0.13 μm CMOS process and utilises eight metal layers for high density routing. Each pixel layout is restricted to an area of 110 μm × 110 μm. The sensor area of each chip is 1.408 × 1.408 cm² which is subdivided into a 128 × 128 array of pixels in spectroscopic mode of operation [Ballabriga et al., 2013a]. Each pixel cell contains an analog section which processes the signal induced by the bump-bonded sensor, followed by a digital section which processes the discriminator output for counting the photon above user selectable energy thresholds.

In the analog section of the cell, the global energy threshold is set via a reference current, using a Digital-to-Analog converter (DAC). In this context, I use global to refer to ASIC parameters that are controlled by a single DAC that is applied to all pixels in the chip. Charge generated in the sensor is converted to a voltage pulse whose amplitude is proportional to the magnitude of charge or energy and to the number of photons. The voltage pulse, which is not a clean signal as it is overlaid with background electronic noise, is amplified at the pre-amplifier which is in the analog section.

The discriminator in the analog section of the pixel cell compares the pulse height of an amplified charge with the reference current set by the energy threshold DAC. If the pulse height of the charge is higher than the reference current, the counter in the digital part of the corresponding pixel is incremented. In this way, the energy threshold DAC can be adjusted to select the range of photon energies that will be counted. It is the ability to use an adjustable energy threshold DAC that allows a hybrid pixel detector to be used as a spectral x-ray detector.

The pixels of the Medipix3RX ASIC can be operated in either Single Pixel Mode (SPM) or Charge Summing Mode (CSM). Single Pixel Mode is a basic mode of operation in which each pixel works independently of its neighbours. An important factor that distorts the energy
response of a small (110 \, \mu m) pixel in SPM is the charge sharing effect. Charge sharing causes both spatial and spectral distortion of the signal, and when unaccounted for, the energy of the incident photon is falsely recorded as co-incident lower energy photon interactions in adjacent pixels.

**Charge sharing correction**

The Charge Summing Mode (CSM) in Medipix3RX ASIC is an advanced mode of operation that is designed to account for the charge sharing. CSM operates by summing charges that arrive coincidentally in adjacent pixels of the array to reconstruct the total energy deposited by each interaction. In CSM the Medipix3RX arbitration circuit is used to identify co-incident interactions across clusters of \( 3 \times 3 \) pixels and select the \( 2 \times 2 \) cluster closest to the site of interaction. The reconstructed charge is the summed charge deposited in this \( 2 \times 2 \) pixel cluster. The reconstructed (summed) charge is allocated to the pixel closest to the original site of interaction by the arbitration circuit (The pixel with the largest charge deposition). To enable charge summing, neighbouring pixels communicate on an event-by-event basis.

Further details of CSM in Medipix3RX ASIC can be found elsewhere [Ballabriga et al., 2013a].

**Threshold equalisation**

Manufacturing variations in the CMOS ASIC can cause intrinsic inter-pixel variation in the energy threshold (threshold dispersion) across the pixel matrix [Pelgrom et al., 1989]. This pixel-to-pixel mismatch results in different effective threshold voltages of the analog discriminator.

The Medipix3RX ASIC has 9-bit (0 - 511) energy threshold DACs. The energy threshold DACs are global current DACs which set the same energy threshold values for all pixels in the matrix. Additionally, each of two discriminators in a pixel contains an independent 5-bit (0 - 31) fine adjustment DAC to correct the inter-pixel threshold dispersion and to achieve a more uniform behaviour in the entire pixel matrix. The process of reducing the inter-pixel threshold dispersion by optimising the fine adjustment DAC of each pixel is called **threshold equalisation**.
Chapter 2. Photon-counting spectral CT

The appropriate digital value of the 5-bits for each pixel across the whole pixel matrix can be found in a number of ways, for example by determining the native (unadjusted) pedestal mean of each pixel using analog test pulses or radioactive sources, or by determining the edge of the Gaussian noise distribution by counting discriminated noise-threshold crossings without any external input stimulus.

The spread of effective thresholds seen by the pixels is greatly reduced by the threshold equalisation. However, the threshold dispersion cannot be completely eliminated by the threshold equalisation procedure due to the limited range and resolution of the fine adjustment DAC. The inter-pixel variation of the energy response can be a limiting factor in global spectral resolution and it lowers the precision of energy calibration and causes residual fixed pattern noise [Ballabriga et al., 2013a].

2.6 Summary

1. Photon-counting spectral CT is an exciting imaging modality which aims to measure the x-ray attenuation coefficient of an object at different energy ranges in a single exposure. This may be able to identify and characterise chemical elements within the body non-invasively.

2. By measuring the energy of individual x-ray photons with energy-resolving photon-counting detectors and ability to select the energy thresholds just above the electronic noise, spectral CT increases the contrast-to-noise ratio and improves the intrinsic soft tissue contrast.

3. Spectral CT integrated with functionalised contrast agents could allow targeting the biological hallmarks (bio-markers) of a disease such as atherosclerosis and cancer, and quantify the disease activity. Moreover, spectral CT could allow element-specific imaging by discriminating the K-edge feature of a high-Z contrast agent.

4. Spectral CT uses hybrid pixel detectors, such as Medipix based detector, which provides excellent spatial resolution and spectral resolution.

5. High-Z sensors are critical within the human diagnostic energy range as their high stopping power allows dose efficient imaging without compromising the image quality.
6. Medipix3RX is the latest and most sophisticated member of the Medipix family detectors. Medipix3RX was designed to improve upon its predecessors by correcting spectral performance, improving noise performance and enhancing count rate capability.
Chapter 3

Global energy calibration

3.1 Introduction

This chapter reports the development of an accurate and effective method to measure the global energy response (average energy response across the pixel matrix) of an energy-resolving photon-counting detector. Accurate selection of energy ranges is highly important in spectral CT to maximise the differential x-ray attenuation between multiple components of soft tissue as this determines the contrast. It has direct consequence in tissue characterisation and quantification.

Existing energy calibration techniques employ monochromatic photon sources such as radioisotopes [Fiederle et al., 2008, Koenig, 2011, Guni et al., 2011, Koenig et al., 2012], synchrotron [Ponchut et al., 2002, Gimenez et al., 2011] and x-ray fluorescence (XRF) from metallic targets [Ballabriga et al., 2013a, Ballabriga et al., 2011b, Ronaldson et al., 2011]. Each of these methods has limitations that reduce their usefulness in pre-clinical or clinical applications, such as special setup of equipment, long measurement time, and physical space required for maintaining the proper geometry of x-ray or γ-ray source, detector, and target metallic foils. Also, radioisotopes are not readily available in a small biological laboratory and frequent use of them may not be justifiable from the radiation protection point of view. Moreover, due to limited radioactivity of radioisotopes, it requires longer measurement time
to get sufficient photon statistics at a pixel level.

To address some of the limitations inherent in existing energy calibration techniques, this study aimed to develop pragmatic techniques based on x-ray tube voltage (kVp) for global energy calibration. Global energy calibration aims to measure the energy response of all pixels at whole detector level. Its performance was cross-validated by comparing with the energy calibration techniques based on x-ray fluorescence (XRF) and γ-ray from a radioisotope. Furthermore, this study aimed to investigate the influence of an applied bias voltage on energy response function of an energy-resolving detector. The work presented in this chapter has already been published [Panta et al., 2014c].

### 3.1.1 Overview of pixel architecture in Medipix3RX

Each pixel cell of a Medipix3RX ASIC contains the analog section followed by a digital section. In the analog section of each pixel cell, it is possible to set the global energy threshold which is transferred via a Digital-to-Analog Converter (DAC) into a reference-voltage. If the voltage pulse height of a collected charge in a pixel after amplification is higher compared to the energy threshold DACs, the counter in the digital part of the corresponding pixels gets incremented. The energy threshold DACs can be adjusted to select the range of photon energies that will be counted. Counting photons with user adjustable energy threshold DACs allows the hybrid pixel detector to be used as an energy-resolving detector.

### 3.1.2 X-ray tube voltage for energy calibration

An automated technique for calibrating the global energy threshold using the x-ray tube voltage (kVp) was developed. It requires minimal user intervention, and no extra resources in a pre-clinical or clinical CT scanner using energy-resolving x-ray detectors. The kVp of an x-ray tube is the maximum potential difference applied between anode and cathode. According to Duane-Hunt Law [Podgorsak, 2010], the maximum energy in the x-ray emission spectrum is equal to the peak potential applied to the x-ray tube. Figure 3.1 illustrates the effect of kVp on the energy end-point of an x-ray emission spectrum, the energy end-point shifts to a higher energy as x-ray kVp increases. The x-ray spectra were simulated using the Poludniowski
Chapter 3. Global energy calibration

Figure 3.1: X-ray emission spectra emitted from an x-ray tube simulated using the Poludniowski model [Poludniowski and Evans, 2007]. It illustrates the effect of kVp on the energy end-point of a spectrum.

model [Poludniowski and Evans, 2007]. With the advancement of x-ray detector technology, the kVp of an x-ray tube can be measured using high atomic number (Z) materials like CdTe [Krmar et al., 2010, Guni et al., 2011] and CdZnTe [Matsumoto et al., 2000]. This study hypothesized that the kVp of an x-ray tube would be used as reference energy to calibrate the energy-resolving detector since operating kVp of an x-ray tube defines the maximum photon energy hitting the detector. Moreover, energy calibration technique based on kVp is immune to differences in tube type and model (which has different total filtration and anode angles) as kVp defines the maximum energy end-point of a spectrum. And also, sufficient photon statistics at a pixel level can be obtained faster than using radioisotopes with limited radioactivity. This reduces the measurement time for energy calibration.

The workflow of the energy calibration technique using x-ray kVp is shown in Figure 3.2(a). For each energy calibration point, the x-ray kVp is set to the selected calibration energy. The corresponding threshold DAC is estimated and set on the detector. Open-beam frames are acquired at this threshold DAC, and the transition threshold corresponding to the selected calibration energy is found by counting the number of pixels either counting (on) or not counting (off). When calibrating the global energy threshold DAC, the transition threshold is taken to be the threshold DAC where 50% of pixels are counting. This represents the mean of the Gaussian threshold dispersion at the selected calibration energy. The slope of pixels counting versus threshold DAC gives an indication of threshold dispersion at the reference
3.1. Introduction

Figure 3.2: (a) The workflow of proposed global energy calibration technique using an x-ray kVp technique. (b) Ideal energy response (step-function) shown for an ideal detector without threshold dispersion for an arbitrary kVp. The energy threshold at which 50% of pixels counts (on) is taken as the corresponding energy threshold for that kVp.

For an ideal detector, the discriminator response would be a step function as shown in Figure. 3.2(b). The calibration algorithm uses an iterative method to locate the threshold values that result in 50% of pixels counting at each kVp setting. If the number of pixels is 50% within our tolerance values (user defined), the energy threshold is assigned to the given kVp and the procedure iterates to the next energy. Otherwise, the iteration re-estimates the threshold DAC that will give 50% within our tolerance values.

Figure 3.3: Experimental setup for measuring (a) XRF from metallic foils by irradiating with polychromatic x-rays from x-ray tube and (b) γ-ray from $^{241}$Am radioisotope.
3.2 Materials and methods

3.2.1 MARS camera with CdTe-Medipix3RX

I used a MARS camera fitted with a Medipix3RX ASIC bump-bonded to a standard high resistivity 2 mm thick CdTe pixel sensor layer for this study. The sensitive area of each chip was $1.408 \times 1.408 \, \text{cm}^2$ which is subdivided into a $128 \times 128$ array of pixels with a pixel pitch of $110 \, \mu\text{m}$. The CdTe sensor layer was configured as a ‘pn junction’ diode supplied with a negative high-voltage bias (-750 V) for collection of electrons. The counter depth was 12-bit providing a dynamic range of 4095 counts per pixel.

3.2.2 Threshold equalisation and noise floor scan

The Medipix3RX has a 5-bit threshold adjustment for each counter in a pixel. The detector was equalized using the electronic noise-floor. The noise floor of each pixel is caused by overall noise contribution from the sensor layer (e.g. leakage current) and readout electronics (e.g. noise from preamplifier and shaper [Tlustos et al., 2006]). Apart from transistor mismatch process, all pixels in ASIC are identical which makes the level of noise uniform across the pixel matrix. This allows the noise floor to be used as a reference signal for equalisation. The inter-pixel variation in energy response across the entire pixel matrix was minimized by individually adjusting the offset of the energy discriminator using the ASIC electronic noise floor using the method previously described [Walsh, 2013]. After threshold equalisation, an integral noise floor scan was run in the absence of radiation flux to establish the noise floor in both SPM and CSM.

3.2.3 Experimental setup and measurement of energy spectra

The calibration of the global energy threshold using the x-ray kVp technique was done over the range of 20 - 100 kVp. The workflow of this technique is shown in Figure. 3.2(a). Calibration energies of 30 kVp, 40 kVp, 60 kVp and 100 kVp were used. For each of these energies open-beam frames were obtained and used to locate the transition threshold value.
where 50% pixels are counting (on) and 50% not counting (off), by the iterative method described by Figure 3.2(a). The tube current of 5 $\mu$A and exposure of 500 ms were used with a source to detector distance of 20 cm.

Energy spectra of individual pixels were measured by two methods. The first method involves the measurement of XRF emitted by metallic foils directly irradiated with a uniform polychromatic x-ray beam. The second method involves the measurement of emission energy spectra from a $^{241}$Am $\gamma$-ray source. Metallic foils of Mo and In with 100 - 300 $\mu$m thickness were used to generate the XRF signal. In separate measurements, each foil was placed on the front face of the MARS camera as shown in Figure 3.3(a). A polychromatic x-ray tube (Model SB-120-700-P-CW, Source-Ray Inc, Ronkonkoma, NY) was used to irradiate the foils at a tube voltage of 40 kVp and the tube current and exposure time were adjusted to get between 1500 - 2000 photon counts per pixel in each measurement. The tube voltage used for measurement was optimized to maximize the XRF signal, and minimize the Bremsstrahlung transmission and scattering contamination from the direct exposure.

A threshold scan is used to acquire the distribution of photons with respect to their deposited energy in the sensor over a range of energy thresholds. The threshold scan can be expressed as:

$$M(E_{THL}) = \int_{E_{THL}}^{\infty} D(E) \, dE$$  \hspace{1cm} (3.1)$$

where $M$ is the number of measured events, $E_{THL}$ is the applied threshold energy, $D$ is the distribution of photons and $E$ is the deposited energy of a photon.

The threshold scan was performed by gradually increasing the threshold DAC to acquire the number of photon events as a function of the applied threshold DAC over the range of interest. The registered integral photon counts in the whole detector were differentiated with respect to the threshold DAC to obtain the actual photon counts at the corresponding energy range.

The second method involves the measurement of the emitted energy spectrum from $^{241}$Am and the experimental setup is illustrated in Figure 3.3(b). The $^{241}$Am gamma ray source (1.56 GBq, emission $\gamma$-ray peak at 59.5 keV) was placed 7 mm away from the CdTe-Medipix3RX detector and 5 second exposures were made at each threshold DAC in the range of 0 - 511.
Figure 3.4: Integral noise floor threshold scan in (a) SPM across 8 counters (C1 - C8) and (b) CSM across 4 counters (C1 - C4) after threshold equalisation using the intrinsic noise of frontend of chip.

with step size of 3. Note that the photon intensity from $^{241}$Am was low (115 counts/pixel at 59.5 keV for 5 sec exposure) which demands a long exposure time to obtain sufficient photon counts in each pixel without affecting the width of the photopeak.

The performance of energy calibration techniques using an x-ray kVp and XRF from metallic targets was compared at the whole chip level. Global energy calibration of x-ray kVp was performed at 18 kVp, 20 kVp, 30 kVp, 40 kVp, 50 kVp, 60 kVp, 70 kVp, 80 kVp, 90 kVp, 100 kVp. To obtain the corresponding threshold DAC at a given kVp, the transition threshold (50% of pixels off) was located. Global energy calibration using XRF and $\gamma$-ray was performed at 17.4 keV, 24.2 keV and 59.5 keV using Mo, In metallic targets and $^{241}$Am respectively.

In a separate experiment, all eight counters available in ‘Spectroscopic Mode’ with CSM were used to measure the energy response with XRF from Mo foil. When Medipix3RX is operated in ‘Spectroscopic Mode’ with CSM, the readout pixels are clustered in four pixels and one out of four is bump-bonded. This increases the pitch to 110 $\mu$m (from 55 $\mu$m in 256 $\times$ 256 array) in 128 $\times$ 128 array. This allows combining the energy thresholds and counters from four pixels (each pixel with two energy thresholds and two counters) which means that eight energy thresholds and eight counters are available. In CSM, four counters collect the reconstructed charge and the other four counters collect locally deposited charge. Out of those four counters which collect local charge, one counter is ‘single pixel arbitrated’ as a threshold
Figure 3.5: Distribution of noise floor in individual pixel in first counter in (a) SPM and (b) CSM after threshold equalisation based on intrinsic noise of frontend of chip.

is applied to the local charge, and arbitration circuitry is applied to suppress the hit from the pixels with lower energy signal.

**Bias voltage dependence of energy response**

The electric field strength applied across the sensor layer affects the charge diffusion and hence the energy response of the detector. In order to investigate the effect of electric field on energy response of Medipix3RX-CdTe, several bias voltages between -100V to -550V were applied. Separate threshold scans were run to measure the energy spectra from $^{241}$Am using each bias voltage.

### 3.3 Results

#### 3.3.1 Noise performance

Establishing the noise floor is important since all measurements should be taken above it. Figure 3.4(a) and Figure 3.4(b) show the integral noise floor scan for both SPM and CSM in which electronic noise dominates below threshold DAC (9-bit) of 30 in both modes of
camera operation. The high level of noise apparent in the lower threshold DAC as shown in Figure. 3.4(a) and Figure. 3.4(b) is due to limitations of sensor layer and readout ASIC. The noise floor zone and threshold dispersion across all the counters are seen to be similar for both SPM and CSM. The electronic noise dominates below threshold DAC of 30 in both modes of camera operation. Figure. 3.5(a) and Figure. 3.5(b) show the distribution of pixels which count more than 10 counts in the absence of radiation in SPM and CSM respectively. The noise floor histograms of SPM and CSM in Figure. 3.5(a) and Figure. 3.5(b) show the full width at half maximum (FWHM) of 5.3 and 7.4 threshold DAC respectively. Therefore, all data below threshold DAC of 30 were excluded from further data analysis.

3.3.2 Energy response spectra: SPM and CSM

The energy spectra acquired from the XRF of Mo and In foils, and a $^{241}$Am source using the SPM and CSM are shown in Figure. 3.6(a) and Figure. 3.6(b) respectively. The photo-peaks obtained in CSM (Figure. 3.6(b)) are seen to be more clearly defined than those obtained in SPM (Figure. 3.6(a)). This implies that the spectroscopic performance in CSM is superior to that in SPM.

Apart from the $\gamma$-ray peak in $^{241}$Am spectrum, two other peaks are prominent at lower threshold DAC (on the left of $\gamma$-ray peak) as shown in Figure. 3.6(b). The energy calibration

![Figure 3.6: Measurement of energy spectra from Mo, In, and $^{241}$Am in (a) SPM and (b) CSM](image-url)
3.3. Results

Figure 3.7: The energy response of all counters measured with XRF from Mo using Medipix3RX-CdTe.

shows these two peaks correspond to 24.2 keV and 35.4 keV. The first peak (24.2 keV) is formed by characteristic x-rays from Cd (23.17 keV) and Te (27.47 keV). And the second peak (35.4 keV) is formed by photo-electrons from Cd (59.5-23.17 = 36.33 keV) and Te (59.5-27.47 = 32.03 keV). The spectral resolution of detector was insufficient to resolve characteristic x-ray peaks from Cd and Te, and photo-electron peaks from Cd and Te as separate peaks.

Figure 3.8: Restoring the characteristic x-ray peak, photo-electron peak and γ-ray peak from \(^{241}\text{Am}\) spectrum (a) spectral enhancement of energy response function measured with \(^{241}\text{Am}\) after blind deconvolution and (b) restored XRF peak, k-escape peak and γ-ray peak.
Table 3.1: A summary of restored peaks from $^{241}$Am spectrum.

<table>
<thead>
<tr>
<th>Centroid of peak (keV)</th>
<th>Spectroscopic resolution (%)</th>
<th>Area under curve</th>
<th>source of peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>24.2</td>
<td>19.66</td>
<td>20.10</td>
<td>XRF from Cd/Te</td>
</tr>
<tr>
<td>35.4</td>
<td>18.56</td>
<td>40.67</td>
<td>Photo-electron from Cd/Te</td>
</tr>
<tr>
<td>59.5</td>
<td>17.76</td>
<td>176.76</td>
<td>$\gamma$-ray from $^{241}$Am</td>
</tr>
</tbody>
</table>

Figure. 3.7 illustrates the importance of accounting for charge sharing effect. It shows well-defined XRF peaks from Mo in four counters (C1, C3, C5, C7) which collect the reconstructed charge using charge summing features. However, energy spectra measured with the other four counters (C0, C2, C4, C6) are poorly defined as shown in Figure. 3.7. This is because of charge sharing effect.

### 3.3.3 Spectral deconvolution of $^{241}$Am spectrum

$^{241}$Am spectrum shows two more peaks in addition to $\gamma$-ray peak in 3.8(a). Spectral deconvolution aims to restore each of those peaks. Blind deconvolution was used to reconstruct the individual peak from a complex $^{241}$Am spectrum. It is mathematically expressed as:

$$E_m = E_r \ast P$$  \hspace{1cm} (3.2)

where $E_m$ is the measured energy response function, $E_r$ is the real energy response function without blurring and P is the Point Spread Function (PSF).

This is an ill-posed problem as both $E_r$ and P are unknown. It is assumed that PSF is Gaussian for measuring the energy response of the $\gamma$-ray from $^{241}$Am.

The energy response function of the $^{241}$Am spectrum was enhanced and sharpened as shown in Figure. 3.8(a). All peaks in the $^{241}$Am spectrum were fitted with the Gaussian function. The individual restored peaks in the $^{241}$Am spectrum are shown in Figure. 3.8(b). Table 3.1 shows the characteristics of all restored peaks. The spectral resolution (FWHM) of measured $^{241}$Am $\gamma$-ray peak was 10.4 keV before deconvolution and after blind deconvolution it was improved to 6.9 keV. This shows that the spectral resolution of the $^{241}$Am $\gamma$-ray peak was improved by 33% after blind deconvolution and Gaussian data fitting.
3.3. Results

3.3.4 Cross-validation of energy calibration techniques

Figure. 3.9(a) shows the number of pixels non-counting (off) and counting (on) as a function of threshold DAC measured at 30 kVp, 40 kVp, 60 kVp and 100 kVp. The ideal curve for 60 kVp is also shown (in red), intersecting through the 50% point of the 60 kVp measurements. These energy calibration points were mapped to threshold DAC of 126, 150, 193 and 273 respectively as shown in Figure. 3.9(a).

A least-squares method was used to fit the threshold DAC corresponding to the peak position of XRF peak (K_{α1}) from Mo and In, and the γ-ray peak from $^{241}$Am as shown in Figure. 3.9(b). The global energy calibration using an x-ray kVp and existing technique (XRF and γ-ray) provides the good agreement as shown in Figure. 3.9(b) across the wide energy range (17 - 100) keV. Both techniques yield linear energy response. The gain of energy calibration curves are 2.58 and 2.44 threshold DAC/keV for x-ray kVp and XRF techniques respectively. The difference between two energy calibration techniques is 1.5 keV at 59.5 keV.

<table>
<thead>
<tr>
<th>Threshold DAC</th>
<th>Fraction of pixels off</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>100</td>
<td>0.5</td>
</tr>
<tr>
<td>150</td>
<td>0.5</td>
</tr>
<tr>
<td>200</td>
<td>0.5</td>
</tr>
<tr>
<td>250</td>
<td>0.5</td>
</tr>
<tr>
<td>300</td>
<td>0.5</td>
</tr>
<tr>
<td>350</td>
<td>1</td>
</tr>
</tbody>
</table>

Figure 3.9: (a) Threshold scan showing the fraction of pixels off at 30 kVp, 40 kVp, 60 kVp and 100 kVp using CdTe-Medipix3RX in Charge Summing Mode. The energy calibration technique using x-ray kVp locates the transition threshold where 50% pixels transition from off to on. An ideal detector has no threshold dispersion and it is shown for 60 kVp as a vertical red line. The slope of each measurement gives the indication of threshold dispersion at given kVp. (b) Global energy calibration performance of x-ray kVp technique, and XRF technique in CdTe-Medipix3RX in CSM.
3.3.5 Bias voltage dependence of energy response

Figure 3.10(a) shows the energy spectra of $^{241}$Am measured using several bias voltages of -100V, -150V, -250V, -350V, -450V and -550V. The position of $\gamma$-ray peak shifts to higher threshold DAC as bias voltage is increased. This effect has been shown in Figure 3.10(b). Figure 3.10(a) also shows that two peaks on lower threshold DAC (left to $\gamma$-ray $^{241}$Am peak) are getting more separable as bias voltage increases. This is because of improvement of charge collection efficiency with increasing bias voltage. Energy calibration shows that the gain (threshold DAC/keV) increases with the bias voltage as shown in Figure. 3.11. This effect increases the accuracy and precision of energy calibration as more threshold DACs are available per keV. $\gamma$-ray peak was fitted with Gaussian function and it was used for measuring the spectral resolution. Figure. 3.12(a) shows how spectral resolution is measured from the FWHM of $\gamma$-ray peak of $^{241}$Am. Figure. 3.12(b) shows that spectral resolution improves as bias voltage across the sensor layer is increased. Global spectral resolution of 9.95 keV (16.7%) with -550V was measured at 59.5 keV.
3.4. Discussion

Automated global energy calibration techniques using an x-ray kVp and XRF from metallic targets were developed and cross-validated. The energy difference between these two techniques is 1.5 keV at 59.5 keV which is less than the global spectral resolution of the detector (FWHM of 9.95 keV at 59.5 keV). The advantage of x-ray kVp based energy calibration technique over the XRF technique is that it does not require any measurement with monochromatic photons, user intervention and requires fewer resources which are easily available in a pre-clinical imaging setup. Users can define as many energy calibration points as available kVp. However, a large number of energy calibration points require longer calibration time.

Energy threshold calibration based on the XRF method needs extra resources like metallic foils of different elements to provide reference energies across the wide energy range of interest. Each metallic foil forms an energy calibration point. The exposure parameters for detecting adequate XRF signal from a foil need to be optimized. Both of the energy calibration techniques are pragmatic ones which can be used as quality control tools on a daily basis for a pre-clinical multi-energy CT scanner using energy-resolving detectors. XRF technique can

Figure 3.11: Variation of gain (threshold DAC/keV) with the function of applied bias voltage using Medipix3RX-CdTe in CSM.
The energy calibration performance of both techniques can be affected due to pulse pile up or any other sort of distortion in the energy spectrum. Setting the accurate kVp value in kVp based energy calibration technique depends on x-ray tube model and manufacturer’s tolerance level. The more accurate kVp value we set, the lesser the measurement uncertainty we get in kVp based energy calibration technique. Finding the peak position in the energy response function measured using XRF technique may introduce uncertainty as several energy threshold points may have the same number of differential counts due to finite width of the peak. Similarly, the accuracy of both techniques depends on the step size of energy thresholds used in the measurement. Measurements with larger step size are faster but introduces more uncertainty in the measurement. However, the difference of 1.5 keV at 59.5 keV between two energy calibration techniques is good enough to implement in pre-clinical or clinical spectral imaging.

XRF from metallic targets and γ-ray from $^{241}$Am radioisotope were used to measure the energy response of the detector. The energy response of CdTe-Medipix3RX in CSM (Figure. 3.6(b)) is more clearly defined than that in SPM (Figure. 3.6(a)). CSM improves the imaging performance by enhancing contrast and spectral resolution of the detector. In SPM, the XRF from different metallic foils and the monochromatic γ-ray emitted from $^{241}$Am are likely to
be detected by the adjacent pixels. When the charge cloud generated from photon interaction with the sensor drifts across the sensor thickness under electric field strength, it spreads across many small (110 \(\mu m\)) pixels in SPM. This charge sharing effect is more severe in the pixel detector with greater sensor thickness and smaller pixel dimension. The splitting of the charge cloud and the false assignment of photon hits to the pixel causes poor energy response of an energy-resolving detector in SPM. However, in CSM, the inter-pixel communication and the assignment of correct number of photon hits or counts to the correct pixel take accounts of charge sharing effect. As a consequence, the spectral and spatial performance of CSM is improved.

The variation of energy threshold with respect to incident photon energy is linear across the measured energy range (17.4 keV to 59.5 keV) in CSM as shown in Figure. 3.9(b). This linear fit of energy response agrees with the previous findings in Medipix detectors [Ronaldson, 2012, Koenig, 2011, Ballabriga et al., 2011b].

In this study, XRF signal was not used for measuring the spectral resolution of detector because of the possible contamination of scattering and transmission x-rays. The contamination of XRF signal from scattering and transmission x-ray can be avoided by changing the experimental settings to allow only the detection of XRF signal by preventing the detector from direct exposure of x-rays. However, one should bear in mind in using XRF signal for measuring the spectral resolution of the detector that there are many XRF lines (such as K-series or L-series) at different energies which are overlapped in a XRF peak. Therefore, the FWHM of XRF peak does not represent the true spectral resolution of the detector. We used XRF signal to localise the position of XRF peak with respect to the threshold DAC. I used monochromatic \(\gamma\)-ray from \(^{241}\)Am for measuring the spectral resolution of the detector.

The improvement of spectral resolution with higher bias voltage suggests that adequate electric field strength is prerequisite for enhancing the spectral performance of an energy-resolving detector. The charge collection efficiency is an important property of a radiation detector that affects the spectroscopic performance and in particular the spectral resolution. High charge collection efficiency ensures good energy resolution which also depends by the statistics of the charge generation and by the noise of the readout electronics. Therefore, the spectral resolution (FWHM) of a radiation detector is mainly influenced by three factors as below:
\[ \Delta E = \sqrt{(2.355)^2(\text{FEW}) + (\Delta E_{el})^2 + (\Delta E_{coll})^2} \]  

where \( F \) is the Fano factor, \( E \) is the incident photon energy, \( W \) is the average pair creation energy, \( \Delta E_{el} \) is the spectral resolution due to electronic noise and \( \Delta E_{coll} \) is the spectral resolution due to charge collection process.

The first factor is the Fano factor which is due to the statistics of the charge carrier generation. This is basically a fundamental limit for spectral resolution of the detector. In semiconductors, the Fano factor, \( F \), is much smaller than unity (0.06 – 0.14) [Devanathan et al., 2006]. The second factor is the electronic noise, which is generally measured directly using a precision pulser, while the third is the contribution of the charge collection process. Applied bias voltage directly affects the contribution of charge collection process and hence the spectral resolution.

Increasing the bias voltage improves not only the spectral resolution but also the gain or slope of energy calibration curve as shown in Figure. 3.10(b). This improves the accuracy and precision of energy calibration.

K-fluorescence x-rays (K\( \alpha_1 \)) are emitted from Cd (23.17 keV) and Te (27.47 keV) detector and the fluorescent yield in CdTe is 87 \%. The mean free path length of those photons is 116 \( \mu \)m and 64 \( \mu \)m respectively, comparable to the dimension of a pixel. These photons can be reabsorbed away from the original site of their generation causing distortion in the energy spectrum measured by the pixel. Similarly, the photo-electron, whose energy equals that of the original photon hitting the sensor minus the fluorescence x-ray energy which deposits its energy away from the original site of interaction. Generation of fluorescence x-rays from CdTe and photo-electrons are fundamental in nature. Secondary products from photon interaction with high-Z sensor materials need to be taken into account for effective material characterisation and quantification in spectral x-ray imaging.

3.5 Summary

1. Automated global energy calibration techniques using an x-ray kVp and XRF from metallic targets were developed which show good agreement with each other (difference
3.5. Summary

of 1.5 keV at 59.5 keV which is far less compared to the spectral resolution of the detector i.e 9.95 keV at 59.5 keV).

2. The energy response function and the spectral resolution of CdTe-Medipix3RX in CSM is well-defined. It can be used in spectroscopic imaging of biological specimens.

3. Adequate electric field strength across the sensor layer is important for enhancing the spectral performance of the detector.

4. The secondary products from photon interaction with the high-Z sensor in a pixel detector may cause the detrimental effect, such as reducing the quality of tissue characterisation, in spectral performance of detector. This needs to be taken into account (for example, by using larger dimension of pixel pitch) in spectral x-ray imaging.
Chapter 4

Per-pixel energy calibration

4.1 Introduction

This chapter reports on measurement of energy response of individual pixels in a hybrid pixel detector. Measuring the energy response on a pixel-by-pixel basis may improve the sensitivity and specificity of tissue characterisation in the framework of photon-counting spectral CT.

Global energy calibration measures the average energy response across the whole pixel matrix. Some outlier pixels can significantly bias the average energy response coefficients (gain and offset) of the detector. Functionally, each pixel is an identical and independent unit with its own dedicated readout electronics comprising analog and digital circuits. The energy thresholds in many pixels on one chip are not identical. They exhibit random variations and possibly systematic fluctuations [Pelgrom et al., 1989, Rossi et al., 2006]. The random variations are due to component mismatch such as transistor mismatch [Ballabriga et al., 2007]. The transistor mismatch between a pair of identical transistors can be expressed as:

\[
\sigma(V_{THL}) \propto \frac{A}{\sqrt{WL}}
\]  

(4.1)

where \( A \) is the matching coefficient, \( W \) and \( L \) are width and length of transistors respectively.
4.1. Introduction

This description is based on the assumptions that mismatch is caused by independent random disturbances of physical properties and that the correlation distance of the statistical disturbance is small compared to the active device area [Lovett et al., 1998]. Transistor matching improves with increasing the active area of transistor and decreasing the matching coefficient (A). Matching coefficient is proportional to the oxide thickness. So, transistor matching improves with the miniaturisation of CMOS technology. This implies that transistor matching in Medipix3.0 (0.13 \( \mu \text{m} \)) or Medipix3RX (0.13 \( \mu \text{m} \)) is better than that in Medipix2.0 (0.25 \( \mu \text{m} \)) and Medipix1.0 (0.6 \( \mu \text{m} \)). Other potential sources of random fluctuations that cause threshold dispersion are production fluctuations of doping concentration and geometrical size etc.

The systematic fluctuation of threshold may be caused due to voltage drop along the column or component mismatch from mirrored layouts. Furthermore, the energy thresholds vary as a function of the capacitance connected to the preamplifier input. This is due to the finite gain of the preamplifier which leads to the loss for increasing input capacitance [Rossi et al., 2006].

4.1.1 Threshold equalisation and its limitation in Medipix3RX

The Medipix3RX ASIC has 9-bit (0 - 511) energy threshold DACs. The energy threshold DACs are global current DACs which set the same energy threshold values for all pixels in the matrix. Additionally, each of two discriminators in a pixel contains an independent 5-bit (0 - 31) fine adjustment DAC to correct the inter-pixel threshold dispersion. The process of reducing the inter-pixel threshold dispersion across the pixel matrix by optimising the fine adjustment DAC of each pixel is called threshold equalisation. However, the threshold dispersion cannot be completely eliminated by the threshold equalisation procedure due to the limited range and resolution of the fine adjustment DAC. The inter-pixel variation of the energy response can be a limiting factor in global spectral resolution, the precision of energy calibration and causes residual fixed pattern noise [Ballabriga et al., 2013a]. Calibrating the energy response of individual pixels is necessary since the residual threshold dispersion can degrade the contrast and spatial resolution [Manuilskiy et al., 2004].

This study aimed to investigate energy response of individual pixels in an energy-resolving detector using XRF from metallic targets and \( \gamma \)-ray from a radioisotope of an energy-resolving
Chapter 4. Per-pixel energy calibration

Table 4.1: A summary of metallic targets and reference energies used for energy calibration.

<table>
<thead>
<tr>
<th>Atomic No. (Z)</th>
<th>Metallic targets</th>
<th>XRF (Kα₁) energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>Molybdenum (Mo)</td>
<td>17.48</td>
</tr>
<tr>
<td>46</td>
<td>Palladium (Pd)</td>
<td>21.18</td>
</tr>
<tr>
<td>49</td>
<td>Indium (In)</td>
<td>24.20</td>
</tr>
<tr>
<td>73</td>
<td>Tantalum (Ta)</td>
<td>57.53</td>
</tr>
<tr>
<td>82</td>
<td>Lead (Pb)</td>
<td>74.97</td>
</tr>
</tbody>
</table>

detector. The second aim of this study was to measure the threshold dispersion, gain variation and dispersion on spectral resolution across pixel matrix in a CdTe-Medipix3RX operated in Charge Summing Mode. The work presented in this chapter has already been published [Panta et al., 2014c].

4.2 Materials and methods

4.2.1 Measurement of energy response with XRF and γ-ray

Threshold equalisation and integral noise floor scan were run in the absence of radiation flux to establish the noise floor in CSM. Energy spectra of individual pixel were measured by two methods. The first method involves the measurement of XRF emitted by metallic foils directly irradiated with a uniform polychromatic x-ray beam. The second method involves the measurement of emission energy spectra from a ²⁴¹Am γ-ray source. Different metallic foils of molybdenum (Mo), palladium (Pd), indium (In), tantalum (Ta), lead (Pb) with 100 - 300 µm thickness were used to generate the XRF signal. The corresponding XRF (Kα₁) energy from these metallic targets are presented in Table 4.1.

In separate measurements, each foil was placed on the front face of the MARS camera as shown in Figure. 3.3(a). A polychromatic x-ray tube (Model SB-120-700-P-CW, Source-Ray Inc, Ronkonkoma, NY) was used to irradiate Mo, Pd, In, Ta and Pb foil at a tube voltage of 30 kVp, 35 kVp, 40 kVp, 70 kVp and 90 kVp respectively and the tube current and exposure time were adjusted to obtain sufficient counts in the range of 1500 - 2000 photon counts.
4.2. Materials and methods

Figure 4.1: Energy calibration of the CdTe-Medipix3RX in CSM (a) Energy response function of a pixel measured with XRF of Mo, Pd, In, Ta, Pb and the $\gamma$-ray peak from $^{241}$Am. The height of each peak is normalised to one for better visualisation of its relative position in x-axis with other peaks and (b) Establishing the relationship of threshold DAC at XRF-peaks and photo-peak position with the corresponding reference energy for a pixel.

per pixel in each measurement. The tube voltage used for measurement with each foil was optimized to maximize the XRF signal, and minimize the Bremsstrahlung transmission and scattering contamination from the direct exposure. A threshold scan was used to acquire the distribution of photon with respect to their deposited energy in the sensor over a range of energy thresholds. It took about 1 hour to collect sufficient photon counts in each pixel for each metallic target.

The second method involves the measurement of the emitted energy spectrum from $^{241}$Am. The $^{241}$Am gamma ray source (1.56 GBq, emission $\gamma$-ray peak at 59.5 keV) was placed 7 mm away from the CdTe-Medipix3RX detector and 5 second exposures were made at each threshold DAC in the range of 0 - 511 with step size of 3. Note that the photon intensity from $^{241}$Am was low (115 counts/pixel at 60 keV for 5 sec exposure) which demands a long exposure time to obtain sufficient photon counts in each pixel without affecting the width of the $\gamma$-ray peak. It took about 21 hours to collect sufficient photon counts in each pixel level.
Chapter 4. Per-pixel energy calibration

Table 4.2: A summary of threshold dispersion for different counters in Charge Summing Mode.

<table>
<thead>
<tr>
<th>Counter</th>
<th>Threshold dispersion (keV) at 24.2 keV</th>
<th>Threshold dispersion (keV) at 59.5 keV</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.30</td>
<td>4.68</td>
</tr>
<tr>
<td>2</td>
<td>2.30</td>
<td>4.71</td>
</tr>
<tr>
<td>3</td>
<td>2.37</td>
<td>4.65</td>
</tr>
<tr>
<td>4</td>
<td>2.30</td>
<td>4.78</td>
</tr>
</tbody>
</table>

4.3 Results

4.3.1 Energy response spectra in Charge Summing Mode

Multiple metallic targets of Mo, In, Pd, Ta and Pb were used to locate the threshold DAC corresponding to the XRF peak. The measured energy spectra from each of the reference energy sources show a positive linear relationship between the XRF peak position and the threshold DAC as shown in Figure. 4.1(a) and Figure. 4.1(b). A least-squares method was used to fit the threshold DAC corresponding to the peak position of XRF peak ($K_{\alpha 1}$) and the $\gamma$-ray peak against the corresponding reference energies which yields $R^2 = 0.9972$ as shown in Figure. 4.1(b).

4.3.2 Threshold dispersion and gain variation

The threshold DAC corresponding to the XRF peak from In foil (24.2 keV) and $\gamma$-ray-peak of $^{241}$Am (59.5 keV) were measured for each pixel across the pixel matrix. The threshold dispersion is a measure of the inter-pixel variation of the threshold DAC corresponding to a reference energy. The threshold dispersion ($\sigma$) of 4.77 and 9.73 threshold DAC steps were measured at 24.2 keV and 59.5 keV respectively as shown in Figure. 4.2(a) and Figure. 4.2(b) respectively. Table 4.2 shows the threshold dispersion in a pixel matrix of each counter in CSM. Higher threshold dispersion was observed at higher energy.

Based on the threshold dispersion across the whole pixel matrix using the XRF from In
4.3. Results

Figure 4.2: The distribution of inter-pixel threshold dispersion in CdTe-Medipix3RX in CSM across pixel matrix at (a) 24.2 keV and (b) 59.5 keV.

foil and the γ-ray from $^{241}$Am, the gain variation (threshold DAC/keV), was calculated for each pixel across the matrix and is shown in Figure. 4.3(a) and Figure. 4.3(b). Table 4.3 shows the statistics of gain variation in a pixel matrix of each counter. The gain is expressed as the number of threshold DACs per keV. The coefficient of gain variation ($\sigma x 100%/\mu$) in each counter varies in the range of 6.13% - 6.51%. Similarly, the mean and median gain of whole pixel matrix are 2.08 threshold DAC/keV and 2.10 threshold DAC/keV respectively in each counter. The gain is mainly controlled by the feedback capacitor in the analog circuit [Frojdh et al., 2013]. The gain increases with increasing the applied bias voltage as shown in Figure. 3.11. The greater the number of threshold DAC per keV, the more precise and accurate is the energy calibration. This implies that energy calibration at higher bias voltage is more precise and accurate.

4.3.3 Dispersion of spectral resolution across pixel matrix

The spectral resolution of each pixel was measured at the 59.5 keV $^{241}$Am γ-ray peak. A map of the spatial variation of spectral resolution of individual pixels is shown in Figure. 4.4(a) and the distribution of FWHM for each pixel is shown in Figure. 4.4(b). The average FWHM for all pixels is 15% which is equivalent to 8.9 keV at 59.5 keV. The spectral resolution of the individual pixel in CdTe-Medipix3RX varies in the range of (10% - 30%) at 59.5 keV.
Chapter 4. Per-pixel energy calibration

Table 4.3: A summary of gain variation (threshold DAC/keV) in all pixels of different counters in Charge Summing Mode.

<table>
<thead>
<tr>
<th>Counter</th>
<th>Coefficient of gain variation(%)</th>
<th>Mean of gain variation (Threshold DAC/keV)</th>
<th>Median of gain variation (Threshold DAC/keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.13</td>
<td>2.08</td>
<td>2.10</td>
</tr>
<tr>
<td>2</td>
<td>6.51</td>
<td>2.08</td>
<td>2.10</td>
</tr>
<tr>
<td>3</td>
<td>6.28</td>
<td>2.08</td>
<td>2.10</td>
</tr>
<tr>
<td>4</td>
<td>6.44</td>
<td>2.09</td>
<td>2.10</td>
</tr>
</tbody>
</table>

across the whole pixel matrix. The coefficient of spectral resolution variation ($\sigma \times 100%/\mu$) across the pixel matrix is 21%. The pixels nearby poor bump bonding regions show zero spectral resolution. The most important factors that affect the spectral resolution in readout electronics are threshold dispersion, gain variation and electronic noise. Similarly, charge sharing, variation in the charge collection efficiency, leakage current and Fano factors are other major factors in the sensor that influence to spectral resolution of the detector [Frojdh et al., 2013].

Figure 4.3: (a) Spatial map of gain (Threshold DAC/keV) across pixel matrix of first counter operated in CSM using CdTe-Medipix3RX. The dead pixels due to poor bump-bonding during manufacturing of the detector show zero gain. (b) distribution of gain of individual pixel across the whole pixel matrix.
4.4 Discussion

A pixel-by-pixel energy calibration technique using an XRF from metallic targets and γ-ray from $^{241}$Am radioisotope was used to measure the energy response of individual pixel. The variation of energy threshold with respect to incident photon energy is linear ($R^2 = 0.9972$) across the measured energy range (17.4 keV to 75 keV) in CSM as shown in Figure. 4.1(b). This linear fit of energy response agrees with the previous findings in Medipix detectors [Koenig, 2011, Ballabriga et al., 2011b, Ronaldson, 2012].

The quality of threshold equalisation directly affects the contrast resolution and the level of fixed pattern noise in an image. The measurement of threshold dispersion across different counters at different energy shows that threshold dispersion increases with energy. The threshold dispersion is directly related to CMOS manufacturing variation and the effectiveness of threshold equalisation. Similarly, the gain variation (variation in energy response) across the pixel matrix is 6.1 - 6.5% for different counters. This is consistent across all the 4 counters in CSM. At higher energies, the higher residual threshold dispersion after threshold equalisation is more likely to be observed as shown in Figure. 4.2.

The threshold equalisation is likely to be more effective by using a higher reference energy or equivalent test pulse rather than using the noise floor. However, when using test pulse, the variations in the charge injection capacitor across the pixel matrix can distort the

Figure 4.4: (a) Spatial map of spectral resolution (FWHM) across pixel matrix of first counter operated in CSM using CdTe-Medipix3RX. The spectral resolution was measured using γ-ray (59.5 keV) of $^{241}$Am source. The dead pixels due to poor bump-bonding during manufacturing of the detector show zero spectral resolution. (b) the distribution of spectral resolution (FWHM) of the individual pixel.
spectroscopic response [Frojdh et al., 2013]. So, using higher photon reference energy close to the energy of interest in threshold equalisation is the most promising solution even though it takes longer time. The performance of threshold equalisation can be enhanced if the next design of readout chips incorporates wider range and finer resolution of adjustment DAC on each pixel. Currently, Medipix3RX ASIC contains an independent 5-bit (0 - 31) fine adjustment DAC in each pixel for threshold equalisation.

The spectral resolution of the individual pixel in CdTe-Medipix3RX was found to be widely varying (10% - 30%) at 59.5 keV across the whole pixel matrix. The average FWHM for all pixels is 15% (8.9 keV) as shown in Figure. 4.4(b). There are two main underlying sources of spectral broadening of the \( \gamma \)-ray peak which can be broadly divided into two parts: the sensor and the Medipix3RX readout ASIC. The major causes of spectral broadening arising from the sensor layer are: higher leakage current, lower charge collection efficiency, thicker sensor layer and the statistical nature of the charge generation (Fano factor). Thick layers of CdTe polarize quickly, a well-known problem in CdTe [Sordo et al., 2009]. The effect of polarization on spectral resolution needs further investigation, for example, by refreshing the bias voltage frequently during the data acquisition from CdTe sensor [Sordo et al., 2009]. It is worth noting that without the interaction depth correction, thicker CdTe will inherently cause spectral degradation as the charge carriers originating from interactions at the surface have a longer drift length and will be more likely to encounter material defects in the CdTe.

The other sources of spectral broadening arising from the readout ASIC are threshold dispersion, gain variation and the electronic noise and quantization of signals. In CSM, the performance of one pixel is affected by the electronic noise of adjacent pixels. The threshold variation between intercommunicating pixels will be summed which may cause the broadening of \( \gamma \)-ray peak from \(^{241}\text{Am}\).

4.5 Summary

1. The energy response of each pixel was measured with XRF from metallic targets bombarded with polychromatic x-ray source and radioisotope. Measuring energy response of an individual pixel with XRF emitted from metallic targets bombarded with high flux polychromatic x-ray beam is much faster (21 times) than measuring energy response
4.5. Summary

using radioisotope with limited activity.

2. The energy response function and the spectral resolution of individual pixels in CdTe-Medipix3RX using CSM is well defined.

3. The energy-resolving performance of the detector can be enhanced by minimizing the electronic noise and threshold dispersion.

4. Pixel-by-pixel energy calibration is highly desirable for taking account of gain variation across the pixel matrix and enhancing the spectral resolution of energy-resolving detectors.

5. Pixel-by-pixel energy calibration technique may improve the sensitivity and specificity of tissue characterisation in the framework of spectral CT.
Chapter 5

Count rate capability of photon-counting detector

5.1 Introduction

This chapter reports on investigations carried out to measure the count rate capability of a photon-counting detector. The count rate of a photon-counting detector needs to be optimised in order to avoid overflow (saturation) of the counter at high x-ray flux, and yet obtain enough photons to get the best possible quantum signal-to-noise ratio (SNR) and to reduce the image acquisition time in spectral imaging.

There are two distinct approaches of pulse processing in x-ray detectors: photon-counting and energy-integrating. Photon-counting detector offers many advantages over energy-integrating detector such as being free from electronic noise and Swank noise [Mikulec, 2000, Schwarz et al., 2001, Swank, 2003], giving the possibility of energy weighting [Shikhaliev, 2006] and K-edge imaging [Schlomka et al., 2008].

Figure 5.1 demonstrates two approaches of pulse processing in energy-integrating and photon-counting. Simulation of the principle of an integration system (bottom row) and preamplifier output (preamplifier reset time constant of 1 µs) for photon-counting (middle
5.1. Introduction

Figure 5.1: Timing diagrams illustrating (top row) photon arrival time that follows the Poisson statistics. Mean time constant between arrival of two consecutive photons of 4 µs. (middle row) simulation of principle of photon-counting detector with preamplifier reset time constant of 1 µs. (bottom row) simulation of principle of energy-integrating detector. (Source: R. Ballabriga. Medipix: Collaboration and Detectors.)

row) have been demonstrated. Similarly, photon time of arrival that follows the Poisson random statistics also has been simulated (top row). In energy-integrating mode of detector operation, information of total deposited energy is obtained. This is the case in clinical CT where x-ray flux as high as $10^9$ counts/s/mm$^2$ is used [Rink et al., 2013].

It can be observed in Figure. 5.1 that as the time interval between two consecutive photon events reduces, the photon-counting detector combines the successive pulses into a single photon pulse. This means that a photon-counting detector needs a minimum amount of time to separate successive events in order that they are recorded as separate pulses. This minimum time required for separation of two successive pulses is called dead time and overlapping of two pulses is called pulse pile up effect [Knoll, 2000, Taguchi et al., 2010]. Because of the stochastic (random) nature of photon arrivals, there is always non-zero probability that a true photon event will be lost because it occurs too quickly following a preceding event, which is also called dead time loss.

In a photon-counting detector, two principal components are: sensor and readout ASIC.
Table 5.1: A summary of Ikrum DAC used for measuring the count rate capability of CdTe-Medipix3RX.

<table>
<thead>
<tr>
<th>DAC name</th>
<th>Depth</th>
<th>DAC range</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I_Ikrum</td>
<td>0 - 255 (8 bits)</td>
<td>0 - 60 nA</td>
<td>It discharges the capacitor and compensates the leakage current. As the I_Ikrum value increases, the amount of leakage current tolerance also increases, but the problem is that the capacitor is discharged more quickly and noise increases. It also controls the return to baseline of the preamplifier output signal.</td>
</tr>
</tbody>
</table>

When x-ray photons interact with the sensor, free charge carriers are generated. It takes finite time to collect those charge carriers. On the other hand, the readout ASIC requires finite time to process the individual photons. These combined effects and others [Taguchi and Iwanczyk, 2013] result in a non-zero overall detector response time and there will be pulse pile up if photons enter the sensor during the response time or dead time. Pulse pile up distorts the count signals and measured energy response of the detector [Taguchi and Iwanczyk, 2013].

The dead time loss of a photon-counting detector is mainly determined by the speed of the frontend readout electronics [Schwarz, 2001]. The performance of frontend analog readout electronics in Medipix3RX ASIC is controlled by different digital-to-analog (DAC) currents which are implemented to properly set the analog circuit reference currents.

In this chapter, I report (1) the count rate capability of CdTe-Medipix3RX in Single Pixel Mode (SPM) and Charge Summing Mode (CSM), and (2) the effect of external electric field and Ikrum Digital-to-Analog Converter (DAC) values on count rate capability of CdTe-Medipix3RX. Ikrum Dac (I_Ikrum in Medipix3RX) sets the biasing signal for the preamplifier circuit [Ballabriga and Llopard, 2012]. It is set globally to all pixels. The summary of Ikrum DAC in CdTe-Medipix3RX is presented in Table 5.1.
5.2 Materials and methods

5.2.1 Experimental setup and measurements

All the experiments were conducted using a polychromatic x-ray source (Model SB-120-700-P-CW, Source-Ray Inc, Ronkonkoma, NY) in MARS scanner. Polychromatic x-ray energy spectrum (18 keV - 120 keV) at 120 kVp was used to measure the count rate capability of Medipix3RX with 2 mm thick CdTe sensor and pixel pitch of 110 µm. An external bias voltage of -600 V was applied across the sensor. Prior to the measurements, both threshold equalisation and energy calibration were performed using the KVP technique as described in Chapter 3.

All the measurements were performed by setting the lower energy threshold just above the noise and counting all the x-rays above this energy. A total aluminium equivalent filtration of 3.6 mm (1.6 mm of inherent filtration & 2 mm of added filtration) was used to block all the photons below 18 keV. The incident x-ray flux was increased steadily by changing the

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Figure 5.2: (a) Schematic diagram of experimental setup for measuring the output count rate of the detector. The Medipix3RX chip in its usual form measures 1.59 × 1.41 cm². (b) X-ray spectrum emitted from an x-ray tube with the experimental setup as shown in Figure 5.2(a). X-ray spectrum was simulated using the Poludniowski model [Poludniowski and Evans, 2007].
The count rate capability of Medipix3RX detector was measured in three different experiments. In the first experiment, both Single Pixel Mode and Charge Summing Mode were used to measure the count rate by varying the x-ray tube current (which determines x-ray flux) between 5 µA - 340 µA under similar conditions of x-ray irradiation. In the second experiment, the effect of altering the external electric field was studied by varying the applied tube current between 5 µA - 340 µA at a fixed source to detector distance (SDD) of 26 cm. 200 frames with exposure time of 5 ms/frame were collected and summed up to get reliable measurements. Before actual acquisition of count rate measurement data, x-ray tube was activated for 20 seconds to ensure x-ray flux output was stable. The schematic diagram of experimental setup for measuring the output count rate of the detector is illustrated in Figure 5.2(a) and the x-ray spectrum used in this experimental setup is shown in Figure 5.2(b).

Figure 5.3: Count rate capability of CdTe-Medipix3RX in Charge Summing Mode (CSM) and Single Pixel Mode (SPM) at Ikrum DAC of 30 under same x-ray flux. CSM and SPM show deviation in count rate from linear fit beyond 40 and 80 µA of tube current (120 kVp) respectively. Detector was equalised and energy calibration was performed separately in each mode of detector operation.
bias voltage in the range of 300 V - 600 V and tube current between 10 µA - 280 µA. And in the third experiment, the effect of different Ikrum DAC values (10 - 100) on count rate capability of CdTe-Medipix3RX was studied. The second and third experiments were run only in CSM.

### 5.3 Results

#### 5.3.1 Count rate capability of CdTe-Medipix3RX

Figure 5.3 shows the output count rate measured as a function of x-ray flux using CdTe-Medipix3RX in Single Pixel Mode and Charge Summing Mode. The measured output count rate was averaged over a selected region of interest of a chip with 110 pixels (excluding pixels counting zero). Linear least square fit of count rate was performed based on lower region (below 50 µA) of count rate in SPM. CSM and SPM show deviation in count rate from linear fit beyond 40 and 80 µA of tube current respectively. There is a notable difference in the count rate capability of these two modes of detector, especially at higher x-ray flux. This difference in count rate capability is due to the difference in functional pixel architecture between two modes of detector operation.

In Charge Summing Mode, inter-pixel communication takes place to perform charge summing that takes account of spread of charge across the adjacent pixels. The inter-pixel communication network involves an arbitration circuit that unambiguously allocates the hit to the pixel that has the largest charge deposit, and a summing circuit that reconstructs the charge in clusters of 2 × 2 pixels. When a photon is recorded by a pixel in Charge Summing Mode, its adjacent 8 neighbours become disabled from getting the hit [Ballabriga et al., 2011a]. However, in Single Pixel Mode, each pixel is independent of its neighbouring pixel. Because of absolute time delay and larger dimension in executing charge summing algorithm, the dead time (≈ 7 µs) is longer in Charge Summing Mode than the dead time (≈ 0.7 µs) in Single Pixel Mode. This makes Charge Summing Mode less capable of coping with high x-ray flux.
Chapter 5. Count rate capability of photon-counting detector

(a) Figure 5.4: (a) Effect of bias voltage on count rate capability of CdTe-Medipix3RX operating in Charge Summing Mode. The higher the bias voltage, the higher the measured count rate at higher x-ray fluxes. (b) Effect of Ikrum DAC values on count rate capability of CdTe-Medipix3RX operating in Charge Summing Mode. The higher the Ikrum DAC value, the higher the measured count rate at higher x-ray flux. However, the lower Ikrum DAC values result low measured count rate at lower flux.

5.3.2 Effect of bias voltage and Ikrum DAC values on count rate

Figure. 5.4(a) shows the effect of bias voltage on count rate capability of CdTe-Medipix3RX operated in Charge Summing Mode. By increasing the bias voltage, the charge collection efficiency of the detector increases due to reduced charge trapping and recombination. The increased charge collection efficiency leads to improvement in count rate.

Similarly, Figure 5.4(b) shows the effect of Ikrum DAC on count rate capability of CdTe-Medipix3RX. Ikrum DAC value controls the discharge current of the charge sensitive preamplifier. It can be observed that after the x-ray tube current reaches a critical flux (150 µA), the linear response of the count rate capability breaks down at Ikrum DAC value of 10. However, the count rate capability at higher Ikrum DAC follows a roughly linear trend-line until higher x-ray flux. This shows that by increasing the Ikrum DAC value, the linear range of the measured count rates can be extended.

Figure. 5.5 shows the image inhomogeneities induced by changing the bias voltage and Ikrum DAC values. The most likely cause for image inhomogeneity is due to increased leakage current in the sensor pertaining to the defect areas. The higher the leakage current,
5.3. Results

Figure 5.5: Flat field images obtained with the CdTe-Medipix3RX in CSM at (a) different bias voltages above lower energy threshold of 18 keV at x-ray tube voltage of 120 kVp, tube current of 160 µA and Ikrum DAC of 30. The image inhomogeneity of the detector increases as the number of non-counting pixels increases with the bias voltage. It is observed that the wrinkle pattern diminishes with the bias voltage. (b) Different Ikrum DAC values above an energy energy threshold of 18 keV at x-ray tube current of 170 µA and bias voltage of 600 V. The image inhomogeneity of the detector decreases as the number of non-counting pixels decreases with the Ikrum DAC values.

the higher the temperature and it may lead to higher polarisation effect in CdTe. The increased leakage current may cause a voltage at the low discriminator input to exceed its threshold. The higher bias voltage increases the leakage current and results in a greater number of non-counting pixels as shown in Figure. 5.6(a). However, increased level of leakage current can be compensated for by increasing the Ikrum DAC values which reduces the number of non-counting pixels as shown in Figure. 5.6(b).
Figure 5.6: Number of non-counting pixels (counting 0 counts) at (a) different applied bias voltage and (b) Ikrum DAC values. The higher the bias voltage, the higher the number of non-counting pixels. The higher the Ikrum DAC, the lower the number of non-counting pixels. In both cases, the lower energy threshold was set at 18 keV.

5.4 Discussion

The count rate capability of CdTe-Medipix3RX operated in Charge Summing Mode is notably lower than in Single Pixel Mode. This result agrees with the finding from Ballabriga et al [Ballabriga et al., 2011a]. The charge summing feature implemented in Charge Summing Mode involves inter-pixel communication that has an influence on the system’s ability to cope with high x-ray flux. In Charge Summing Mode, when a photon is recorded by a pixel, its adjacent 8 neighbouring pixels are disabled from registering the hit. This introduces a longer dead time in Charge Summing Mode than in Single Pixel Mode. This reduces the count rate capability of the detector in Charge Summing Mode.

A photon-counting detector is subjected to various effects that limit its count rate capability. In general, all these effects arise either from sensor or from ASIC. One of those effects that rises from the sensor is polarisation which is caused by insufficient charge transport properties of the sensor materials employed. The charge transport property of a sensor is most commonly expressed in terms of the mobility-lifetime product ($\mu\tau$), which determines the mean free path length ($\lambda = \mu\tau E$) of the charge carrier under an external electric field of E. In a CdTe sensor, the $\mu\tau$ of a hole is lower by one order of magnitude than $\mu\tau$ of an electron.
5.4. Discussion

[Sordo et al., 2009]. This implies that there is an accumulation of holes beyond a threshold of incident x-ray flux that results in a weakening or complete breakdown of the electric field applied [Bale and Szeles, 2008].

The other effect, rising from the ASIC that limits the count rate capability of a photon-counting detector is due to speed of readout electronics. The speed of readout electronics can be expressed in term of peaking time and dead time. The peaking time is the time required for a pulse shaped by the ‘Shaper’ in pre-amplifier circuit to reach its maximum amplitude, while the dead time is the minimum amount of time that must separate two pulses in order for them to be recorded as separate pulses. The dead time is related to the peaking time, and the theoretical minimum dead time is equal to two times the peaking time. However, the dead time is much longer in practice in a photon-counting detector, due to a very large number of channels [Bale and Szeles, 2008].

Additionally, pulse pile up can also occur on the “digital” side of the ASIC and it can affect the count rate capability of the detector. Pulse pile up is a function of count rate and dead time in a photon-counting detector. Due to digital pulse pile up, the counter of each pixel will not be able to differentiate multiple quasi-coincident photons above a certain threshold of incident x-ray flux. As a consequence pulses overlap (as shown in Figure 5.1) and counts are lost. This leads to registration of incorrect energy information.

The count rate capability improves with bias voltage and Ikrum DAC values (Figures 5.4(a) and 5.4(b)). Higher bias voltage improves the charge collection efficiency and the count rate capability at higher x-ray flux. A higher degree of image inhomogeneity is observed by increasing the bias voltage due to increased number of non-counting pixels. By increasing the bias voltage, the leakage current level increases to the sensor pertaining to the defect regions which results in more non-counting pixels. The higher the leakage current, the higher the temperature of the pixels. This may increase the polarisation effect in CdTe.

Similarly, by increasing the Ikrum DAC value, which controls the return to zero of the preamplifier, the count rate capability is increased at higher x-ray flux. The higher Ikrum DAC values compensate the leakage current, reducing the number of non-counting pixels and image inhomogeneity. However, equivalent noise charge (ENC) of the pulse shapers increases with the Ikrum DAC. This degrades the energy response of the detector [Koenig et al., 2012].
5.5 Summary

1. I investigated the count rate capability of CdTe-Medipix3RX operated in Charge Summing Mode and Single Pixel Mode. I found that count rate capability in Charge Summing Mode is notably lower than in Single Pixel Mode, especially at higher x-ray flux. CSM and SPM show deviation in count rate from linear fit beyond 40 and 80 µA of tube current respectively. To avoid count loss, we need to use a tube current as small as possible in CSM.

2. Count rate capability of CdTe-Medipix3RX operated in Charge Summing Mode improves with bias voltage due to enhanced charge collection efficiency. However, image inhomogeneity increases due to increased number of non-counting pixels with the bias voltage.

3. Count rate capability and image inhomogeneity of CdTe-Medipix3RX operated in Charge Summing Mode improves with Ikrum DAC Values due to compensation of leakage current. However, the selection of Ikrum DAC value needs to be optimised for good noise and spectral performance of the detector.
Chapter 6

Performance evaluation of MARS scanner

6.1 Introduction

This chapter evaluates the overall performance of a MARS scanner incorporating a CdTe-Medipix3RX detector. Methods to evaluate the performance of an x-ray tube and energy-resolving detector are presented. The performance of an x-ray tube was evaluated by measuring the temporal stability and operational characteristics of tube voltage and tube current. Similarly, the performance of an energy-resolving detector was evaluated by measuring its spatial resolution, noise performance, spectral resolution, linearity of energy response with various concentrations of a contrast agent for reliable quantification, and contrast-to-noise ratio at different energies. In this chapter, I also aim to demonstrate the number of flat field images required to reduce the inter-pixel variation of counts across a pixel matrix consistently.

Knowledge of the performance of an imaging system is very important because it allows one to optimise the imaging parameters in advance of a particular study. The impact of image quality on an imaging task, such as sensitivity and specificity of detecting a lesion, can also be determined. Various imaging tasks require differing levels of image quality; an image may be
of sufficient quality for one task, but may be inadequate for another task. The requirements of image quality for soft tissue imaging with CT are stricter than other studies such as phantom study or bone imaging as multiple soft tissues possess low contrast due to similar x-ray attenuation properties. Random and systematic uncertainties for soft tissue imaging from all sources should be as low as possible to maximise the conspicuousness of tissue components. The metrics for assessment of system performance presented in this chapter can be used as quality control tools to check the design, performance and consistency of different imaging systems.

The findings reported in this chapter have been presented in numerous departmental seminars and have led to the improvement of image quality across the whole MARS project.

6.2 Materials and methods

6.2.1 MARS scanner overview

A MARS scanner is a pre-clinical spectral imaging system, comprised of a MARS camera, a micro-focus x-ray source (Source-Ray Inc, Ronkonkoma, NY, USA) and various mechanical components. The components and imaging performance depends on the model of MARS scanner, however, the overall architecture of MARS scanners are more or less the same. The x-ray source (Source-Ray SB-120-700-P-CW), used for this study, has a tungsten anode and intrinsic filtration of 1.8 mm aluminium (equivalent) and focal spot of \(\approx 50 \mu m\).

The detector model was Medipix3RX ASIC bump-bonded to a standard high resistivity 2 mm thick CdTe pixel sensor layer attached to a Peltier cooling device. The sensitive area of each chip was \(1.408 \times 1.408 \, cm^2\), which is subdivided into a 128 \(\times\) 128 array of pixels with a pixel pitch of 110 \(\mu m\). The CdTe sensor layer was configured as a ‘pn junction’ diode supplied with a negative high-voltage bias (-750 V) for collection of electrons. A custom readout circuit is used to interface the Medipix ASICs within the MARS camera to standard high speed 1000BASE-T (also known as IEEE 802.3ab) Ethernet. The software system comprises a custom built libMars C library and a python interface, which provides control of the MARS camera through a gigabit ethernet cable. Communication with the x-ray source and motors was enabled through an RS-485 serial interface.
For typical spectral x-ray imaging, a user mounts a sample in a sample holder and selects the region of interest (ROI) to scan. Then the user specifies all the image acquisition parameters such as x-ray exposure (tube voltage (kVp), tube current (µA) and acquisition time (ms)), energy thresholds and runs the scan. Once such a scan is initiated, the control computer instructs the gantry to rotate to the desired orientation as specified by the user. The computer then sends instructions to the x-ray generation system and a scan is performed. The high-voltage x-ray generator quickly reaches the specified tube voltage and keeps both the voltage and the current of an x-ray tube at the specified level during the scan. The x-ray tube produces x-ray flux, and the x-ray photons are detected by a MARS camera equipped with an energy-resolving detector.

The energy-resolving detector measures the energy of each individual transmitted x-ray photon and generates the electrical signal for each photon. The amplitude of an electrical signal (pulse) is proportional to the energy of each photon. At the same time, the energy-resolving detector samples the detector outputs at a uniform sampling rate and converts analog signals to digital output, and provides photon counts which are registered in each pixel individually. The sampled data are then sent to the Picture Archiving and Communication System (PACS) for archiving. Typically, the system contains high-speed ethernet network. The archived data are stored in Digital Imaging and Communications in Medicine (DICOM) standard and then transferred to image pre-processing and reconstruction workstation.

6.2.2 Phantom designs

1. **Slanted edge phantom**: A 250 µm thick lead foil, which can be angulated with respect to pixel matrix, was used as an attenuating object. Since lead is soft, it was protected with Perspex. The design of this phantom is similar to the phantom used by Samei et al [Samei et al., 1998]. This phantom was prepared to measure the pre-sampling MTF of detector. The photograph of a slanted edge phantom and its holder is shown in Figure 6.1.

2. **Multi-contrast phantom**: A 33-mm diameter phantom with multiple inserts (diameter of 6 mm) filled with various concentrations of iodine (9, 18, 36 mg/ml) and gold (2, 4, 8 mg/ml) based contrast agents. This phantom was used for measuring the linearity of the detector and contrast-to-noise ratio (CNR).
6.3 Performance evaluation

6.3.1 Temporal stability of x-ray source

The main x-ray exposure parameters in a MARS scanner are tube voltage (kVp), tube current (µA) and image acquisition time (ms). X-ray tube voltage determines the x-ray beam quality (penetration) and quantity (fluence) of an x-ray beam whereas tube current and image acquisition time affects only the quantity of x-ray beam. As the MARS scanner aims to accurately measure the quality and quantity of x-rays using single photon-counting detector (MARS camera), both of voltage and current need to be stable throughout the scanning time of a sample for reliable measurement of the x-ray attenuation of a scanned object.

The temporal stability of x-ray source was assessed by monitoring two independent signals simultaneously: (a) photon counts measured with the detector and (2) Analog-to-Digital Converter (ADC) signal of an x-ray tube. X-ray tube was energised using 120 kVp at 30 µA tube current. CdTe-Medipix3RX operated in Charge Summing Mode was used to acquire 3000 frames with the exposure time of 5 ms/frame acquisition time when x-ray tube was
energised. The ADCs are used in an x-ray tube to convert electrical signal into digital signal. Analog signal sent to ADC which is in proportion to the tube voltage and tube current that was monitored and it is written to DICOM header of each frame. Retrospectively, the mean counts across the frame and ADC signal of tube voltage and tube current were analysed.

Figure 6.2 shows the temporal stability of an x-ray source as a function of acquisition time. It can be observed that mean counts (upper row) vary by $\approx 2\%$, ADC signal of tube voltage (middle row) varies by $\approx 0.03\%$ and tube current (bottom row) varies by $\approx 1\%$ over 3000 frames. It can also be observed that mean counts, and ADC signal of tube voltage and tube current show maximum variation over first 700 frames. This implies that the x-ray tube needs few minutes to reach the more stable state.
6.3. Performance evaluation

Figure 6.3: Establishing the relationship between x-ray exposure and measured counts. Measured counts forms the (a) linear relationship with x-ray tube and (b) parabolic relationship with x-ray tube voltage. The error-bar is based on Poisson statistics of photon counts. Measurements were taken using CdTe-Medipix3RX with 25 ms acquisition time and source to detector distance of 28.2 cm.

6.3.2 Operational characteristics of x-ray exposure parameters

Photon counts measured by the detector are determined by x-ray exposure parameters such as tube voltage and tube current. The major objective of studying the operational characteristics of exposure parameters is to ensure that an x-ray tube in MARS scanner can deliver a one-to-one proportionate exposure when increasing or decreasing the tube voltage (kVp) and tube current (µA).

X-ray tube current in an x-ray tube is the flow of electrons from the cathode (filament) to the anode (target) at a given tube voltage. Each electron has the potential to produce an x-ray when bombarding the target (anode). By increasing the tube current, or number of electrons, the probability of x-ray generation will increase linearly.

The increase in the x-ray output with increase in voltage, however, is much greater than that given by a linear relationship; the output of an x-ray tube varies approximately as a square of tube voltage (kVp). The actual shape of the x-ray spectrum depends on the total filtration, anode angle and applied tube voltage in the x-ray tube.
To study the operational characteristics of tube current and tube voltage, multiple images were acquired at different tube currents of 20, 60, 100, 140, 180, 220, 260, 300 and 340 $\mu$A at 60, 80, 100 and 120 kVp. Figure 6.3(a) establishes the linear relationship between various tube currents (at various tube voltages) and measured photon counts. Similarly, Figure 6.3(b) establishes the parabolic relationship between tube voltage (at various tube currents) and measured photon counts. The error bars in Figures 6.3(a) and 6.3(b) were calculated from Poisson statistics.

### 6.3.3 Spatial resolution

Any imaging system should resolve the structural detail to delineate the morphological or anatomical information of an object. The spatial resolution is a metric to quantify the ability of an imaging system to resolve two unique objects closely separated in space. The limiting spatial resolution is typically defined as the maximum spatial frequency for which modulation is preserved without aliasing. The limiting spatial resolution is typically measured in line pairs per unit length (usually mm in CT or x-ray radiography). The ability to detect an object, and hence resolve it from its neighbour, is related to the signal-to-noise ratio (SNR) of the object.

In any digital system, the Nyquist theory must be taken into account. The frequency corresponding to the sample distance which is equivalent to the pixel size should be at least twice the highest spatial frequency to detect [Schwarz, 2001]. The Nyquist frequency is the highest frequency that may be reconstructed from the sampled data and, for pixel detectors is calculated as

$$f_{\text{Nyquist}} = \frac{1}{2 \times \text{Pixel pitch}}$$

(6.1)

The modulation transfer function (MTF) is a measure of the spatial resolution which combines contrast transfer and resolution in one figure of merit. It expresses the contrast transfer as a function of the spatial frequency. MTF is defined as the absolute value ratio of modulation contrast of object and modulation contrast of image at a given spatial frequency. The MTF quantifies the degradation of the details of an imaging system as a function of spatial frequency.
6.3. Performance evaluation

Figure 6.4: Demonstration of different steps of calculating pre-sampled Modular Transfer Function (MTF) of CdTe-Medipix3RX with pixel pitch of 110 µm operated in Charge Summing Mode using slanted edge technique. (a) Step 1: selection of region of interest within a flat-field corrected image for measuring the MTF (b) Step 2: measured oversampled edge spread function (ESF) within the region of interest selected from Step 1. (c) Step 3: oversampled line spread function (LSF) which is the derivative of ESF (d) Step 4: Calculation of MTF obtained by performing Fourier transformation of the first derivative of the corresponding ESF. The Nyquist frequency (4.55 lp/mm) corresponding to the pixel pitch of 110 µm is indicated by the vertical red line. 50% MTF corresponds to 234 µm.
Table 6.1: A summary of pre-sampling MTF measurement.

<table>
<thead>
<tr>
<th>Detector</th>
<th>CdTe-Medipix3RX</th>
<th>Si-Medipix3.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camera operation mode</td>
<td>Charge Summing Mode</td>
<td>Single Pixel Mode</td>
</tr>
<tr>
<td>Pixel pitch (µm)</td>
<td>110</td>
<td>55</td>
</tr>
<tr>
<td>Nyquist frequency (lp/mm)</td>
<td>4.54</td>
<td>9.09</td>
</tr>
<tr>
<td>X-ray exposure</td>
<td>120 kVp, 150 ms, 30 µA</td>
<td>50 kVp, 600 ms, 400 µA</td>
</tr>
<tr>
<td>Focal spot size (µm)</td>
<td>≈ 50</td>
<td>≈ 35</td>
</tr>
</tbody>
</table>

It is common to report the so-called pre-sampling MTF, which gives the spatial resolution of the sensor in a manner independent of the pixel pitch, i.e. prior to spatial sampling. As Line spread function (LSF) is difficult to obtain in the x-ray regime, the Edge Spread Function (ESF) is the preferred method of measuring the system response function of radiographic systems. There are two clear benefits of using ESF for measuring MTF. Firstly, an edge is easy to produce for almost any imaging system, although issues such as the position of the edge need to be carefully considered. Secondly, the ESF is amenable to measuring the pre-sampled MTF of digital systems [Dance et al., 2014]. The ESF can be measured readily by tilting a strongly attenuating edge (I used lead) at a few angles against a pixel row or column.

The different degrees by which individual pixels are shadowed then results in an effective over-sampling of the ESF and hence the ESF can be measured even for cases where pixels are much larger than the characteristic length scale at which it changes from zero to its maximum [Koenig et al., 2014].

Two separate pre-sampling MTF measurements, as described by Buhr et al ([Buhr et al., 2003]), were performed: with CdTe-Medipix3RX operated in Charge Summing Mode with pixel pitch of 110 µm, and Si-Medipix3.1 operated in Single Pixel Mode with pixel pitch of 55 µm. Image acquisition parameters for both measurements are illustrated in Table 6.1. The pre-sampling MTF measurement starts with imaging a well-defined edge placed at a small angle to the pixel matrix/array.

The algorithm for the determination of the pre-sampled MTF from the image of a slanted edge generally consists of the following steps:

1. Finding the position of edge in the selected region of interest of an image
6.3. Performance evaluation

Figure 6.5: Measurement of pre-sampled Modular Transfer Function (MTF) of Si-Medipix3.1 with pixel pitch of 55 µm operated in Single Pixel Mode using slanted edge technique. The Nyquist frequency (9.09 lp/mm) corresponding to the pixel pitch of 55 µm is indicated by the vertical red line. 50% MTF corresponds to 119 µm.

2. Using the edge position information, find the distance of each point from the edge to construct a oversampled Edge spread function (ESF).

3. Using a local weighted linear fit approach to to smooth the edge spread function

4. Differentiating the SS-ESF, and smoothing to get the line spread function (LSF)

5. Performing fourier transform (FFT) on LSF to get MTF

Figures 6.4(a), 6.4(b), 6.4(c), 6.4(d) show the different steps used for measuring the Modular Transfer Function (MTF) of CdTe-Medipix3RX (110 µm of pixel pitch) operated in Charge Summing Mode; 50% of MTF corresponds to 234 µm. Similarly, Figure 6.5 shows the MTF of Si-Medipix3.1 (55 µm) operated in spectroscopic Single Pixel Mode is 119 µm at 50% MTF.
6.3.4 Noise performance

The process of generating x-ray photons is random in nature. The intrinsic statistical fluctuation in the number of x-ray photons is called x-ray quantum noise. X-ray quantum noise follows the Poisson distribution. A fundamental principle of the Poisson distribution is that the variance, \( \sigma^2 \), is equal to the mean value, \( \mu \). It is useful to test whether the images recorded by a MARS scanner are limited by the x-ray quantum noise or not on the basis of mean variance equality. To test it, 3000 flat field images were acquired at 120 kVp and 30 \( \mu \)A of tube current with the exposure time of 5 ms/frame and 150 ms/frame acquisition time. The mean and variance were calculated and evaluated on per pixel basis. Figures 6.6(a) and 6.6(b) show the mean-variance equality of photon counts measured with CdTe-Medipix3RX operated in Charge Summing Mode at 5 ms/frame and exposure time of 150 ms/frame respectively. It confirms that photon counts measured with MARS scanner follows the Poisson distribution.

CdTe-Medipix3RX is an energy-resolving photon-counting detector. The lowest possible energy (lower energy boundary) that can be measured with this detector is limited by the noise level of the detector. To determine the lower energy boundary of the detector, a threshold scan (energy threshold was swept from 0 to 150 threshold DAC with the step size of 2 and image frame was acquired at each threshold DAC - further detail on threshold scan can be found on Chapter 3 was run in dark condition (without exposing with x-ray photons).

Then, the number of pixels counting equal or more than 1, 10, 100 and 1000 were counted (Figure 6.7). It shows that there are a significant number of noisy pixels up to 35 threshold DAC (\( \approx 9 \) keV). So, the lowest energy boundary of detector is 9 keV. This is the energy level to which we set the arbitration counter of Charge Summing Mode for acquiring the images.

Image noise is said to be uncorrelated if the value in each pixel is independent of the values in other (neighbouring) pixels. Uncorrelated noise is called ‘white noise’ because all spatial frequencies are represented in equal amounts. All x-ray noise in images starts as white noise, since the production of x-ray quanta is uncorrelated both in time and in space. Thus, the probability of creating an x-ray at any point in time and in any particular direction does not depend on the previous quanta that were generated, nor on any subsequent quanta [Dance et al., 2014].

The correlation of image noise in spatial frequency domain can be evaluated by measuring the Noise Power Spectrum (NPS) which is defined as the variance per frequency range of
6.3. Performance evaluation

the stochastic signal in the spatial frequency domain. It describes the spatial decomposition of the noise variance in an image as a function of spatial frequency. According to Sampling theorem, aliasing in a digital system occurs when the image contains frequencies higher than the Nyquist frequency.

To measure the NPS of MARS camera, 2000 flat field images were acquired at 120 kVp with 200 ms exposure time and 30 µA tube current. Source to detector distance (SDD) was maintained at 28.2 cm and total filtration of 4.6 mm Al was used. The region of interest avoiding dead (counting 0) and hot pixels (counting 4095) was selected and an algorithm to calculate the NPS was applied. NPS can be determined by calculating the modulus-squared Fourier transform of homogenously irradiated images with large sampling size.

Figure 6.8 shows the NPS measurement of CdTe-Medipix3RX operated in Charge Summing Mode. It was observed that NPS is maximum at zero frequency and relatively flat response at higher spatial frequencies (> 1.4 lp/mm) implying that the detector system is working within quantum noise.

![Figure 6.6(a)](image1)
![Figure 6.6(b)](image2)

Figure 6.6: Demonstration of per pixel mean-variance equality of Poisson distribution of photon counts measured with CdTe-Medipix3RX detector operated in Charge Summing Mode over 3000 frames acquired with 120 kVp, 30 µA tube current and exposure time of (a) 5 ms per frame and (b) 150 ms per frame.
6.3.5 Spectral resolution

Even though Fano factor is the fundamental limit for the spectral resolution of a semiconductor detector (further details are given in chapter 2), different underlying physical processes such as charge trapping in the sensor as well as the noise from the leakage current in the sensor and the electronics noise in the readout circuit will reduce the spectral resolution of the detector. Spectral resolution determines the ability of an energy-resolving detector to differentiate two photons closely separated in energy. It affects the sensitivity and specificity of material identification and characterisation. So, spectral resolution of the detector needs to be assessed before using it in biomedical applications.

Ideally, spectral resolution is determined by measuring the energy response function of a well-defined reference energy source such as monochromatic photon beams emitted from a radioisotope or a synchrotron. However, these types of energy sources are not easily available in a pre-clinical imaging lab. As explained in Chapter 3, we can measure the x-ray fluorescence (XRF) generated from metallic targets irradiated with a polychromatic x-ray

![Figure 6.7: Integral noise floor threshold scan showing pixels counting 1, 10, 100 and 1000 counts at different threshold DACs in dark frame.](image)

![Figure 6.8: Noise power spectrum (NPS) of CdTe-Medipix3RX (CSM) measured within ROI consiting 19 × 19 pixels averaged over 2000 flat field images. The NPS demonstrates the highest noise power (variance) at close to zero spatial frequency and the flat behaviour at higher spatial frequencies (> 1.4 lp/mm).](image)
beam to determine the spectral resolution of the detector. This experiment can easily be run in
any bio-medical imaging lab using a commercially available x-ray tube. But one should note
that the width of the Gaussian peak measured with XRF from a metallic target by directly
irradiating it with polychromatic x-ray beam is affected by the transmission x-ray photons.
So, I used a different geometry, in contrast to the geometry used in Chapter 3, so that the
polychromatic x-ray beam irradiates only the metallic targets and the detector is offset to the
x-ray beam so that it measures only the XRF.

I used Mo foil to measure the spectral resolution by using polychromatic x-ray beam in
both geometries: (1) MARS camera detecting both transmitted x-ray photons and XRF from
metallic targets and (2) MARS camera detecting only XRF from a metallic foil. The spectral
resolution using two geometries was compared. Even though only XRF from a metallic target
is measured in the latter, the width of the Gaussian peak of XRF is affected by different
accompanying K-series photons; and the measured spectral resolution is wider than the true
spectral resolution of the detector. However, XRF emitted from a metallic target can be used
for measuring the ‘relative’ spectral resolution performance of different pixels or detectors
easily in a pre-clinical imaging lab.

Figure 6.9 shows the energy response function of Mo-XRF measured with CdTe-Medipix3RX
(110 µm of pixel pitch) operated in Charge Summing Mode. Full-width at half maximum
(FWHM) of XRF peaks was measured. It shows that FWHM of Mo-XRF peak measured
with direct irradiation of MARS camera with x-ray beam is 9.24 keV whereas the FWHM
of Mo-XRF peak measured without direct irradiation of MARS camera with x-ray beam is
7.93 keV. This is due to the fact that there were no transmitted x-ray photons in the latter.
However, the true spectral resolution of the detector should be lower than 7.93 keV at 17.48
keV (Kα₁ of Mo) as it is broadened by accompanying K-series photons such as Kα₂ (17.34
keV) or Kβ₁ (19.60 keV) or Kβ₂ (19.96 keV) of Mo.

6.3.6 Linearity

Linearity of a spectral imaging system can be determined by measuring the x-ray attenuation
of various concentrations of contrast agents as a function of energy. A phantom with different
inserts filled with solution of iodine contrast agent (9, 18, 36 mg/ml) was scanned with the
MARS scanner using CdTe-Medipix3RX operated in Charge Summing Mode. It was scanned
Figure 6.9: Measurement of spectral resolution of CdTe-Medipix3RX in CSM using XRF from Mo. The XRF from Mo was generated under two geometry conditions: (1) Mo foil was mounted on the front of the detector and direct x-ray irradiation was made. (2) Mo foil was mounted on the exit window of x-ray tube and the detector was off from the x-ray beam.

with 118 keV and the detector lower energy thresholds of 27, 33, 49 and 81 keV. The x-ray attenuation (HU) and standard uncertainties for ROIs comprising \( \approx 300 \) voxels over the centre of each phantom insert were measured from the reconstructed CT images at each energy threshold. The relationship between x-ray attenuation and various concentrations of different contrast agents was determined by least square linear regression for each energy threshold.

Figure 6.10 shows the linear relationship between x-ray attenuation and various concentrations of iodine contrast agent at different energy ranges. The least square linear regression indicates that the system of measurement is linear \( (R^2 \approx 0.999) \) at all energy ranges.
6.3. Performance evaluation

Figure 6.10: Linearity of x-ray attenuation (Hounsfield units) with the concentration of iodine contrast agent. The error bars are of the same order as the size of the symbols (± 9 to 35 HU), so are not shown.

6.3.7 Contrast-to-noise ratio (CNR)

Contrast-to-noise ratio (CNR) is a quantitative measure of contrast (difference in x-ray attenuation values) in a digital imaging system. CNR is an object size-independent measure of the signal level in the presence of noise. For CNR measurements, the mean values of x-ray attenuation in terms of Hounsefield Unit (HU) of the contrast elements (different concentration of I) and background material (Perspex) were measured within the circular region of interest (ROI). The pixel values of the x-ray attenuation (HU) were averaged over ≈ 300 voxels in each ROI. Additionally, the x-ray attenuation values of the background material were measured in six non-overlapped ROIs. The mean value of the x-ray attenuation of the background material and the mean value of standard deviation of the x-ray attenuation values were calculated from the data measured in these six ROIs. The CT contrast was determined as the difference between the x-ray attenuation of contrast elements and background material. The CNR was calculated as measured CT contrast related to measured CT noise as below:
Figure 6.11: Contrast-to-noise ratio (CNR) as a function of energy range for various concentration of iodine contrast agent.

\[
CNR = \frac{\mu_{\text{contrast}} - \mu_{\text{background}}}{\sigma^2_{\text{contrast}} + \sigma^2_{\text{background}}}
\]  

(6.2)

The CNR of iodine contrast agent in all subtracted energy ranges of spectral CT images was measured using the method described above. The results are presented in Figure 6.11. It shows that CNR increases with the concentration of contrast agent and it also depends on energy range used for generating the spectral images. Maximum CNR of iodine was obtained at the energy range containing the K-edge (33 - 49 keV).

### 6.3.8 Flat field corrections

Due to imperfections in the manufacturing process, the measured counts of individual pixels will vary slightly (usually by a few percent) across the grid. This effect is essentially random, and is not a function of, for example, position on the pixel matrix. The relative variation of counts of the pixels across the matrix can be reduced by normalising with the open beam frames collected by irradiating the detector uniformly with x-ray source. This is known as
6.3. Performance evaluation

Figure 6.12: Standard box plots showing the number of flat field images normalised to reduce the inter-pixel variation of counts across the pixel matrix consistently for a CdTe-Medipix3RX operated in Charge Summing Mode. Legend: Inside the box, the red line represents the median (50th percentile). The bottom and top of the box are the lower and upper quartiles (25th and 75th percentile, respectively) or inter-quartile range (IQR). The range of the whiskers is 2.7 standard deviation or 99.7% coverage.

It is commonly believed that the inter-pixel variation of counts can be improved by normalising with a large number of flat field images. But, the number of flat field images acquired needs to be limited to reduce the image acquisition time. So, the optimum number of flat field images is assumed to be a trade-off between the quality of flat field correction and total image acquisition time. I sought to test this assumption. To investigate the effectiveness of number of flat field images to reduce the inter-pixel variation of counts, 3000 flat field images were acquired at 120 kVp, 30 µA of tube current, 200 ms of exposure time per frame, 4.6 mm Al of total filtration, and 28.2 cm source to detector distance using CdTe-Medipix3RX operated in Charge Summing Mode. Flat field normalisation was done by using different numbers of flat field images and the relative x-ray attenuation values ($\frac{I}{I_0}$) across the pixel matrix were
calculated and compared. Figure 6.12 shows the number of normalised flat field images used for decreasing the inter-pixel variation of counts across the matrix consistently. It shows that beyond 300 flat field images, there is effectively no improvement in reducing the inter-pixel variation of counts.

### 6.4 Discussion

The temporal stability of an x-ray tube was demonstrated (in Figure 6.2) by measuring the photon counts measured with CdTe-Medipix3RX operated in Charge Summing Mode, and monitoring the analog-to-digital signal used for controlling the tube voltage and tube current simultaneously. It shows that x-ray tube needs a few minutes to reach the more stable state. Similarly, operational characteristics of x-ray exposure parameters such as tube current and tube voltage were determined. It was demonstrated that the number of measured photon counts varies linearly with tube current (at different tube voltages as shown in Figure 6.3(a)) and parabolically with tube voltage (at different tube currents as shown in Figure 6.3(b)). This shows that a small change in x-ray tube voltage cause a large change in the x-ray output (proportional to the square of tube voltage). As a part of quality control of an imaging system, stability and operational characteristics of x-ray exposure parameters, such as tube voltage and tube current, should be measured for ensuring consistent x-ray output.

The spatial resolution of CdTe-Medipix3RX (110 µm of pixel pitch) operated in Charge Summing Mode is 234 µm (corresponding to 50% of MTF) and that of Si-Medipix3.1 (55 µm of pixel pitch) operated in spectroscopic Single Pixel Mode is 119 µm (corresponding to 50% of MTF). Even though smaller pixel pitch is desirable for providing higher spatial resolution for soft tissue imaging, it needs to be balanced with the optimal spectral resolution of the detector. So, selection of pixel pitch is a trade-off between spatial resolution and spectral resolution. Spatial resolution of 234 µm of CdTe-Medipix3RX is superior to that of clinically available CT scanners which have the spatial resolution of a few mm. However, some small structures such as small calcifications and iron deposits may be too small to resolve with existing spatial resolution [Langheinrich et al., 2009] of the MARS scanner. The spatial resolution of the MARS scanner can be increased once it is scaled to human imaging range by using higher x-ray magnification geometry. The spatial resolution of an imaging
system is primarily determined by detector pixel size at the isocenter (this is influenced by magnification), focal spot size, and reconstruction voxel size.

It was demonstrated that pixels of CdTe-Medixi3RX detector in MARS scanner follow the Poisson distribution (or Photon statistics) as mean-variance equality was observed as shown in Figures 6.6(a) and 6.6(b). It is very important for an imaging system to show the Poisson distribution to ensure reliable measurement of photon counts. Moreover, statistical noise performance affects the ability to detect low contrast materials [Lin et al., 1993, Du et al., 2007, Zarb et al., 2011]; it should be as low as possible. Similarly, the lower energy boundary of the energy-resolving detector (CdTe-Medipix3RX) was found to be close to 9 keV based on noise floor analysis of the detector. This implies that any measurement involving CdTe-Medipix3RX operated in Charge Summing Mode should operate above 9 keV to avoid the influence of noise on measured data. However, the lowest usable energy boundary is determined by total filtration used in the x-ray tube.

Similarly, measurement of Noise Power Spectrum (NPS) shows that the noise present in open uniformly irradiated images is uncorrelated or ‘white noise’ above 1.4 lp/mm spatial frequency. This is important to observe in an imaging system because all x-ray induced noise in images starts as white noise, since the generation of x-ray photons is uncorrelated both in time and in space.

This chapter has reported a pragmatic method to measure the spectral resolution of an energy-resolving detector. This can be achieved by measuring the x-ray fluorescence (XRF) generated from a metallic target by avoiding direct x-ray irradiation of the detector. This technique can be used to compare the spectral resolution performance of different pixels or different detectors. However, this technique underestimates the absolute spectral resolution as the width of an XRF peak is unreliable due to contamination of accompanying K-series photons emitted from metallic target. Monochromatic x-ray (synchrotron) or $\gamma$-ray sources (radioisotopes) are recommended for measuring the true spectral resolution of the energy-resolving detector.

Linearity of x-ray attenuation with concentration of different contrast agents in different energy range (Figure 6.10) is a \textit{sine qua non} for an imaging system to use as a quantitative tool. This shows that different amounts of calcification or iron deposits in an atherosclerotic plaque could be measured within the linear dynamic range of the detector.
Contrast-to-noise ratio (CNR) changes with the energy of photon and concentration of a contrast agent. For any spectral imaging, the energy range needs to be optimised for getting maximum CNR and energy information. Moreover, CNR improvements can be achieved by maximising the photon fluence as this reduces the statistical noise level of the detector. Similarly, the inter-pixel variation counts need to be minimised to achieve higher CNR. The inter-pixel variation of counts beyond flat field normalisation can be improved by performing pixel-by-pixel energy calibration as described in Chapter 4.

The effectiveness of number of flat field normalisation to reduce the inter-pixel variation of counts was studied. It shows that there is no additional benefit for reducing the residual inter-pixel variation of counts by increasing the number of flat field images beyond 300 frames. Apart from bad pixel masking and subtraction of dark count subtraction in flat fielding, effective removal of outlier pixels may also reduce the inter-pixel variation of counts. However, the inter-pixel variation in counts across the matrix may not be improved beyond certain point. Pixel-by-pixel energy calibration or/and threshold equalisation with higher (compared to the noise floor of the detector) reference energy may be useful to reduce the inter-pixel variation of counts.

Despite some limitations as discussed above, the current performance of MARS scanner is adequate for spectral imaging. The methods of assessing the performance of MARS scanner presented in this chapter can be used as quality control tools for studying the consistency of the system. The performance has been demonstrated in terms of x-ray source stability, operational characteristics of x-ray exposure parameters, spatial resolution, noise performance, spectral resolution, linearity, contrast-to-noise ratio in a phantom study and effectiveness of number of flat field normalisation. The combined benefits of the spatial and spectral resolution offered by using CdTe-Medipix3RX in MARS scanner will enable material quantification and characterisation in spectral imaging.

6.5 Summary

1. X-ray exposure parameters, such as tube current and tube voltage, in the MARS scanner are stable for spectral imaging after few minutes of x-ray tube operation. Operational characteristics of x-ray exposure parameters are found to be consistent as expected.
2. The spatial resolution of CdTe-Medipix3RX (110 µm of pixel pitch), measured with slanted edge phantom, was found to be 234 µm, corresponding to pre-sampled MTF of 50%. The combined benefits of the spatial and spectral resolution offered by using CdTe-Medipix3RX in MARS scanner will enable material quantification and characterisation in spectral imaging.

3. Pixels of CdTe-Medipix3RX operated in Charge Summing Mode shows the intra-pixel mean-variance equality which confirms that the pixels follow the Poisson distribution. The lower boundary energy of detector was found to be close to 9 keV, below which electronic noise predominates. However, the lower useful energy boundary for spectral imaging depends on the total filtration used in the x-ray spectrum. All measurement should be made above this energy threshold. Noise above 1.4 lp/mm of spatial frequency found to be uncorrelated noise or ‘white noise’.

4. Spectral resolution performance of pixels or detectors can be determined by measuring the energy response function of x-ray fluorescence emitted from metallic targets. However, the width of XRF peak is overestimated by accompanying K-series photons which need to be taken into account for measuring the ‘true’ spectral resolution of the detector.

5. The linearity of x-ray attenuation with concentrations of contrast agents (iodine and gold nano-particles) was established at different energy ranges.

6. Contrast-to-noise ratio changes with energy and concentration of iodinated contrast agent. Photon fluence needs to be optimised with the energy range width to maximise CNR.

7. Flat field normalisation beyond 300 frames does not provide any benefits in reducing residual inter-pixel variation of counts, in this particular study. However, this needs further investigations at different imaging geometry and x-ray exposure settings. Per-pixel energy calibration and threshold equalisation with high reference energies may be helpful to reduce the residual inter-pixel variation of counts.

8. Imaging performance of a MARS scanner is adequate for spectral imaging.
Chapter 7

Ex-vivo characterisation of human atherosclerotic plaque

7.1 Introduction

This chapter reports on investigations carried out to study the potential of spectral CT for ex-vivo characterisation of composition of human atherosclerotic plaque within human imaging energy range (30 - 120 keV). Spectral CT measures the energy response (x-ray attenuation as a function of photon energy) of multiple-components of an atherosclerotic plaque in a single scan and may allow them to be quantified and differentiated from each other simultaneously. Characterisation of plaque composition is important to assess the plaque’s vulnerability to rupture.

The study reported in this chapter can potentially have a high clinical impact when spectral CT is translated into human imaging as it may help in non-invasive detection of vulnerable plaques within vulnerable patients before disruption or rupture of the plaque. This may allow clinicians to identify and diagnose the vulnerable plaques before they cause adverse cardiovascular events (stroke, myocardial infarction and peripheral vascular diseases). This technique can also be used for monitoring the treatment response of atherosclerosis.
7.1. Introduction

Unstable plaque or vulnerable plaque is the dangerous by-product of atherosclerosis. Rupture of vulnerable atherosclerotic plaques is the major cause of morbidity and mortality in the Western world accounting for \( \approx 70\% \) of heart attacks [Bhatt et al., 006c, Naghavi et al., 2003]. It is widely recognized that the risk of vulnerable plaque rupture and consequent adverse cardio-vascular events is primarily related to the composition of the plaques [Davies and Thomas, 1985].

A bio-marker of plaque instability or vulnerability is a measurable characteristic features which can be used as an indicator of the presence or severity of a particular pathophysiological status of atherosclerosis. Individuals with such atherosclerotic lesions would make them at increased risk of cardio-vascular events in the future. A bio-marker of plaque vulnerability is intended to be used not for diagnosis but for risk stratification. The concept of bio-markers in atherosclerotic lesion also implies some sort of mechanistic link between the bio-marker and plaque rupture. A vulnerable plaque is characterised by following biomarkers: thin fibrous cap, low collagen content, large lipid (fat) pool, many inflammatory cells, angiogenesis, and intra-plaque haemorrhage [Finn et al., 2010, Cai et al., 2002]. All these bio-markers are related to the composition of a plaque or its patho-physiological status.

The major goal of atherosclerosis imaging is to detect, treat and monitor vulnerable plaque which may cause strokes and cardio-vascular events caused by acute thrombotic or embolic events occurring due to rupture of the fibrous cap [Cormode et al., 2010, Falk et al., 2011]. In order to improve the clinical outcome, imaging needs to determine the composition of the plaque rather than plaque burden or luminal stenosis [Zhao et al., 2011]. Current commonly used clinical imaging techniques are limited to assessing the severity of luminal narrowing in symptomatic patients [Stary HC, 1995] as stenosis grading is still used in therapeutic decision making [Rothwell et al., 2004]. Clinically available screening and diagnostic methods in atherosclerosis imaging are insufficient for identifying a vulnerable patient before a cardio-vascular event occurs.

The study reported in this chapter aims to distinguish multiple intrinsic bio-markers such as fat component, water (soft tissue) component and calcium deposits in an excised human atherosclerotic carotid plaque simultaneously within human imaging energy range (30 - 120 keV). As explained in section 2.2, x-ray interaction cross section varies distinctly with photon energy. The lower energy photons provide excellent soft tissue contrast due to dominance of photo-electric effect. Figure 2.2 demonstrates that different soft tissue components such
as water, adipose tissue (lipid), blood (haemorrhage) have maximum separation in x-ray attenuation below 50 keV. Moreover, Si is a matured sensor material which shows good imaging performance due to its remarkably homogenous and pure crystals. So, I have used spectral CT to characterise the plaque composition within pre-clinical imaging range (15-50 keV) using Si based detector as a preliminary step towards transiting to human imaging energy range to characterise the plaque composition. It is observed that soft tissue contrast diminishes above 50 keV as shown in Figure 2.2. And also, Compton scattering and charge sharing which dominate at higher energies, degrade the spectral performance of energy-resolving photon-counting detector, particularly when the detector is operated in Single Pixel Mode as in this study. So, characterising the soft tissue components in human energy range is an extremely challenging task.

Furthermore, the photon interaction cross section for a 300 µm thick silicon sensor is rather low (flux weighted average efficiency ≈ 14%) and radiation dose may be an issue for some in vivo studies. As MARS project aims to build up a spectral CT scanner for human imaging, Si is not the suitable sensor material due to its low stopping power within human imaging energy range. So, I used GaAs based detector for spectral imaging of an atheroma within human energy range. GaAs is high-Z (Z = 31 & 33) sensor material which has the quantum detection efficiency of ≈ 70 % with 2 mm thickness. This makes GaAs a more dose efficient sensor than Si.

Some parts of the investigation reported in this chapter have already been published and presented in national and international conferences [Panta et al., 2014b, Gieseg et al., 2014, Panta et al., 2013b, Panta et al., 2013a]. A manuscript based on some parts of the investigation reported in this chapter is under preparation for a peer-reviewed journal.

## 7.2 Materials and methods

The technique developed in this work takes advantage of multi-energy information from spectral CT employing energy-resolving photon-counting detectors. It provides the assessment of plaque’s vulnerability by distinguishing independent intrinsic bio-markers.
7.2. Materials and methods

7.2.1 Atheroma sample preparation

From the consented patients undergoing carotid endarterectomy, fresh carotid plaques were obtained, transported on ice, and stored at \(-80^\circ\) C. Each plaque was placed in a 20-mm (diameter) polypropylene tube for spectral imaging and cooled via a modified vacuum flask filled with liquid nitrogen (LN\(_2\)). The photographs of carotid plaque just before acquiring spectral CT images are shown in Figure. 7.1.

7.2.2 Experimental setup and spectral CT data acquisition

A MARS scanner (MARS Bioimaging Ltd., Christchurch, New Zealand) [Butler et al., 2008, Anderson et al., 2010, Walsh et al., 2011] is a spectral imaging system that uses the Medipix detector for acquiring energy-resolving images. It houses a micro-focus x-ray tube (Source-Ray, Ronkonkoma, NY) with \(\approx 50 \mu m\) focal spot, a tungsten anode and 1.8 mm aluminium (equivalent) intrinsic filtration. All experiments were carried out using MARS scanner. The experimental setup for acquiring the spectral CT data of a carotid plaque is shown in Figure. 7.2. A cooling chamber (liquid nitrogen) was used to maintain the temperature of the specimen near \(\approx 0^\circ\) C for the duration of the scan. This helps to avoid bio-degradation of the plaque at room temperature.

The comparative experimental settings used for acquiring spectral CT images of a carotid
plaque within pre-clinical imaging energy range and human imaging energy range are presented in Table 7.1. Si-Medipix3.1 was used at 50 kVp to acquire spectral CT images within pre-clinical imaging energy range (15 - 50 keV) and GaAs-Medipix3.1 was used at 120 kVp to acquire spectral CT images within the human diagnostic energy range (30 - 120 keV). In both cases, MARS camera was operated in spectroscopic Single Pixel Mode for acquiring spectral CT data. A 10 mm Al filter was added and mounted on the exit window of x-ray tube when acquiring spectral CT images within the human diagnostic energy range. Total filtration of 11.8 mm Al blocks all the lower energy photon up to 30 keV. As this study aims to characterise the plaque composition in human energy range, photons with energy lower than \( \approx 30 \text{ keV} \) contribute only to radiation dose because of their low probability of penetrating thorough the body and hence they do not contribute soft tissue contrast.

Some preliminary work was done to find out the best possible acquisition parameters, however the majority of this work includes phantom studies and biological specimen imaging. Before performing any experiments, threshold equalisation and energy calibration of the detector was carried out as explained in Chapter 3.

In both experiments, each sample was scanned using 720 projection angles. Where nec-

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Figure 7.2: Photograph showing the experimental set up for spectral scanning of a plaque. LN\(_2\) was used for maintaining the low temperature during scanning the specimen so that it avoids the bio-degradation at room temperature.
### Materials and methods

Table 7.1: Experimental settings of spectral CT of an excised human carotid atheroma in two different energy regimes.

<table>
<thead>
<tr>
<th>Energy range</th>
<th>Pre-clinical imaging (15-50 keV)</th>
<th>Human imaging (30-120 keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scanner</strong></td>
<td>MARS scanner</td>
<td>MARS scanner</td>
</tr>
<tr>
<td><strong>Biological specimen</strong></td>
<td>Excised human carotid atherosclerotic plaque</td>
<td>Excised human carotid atherosclerotic plaque</td>
</tr>
<tr>
<td><strong>Calibration phantom</strong></td>
<td>H$_2$O, fat, CaCl$_2$(100, 140, 200 mg/ml), air</td>
<td>H$_2$O, fat, CaCl$_2$(100 &amp; 200 mg/ml), Fe(NO$_3$)$_3$(150 &amp; 250 mg/ml)</td>
</tr>
<tr>
<td><strong>X-ray detector</strong></td>
<td>Si-Medipix3.1</td>
<td>GaAs-Medipix3.1</td>
</tr>
<tr>
<td><strong>Sensor thickness</strong></td>
<td>300 µm</td>
<td>600 µm</td>
</tr>
<tr>
<td><strong>Camera mode of operation</strong></td>
<td>Spectroscopic SPM</td>
<td>Spectroscopic SPM</td>
</tr>
<tr>
<td><strong>Mode of scanning</strong></td>
<td>circular start–stop</td>
<td>circular start–stop</td>
</tr>
<tr>
<td><strong>Bias voltage (V)</strong></td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td><strong>Pixel matrix</strong></td>
<td>128 × 128</td>
<td>128 × 128</td>
</tr>
<tr>
<td><strong>Number of chips</strong></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td><strong>Source to detector distance (mm)</strong></td>
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<td>190</td>
</tr>
<tr>
<td><strong>Source to object distance (mm)</strong></td>
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<td>120</td>
</tr>
<tr>
<td><strong>Magnification factor</strong></td>
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<td>1.58</td>
</tr>
<tr>
<td><strong>Detector pixel pitch (µm)</strong></td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td><strong>Number of projection/rotation</strong></td>
<td>720</td>
<td>720</td>
</tr>
<tr>
<td><strong>Number of flat field frames</strong></td>
<td>720</td>
<td>720</td>
</tr>
<tr>
<td><strong>X-ray exposure</strong></td>
<td>50 kVp, 400 µA, 500 ms</td>
<td>120 kVp, 300 µA, 350 ms</td>
</tr>
<tr>
<td><strong>Total filtration (Al)</strong></td>
<td>1.8 mm (only inherent)</td>
<td>11.8 mm (1.8 mm (inherent) + 10 mm (added))</td>
</tr>
<tr>
<td><strong>Lower energy threshold (keV)</strong></td>
<td>15, 19, 23, 27, 31, 35, 39 &amp; 43</td>
<td>30, 35, 40, 45, 50, 60, 70 &amp; 80</td>
</tr>
<tr>
<td><strong>Focal spot size (µm)</strong></td>
<td>≈ 50</td>
<td>≈ 50</td>
</tr>
<tr>
<td><strong>Reconstruction algorithm</strong></td>
<td>Filtered back-projection</td>
<td>Filtered back-projection</td>
</tr>
<tr>
<td><strong>Reconstruction voxel size (µm)</strong></td>
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<td>41</td>
</tr>
<tr>
<td><strong>Slice thickness at isocenter (µm)</strong></td>
<td>65</td>
<td>65</td>
</tr>
</tbody>
</table>
Chapter 7. Ex-vivo characterisation of human atherosclerotic plaque

The field of view (FOV) at each angle was extended by moving the MARS camera vertically. Projection images were acquired at each position by stepping the detector threshold through a sequence of energy levels (8 thresholds are available in spectroscopic Single Pixel Mode) and acquiring an image at each setting. Flat field measurements for each sensor position and energy thresholds were taken before and after the sample scan so that any variations in detector performance over the duration of the scan could be identified and corrected.

After scanning, the raw projection data were corrected and normalized using a combination of the initial and final flat field projection images. Interpolation was used to replace missing or erroneous image data. Energy sensitive images were acquired using the net x-ray attenuation difference between energy thresholds. Sinograms were generated from the normalized projection data and filtered to reduce ring artifacts. Ring artifacts are caused by dead pixels or those pixels whose counts fluctuate with time. CT data were reconstructed using Octopus commercial CT reconstruction software [Dierick et al., 2004].

7.2.3 Spectral calibration phantom

Two separate spectral perspex phantoms of 10 mm diameter with 2 mm diameter inserts were fabricated for both energy schemes of pre-clinical imaging and human imaging energy range. Multiple inserts in a spectral phantom designed for pre-clinical imaging energy range contain H$_2$O, fat, CaCl$_2$ (100, 140 & 200 mg/ml) and air. Similarly, multiple inserts in a spectral phantom designed for human imaging energy range contain H$_2$O, fat, CaCl$_2$ (100 & 200 mg/ml) and Fe(NO$_3$)$_3$ (150 & 250 mg/ml). The energy response of these different materials was determined as a means of calibrating energy response of soft tissue, calcification and iron deposits in an atherosclerotic plaque. The ferric nitrate and calcium chloride solutions were prepared by dissolution and dilution. Canola oil was chosen as a suitable lipid (fat) surrogate because of its high triglyceride content.
Figure 7.3: Spectral images of (a) calibration phantom with different inserts filled with, clockwise from 12 o’clock position, CaCl\(_2\) (200 mg/ml), air, water, fat, CaCl\(_2\) (100 mg/ml), CaCl\(_2\) (140 mg/ml), (b) axial cross section of human carotid plaque (just above the level of carotid bifurcation) acquired using Si-MediPix3.1 operated in spectroscopic SPM within pre-clinical imaging range (15 - 50 keV).
Figure 7.4: Spectral images of (a) calibration phantom with different inserts filled with, clockwise from 12 o’clock position, water, fat, CaCl$_2$ (100 mg/ml), CaCl$_2$ (200 mg/ml), Fe(NO$_3$)$_3$ (150 mg/ml) and Fe(NO$_3$)$_3$ (250 mg/ml)(b) axial cross section of human carotid plaque (just above the level of carotid bifurcation) acquired using GaAs-Medipix3.1 operated in spectroscopic SPM within human imaging energy range (30 -120 keV).
Both the calibration phantoms and atherosclerotic plaques were scanned with identical imaging parameters in each energy scheme separately. The x-ray attenuation and standard deviation for each material within the selected region of interest (ROI) were measured in Hounsfield units. The relationship between x-ray attenuation as a function of its lower energy threshold was examined.

7.2.4 Material decomposition

The advantages of spectral CT are the ability to improve soft tissue contrast and allowing tissue characterisation without loss of spatial resolution. To exploit the advantage of spectral CT, an algorithm using a constrained least squares material decomposition (MD) method [Ronaldson et al., 2012] was implemented which uses the energy and material-dependent x-ray attenuation information obtained from spectral CT scan.

In this method, three-material decomposition (water, fat and calcium) was performed on a voxel-by-voxel basis, assuming there was an arbitrary mixture of materials in the corresponding voxel. Empirical spectral data obtained from calibration phantom was inputted into material decomposition algorithm as priori knowledge of the materials to be searched in an atheroma.

The simplifying assumption made is that a single voxel of an atheroma can contain water component, fat component and calcium component. They can be located in a voxel either together or in any possible combination. In the latter, each individually contributes its fraction to the voxel’s total attenuation. Therefore, a voxel should be considered as a mixture of several materials where the x-ray attenuation corresponds to the attenuation averaged over all materials.

7.3 Results

The spectral CT images of a calibration phantom and atheroma in all 8 energy thresholds within pre-clinical imaging and human imaging energy range, are shown in Figures 7.3(a), 7.3(b), 7.4(a) and 7.4(b). In both energy schemes, it can be observed that both the x-ray
attenuation and their differences (contrast) decreases and noise increases with increasing energy, as expected. Contrast decreases with energy as differential attenuation across multiple-components decreases. Noise increases due to detection of few photons and low quantum detection efficiency of Si and GaAS at higher energies. Some minor ring artifacts are visible in the spectral CT images, particularly at higher energies.

The spectral responses to different materials (CaCl$_2$, Fe(NO$_3$)$_3$, fat, and water) in calibration phantoms are shown in Figures 7.5(a) and 7.5(b) for both energy schemes. The x-ray attenuation profile of each material is consistent with the energy in both energy schemes. At low energies the x-ray attenuation for calcium or iron are much greater than those of water due to the higher probability of photo-electric effect. With increasing energy, the x-ray attenuation for these materials decrease as the relative contribution of the photo-electric effect reduces and Compton scattering becomes more significant.

Figures 7.5(a) and 7.5(b) show that the relative x-ray attenuation (HU) of fat is lower than other materials such as CaCl$_2$, Fe(NO$_3$)$_3$, and water across whole energy range. This is due to the presence of low atomic number element (eg hydrogen) in fat. Fat has lower physical density and lower effective atomic number, and therefore a lower photo-electric interaction, than other materials. For this reason, fat has lower x-ray attenuation than other materials at lower energies where the photo-electric interaction is the dominant effect.

However, Figures 7.5(a) and 7.5(b) show that relative x-ray attenuation of fat is increasing with energy, unlike other materials. This is due to the fact that fat has somewhat higher Compton interactions owing to higher electron density than other materials. Unlike other elements, the nucleus of hydrogen is free of neutrons, giving hydrogen a higher electron density (electrons/mass) than other materials. Because hydrogen contributes a larger proportion of the mass in fat than it does in other materials, fat has a larger electron density than other tissues. This becomes particularly important at higher energies where Compton interactions dominate attenuation.

### 7.3.1 Material decomposition

Multiple-components of an atherosclerotic plaque (calcium, fat and water) have identifiably different x-ray attenuation curves across the energies, making them spectrally distinguishable
7.3. Results

Figure 7.5: X-ray attenuation profiles for different materials in two different phantoms evaluated against lower energy threshold at two different energy schemes: (a) 15 - 50 keV with Si-Medipix3.1 and (b) 30 - 120 keV with GaAs-Medipix3.1. The standard errors are in the range of 3—12 HU. The x-ray attenuation as a function of energy is the characteristic of the given material. In both energy schemes, x-ray attenuation for calcium and iron (Fe) solutions with different concentrations declines as energy increases, whereas the CT number for oil (fat surrogate) increases (low Z material). The information of x-ray attenuation of various materials in a calibration phantom provides an empirical basis for use in spectral CT data analysis to differentiate and quantify unknown materials at each voxel of CT images of complex biological specimens such as atherosclerotic plaque acquired using spectral CT.

(spectrally distinct) in phantoms as shown in Figures 7.5(a) and 7.5(b). Fat-like component in the atheroma can be differentiated from water-like component even in the same voxel within both energy schemes as shown in Figures 7.6 and 7.7. However, the water-only and fat-only components of plaque tend to be complementary; they infrequently occupy the same voxel. The soft tissue component has the highest contrast at the lowest energy. The atherosclerotic plaque shows beam-hardening artefacts around the dense calcified regions, particularly in the low-energy data set, but this reduces with increasing energy as expected.

Exposure volume rendering 3D visualisation images of a segment of a plaque have been shown in Figures 7.8(a) and 7.8(b) at preclinical energy range and human imaging energy range respectively. The top row in both Figures 7.8(a) and 7.8(b) shows the fat component only and bottom row shows the material decomposition of same segment of plaque into fat-
Figure 7.6: A three-material decomposition of spectral images of an atheroma acquired with Si-Medipix3.1 detector after analysis of multi-spectral data in lower energy range (15 - 50 keV) into Ca-only, water-only and fat-only components. The majority of the atheroma is a mixture of water-only and fat-only components.

only (brown), water-only (red) and calcium-only (blue-gray) components. The darker the colour hue, the greater the quantity of the component. Both cross sections are shown just at the level of carotid bifurcation (internal and external carotid arteries) are marked in the images.

7.4 Discussion

It has been demonstrated that spectral CT can simultaneously discriminate multiple intrinsic bio-markers of an excised human atherosclerotic plaque and calibration phantom. This has been demonstrated within pre-clinical imaging energy range (15 - 50 keV) and human imaging energy range (30 - 120 keV). A constrained least squares material decomposition method,
7.4. Discussion

Figure 7.7: A three-material decomposition of spectral images of an atheroma acquired with GaAs-Medipix3.1 detector in human energy range (30 - 120 keV) into Ca-only, water-only and fat-only components. The majority of the atheroma is a mixture of water-only and fat-only components.

that uses the energy and material-dependent x-ray attenuation information obtained from spectral CT scan, was applied to decompose the multiple materials, such as water-only, fat-only and calcium-only, in an atheroma. Material decomposition was performed on a pixel-by-pixel basis, assuming there was an arbitrary mixture of materials in each voxel. The amount of fat component and spotty calcium deposits in an atheroma are bio-markers of plaque’s vulnerability to rupture. So, both of them can be considered as independent markers to test a plaque’s vulnerability. Other important bio-markers of vulnerable plaque such as inflammation, fibrous cap, inter-plaque haemorrhage and positive remodeling will be the subject of future studies.

Different tissues have different energy-dependent x-ray attenuation properties depending on their atomic number, electron density and mass density and thickness. By changing the energy levels, the difference in soft tissue contrast can be observed which forms the basis of characterising the one material from others. At lower energies, excellent soft tissue contrast
Chapter 7. Ex-vivo characterisation of human atherosclerotic plaque

is seen in both dense and non-dense regions of an atheroma or a phantom. As the energy increases, the non-dense regions display less contrast. The higher energy images are noisier due to few photons hitting the detector and lower quantum detection efficiency of the detector for higher energy photons. The spectral differences among multiple tissue components allows them to be distinguished using spectral CT.

Inflammation is an important bio-marker in the assessment of plaque’s vulnerability. High-Z based nano-particles attached to the specific antibodies can be targeted to different inflam-

Figure 7.8: Exposure rendering of spectral longitudinal section of an excised human carotid atheroma, obtained with (a) Si-Medipix3.1 detector within 15 - 50 keV and (b) GaAs-Medipix3.1 detector within 30 - 120 keV. Both detectors were operated in spectroscopic Single Pixel Mode. Cross section is shown at a level just above the carotid bifurcation. Top: Material decomposition showing fat only component. The more concentrated areas of fat are redder and seen in the internal carotid plaque (*). Small gaps are seen at the site of calcification (arrowheads). Bottom: Three-material decomposition of same data-set: fat-only (brown), water-only (red) and calcium-only (blue-gray). The darker the colour hue, the greater the quantity of the component. IC, Internal carotid; EC, external carotid; tubing, falcon tube
matory cells such as macrophages or monocytes or platelets. Spectral CT in combination with targeted contrast agents would allow quantification of the level inflammation in an atheroma. This would allow the non-invasive assessment of plaque’s vulnerability. The immunological response of host could also be quantified on the same spectral scan if labelled macrophages or other markers of the inflammatory response were present. This line of investigation will be the future direction for atherosclerosis imaging using spectral CT for MARS research group. When spectral CT is translated to human imaging, this approach could offer multiple clinical benefits such as identifying patients with vulnerable atherosclerotic plaques and treating them to prevent life-threatening cardio-vascular events such as stroke and myocardial infarctions, and reduce the morbidity from peripheral vascular diseases.

However, the spectral CT employing photon-counting detectors also has certain limitations. Among them, the most noticeable are charge sharing and pulse pile up effects, which introduce distortions to the detected spectrum. Charge sharing occurs when the charge cloud spreads across the adjacent pixels. Smaller pixel dimension provides higher spatial resolution but at the cost of diminished spectral resolution due to charge sharing effect. So, there is complex trade-off between spatial resolution and the spectral resolution of the detector. Spectral resolution of the detector is a critical imaging parameter for achieving the high level of sensitivity, specificity and accuracy of material characterisation in atherosclerosis imaging or other bio-medical applications.

Similarly, pulse pile up occurs when high x-ray flux hits the detector. Photon-counting detector needs a minimum amount of time to separate successive events in order that they be recorded as separate pulses. This time is called dead time. However, under high x-ray flux, the consecutive pulses are registered as a single pulse. This distorts the measured x-ray spectrum. The potential applications and benefits of spectral imaging are in part dependent on the specifications of the photon-counting detector as well. Finding the best possible combination of pixel pitch, semiconductor sensor material, thickness of sensor material, detector size, success of bump-bonding, tiling methods and speed of readout ASIC are major challenges for designing the effective energy-resolving photon-counting detector for human imaging.
7.5 Summary

1. This study has demonstrated the feasibility of using spectral detector CT to simultaneously distinguish multiple intrinsic bio-markers, such as fat, water and calcium in a human carotid atherosclerotic plaque and a phantom. This has been demonstrated within pre-clinical imaging energy range (15 - 50 keV) using Si-Medipix3.1 and human imaging energy range (30 - 120 keV) using GaAs-Medipix3.1 detector.

2. Differentiation and quantification of intrinsic bio-markers using spectral CT allows the assessment of the vulnerability of an atherosclerotic plaque.

3. When spectral CT is translated to human imaging, this approach could offer multiple clinical benefits such as identifying patients with vulnerable atherosclerotic plaques prior to disruption will enable appropriate therapies which, in turn can reduce the rate of life-threatening cardio-vascular events such as stroke and myocardial infarctions, and reduce the morbidity from peripheral vascular diseases.
Chapter 8

Element-specific spectral imaging

8.1 Introduction

This chapter reports on element-specific imaging using spectral CT. The K-edge is a sudden discontinuity in the photo-electric x-ray attenuation profile and it is specific to an element. The technique reported in this chapter exploits the advantage of K-edges of multiple high-Z elements to generate their element-specific images using multiple energy ranges in a single exposure. This may decrease CT radiation dose, drug dose and diagnosis time, with higher sensitivity and specificity [Shilo et al., 2012].

The immediate applications of the study reported in this chapter will be in in-vivo atherosclerosis or cancer imaging in a mouse model. The ability to identify and quantify the composition of tissues and bio-markers (biological hallmarks) of a disease using spectral CT could radically improve the diagnostic accuracy and therapeutic outcome of wide range of diseases [Anderson and Butler, 2014].

Early diagnosis of the disease is important for improving the treatment outcome. Almost all diseases begin with alterations at the cellular level, and detection of these earliest changes calls for imaging techniques with both high sensitivity and high resolution. Unfortunately, clinically available imaging modalities such as conventional CT and MRI are insensitive at finding a microscopic lesion. For example, CT or MRI can detect only relatively large tu-
mour (≈ 1 billion cells). Molecular imaging strategies with cellular resolution and molecular specificity can reveal the dynamic alterations occurring inside the living cells [Jaffer FA and Weissleder R, 2005]. So, molecular imaging is the future of medicine.

Spectral molecular imaging is a new x-ray based imaging technology providing 3D images based on multiple energy levels by integrating with nano-contrast agents targeting specific bio-markers of a disease at high spatial resolution [Anderson and Butler, 2014]. This has the potential to measure the disease activity and response to treatment non-invasively. One exciting possibility of spectral molecular imaging is the ability to discriminate and quantify multiple contrast agents targeting different bio-markers simultaneously. Simultaneous targeting of multiple bio-markers allows narrowing down the differential diagnosis if disease is unknown or it allows determining the extent of the disease, to decide the optimal treatment strategy and monitor the effectiveness of treatment if disease is known. This will finally lead to the personalised medicine.

As soft tissue components do not have K-edges available within the human diagnostic energy range and the intrinsic spectral separation (differential x-ray attenuation) between multiple soft tissue components diminishes with the energy of photon, soft tissue imaging is challenging. High-Z nano-contrast agents are used to improve the differential x-ray attenuation (contrast) between multiple components of soft tissue. Nano-sized contrast agents such as gold nano-particles provide an inherent advantage of increasing x-ray sensitivity. Each nano-particle contains hundreds of atoms that facilitate higher x-ray attenuation due to their K-edges. A sudden discontinuity in the x-ray attenuation coefficient at an energy just exceeding the binding energy of the K-shell of the multi-electrons atom is called K-edge of an element. Since the binding energy of the K-shell in an atom is fingerprint to the element, K-edge imaging is element-specific.

Figure 8.1 shows the individual x-ray interaction mechanism for commonly used high-Z contrast agents: iodine, gadolinium and gold. The dominant x-ray interaction mechanism for these elements is the photo-electric effect. K-edge imaging involves the measurement of x-ray attenuation on either side of the K-edge [Schlomka et al., 2008]. With the advancement of energy-resolving detector with multiple energy thresholds, it has been possible to perform K-edge imaging of multiple elements simultaneously.

The major aim of this study was to establish the methodology to determine the appropriate energy thresholds to perform element-specific spectral imaging by discriminating the
Figure 8.1: Individual photon interaction mechanism for iodine, gadolinium and gold based on NIST database [Berger et al., 2010]. Photo-electric effect, Compton effect (incoherent scattering) and coherent scattering are significant mechanisms of photon interaction within the human diagnostic energy range and photo-electric effect is the most dominant interaction mechanism for all three elements. The discontinuity in the photo-electric cross section is due to the K-edge which is specific to the element and energy of photon. K-edges which appear within the diagnostic energy range can be used for element-specific imaging using spectral CT.

K-edge features of multiple contrast agents simultaneously. K-edge features of I, Gd and Au based commercially available contrast agents were used for element specificity. More specifically, I aimed to establish a method to investigate the multiple K-edge features of various concentrations of I, Gd and Au based nano-particle contrast agents by measuring the spectral performance of various scanning energy thresholds.

The findings of this study were presented at The Annual Conference of the New Zealand Branch of the Australasian College of Physical Scientists and Engineers in Medicine (November 20-21, 2014, Christchurch, New Zealand) [Panta et al., 2014a] and “MedTech in Christchurch” workshop, December 16, 2014, University of Otago, Christchurch, New Zealand.
8.2. Materials and methods

Table 8.1: Summary of different contrast agents used for this study.

<table>
<thead>
<tr>
<th>Contrast agent</th>
<th>Element</th>
<th>Energy (keV) of K-edge</th>
<th>Original concentration (mg/ml)</th>
<th>Prepared concentration (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnipaque(^1)</td>
<td>I</td>
<td>33.2</td>
<td>350</td>
<td>9, 18 &amp; 36</td>
</tr>
<tr>
<td>Magnevist(^2)</td>
<td>Gd</td>
<td>50.2</td>
<td>469</td>
<td>2, 4 &amp; 8</td>
</tr>
<tr>
<td>Aurovist(^3)</td>
<td>Au</td>
<td>70.8</td>
<td>40</td>
<td>2, 4 &amp; 8</td>
</tr>
</tbody>
</table>


8.2 Materials and methods

8.2.1 Multi-contrast phantom

A physical multi-contrast phantom (33 mm of diameter) was designed for performing element-specific spectral imaging. The phantom contains multiple inserts (6 mm diameter) which were filled with water, gadolinium (2, 4 & 8 mg/ml), calcium-chloride (140 & 280 mg/ml), gold (2, 4 & 8 mg/ml) and iodine (9, 18 & 36 mg/ml) based contrast agents. Commercially available contrast agents Omnipaque (iodine), Magnevist (gadolinium) and Aurovist (gold) were used (Table 8.1).

8.2.2 Determination of scanning energy thresholds

Discrimination of elements using multiple energy ranges requires judicious selection of energy thresholds. This is because of the energy-dependent information, such as K-edge features, require relatively narrow energy ranges as wider energy ranges wash out the K-edge feature due to averaging of x-ray attenuation property. However, selection of narrow energy ranges needs to be balanced with the requirements for achieving desirable quantum signal-to-noise ratio (QSNR) which requires wider energy range. This contradictory requirements of energy information and QSNR need to be accounted while selecting the width of energy ranges.
Figure 8.2: X-ray mass attenuation profiles [Berger et al., 1998] for iodine, gadolinium and gold with corresponding K-edge at 33.2 keV, 50.2 keV and 80.7 keV respectively, and x-ray emission spectrum [Poludniowski and Evans, 2007] obtained from an x-ray tube operating at 118 kVp. The choice of energy thresholds for K-edge imaging is the trade-off between energy information (depends on mass attenuation profiles) and quantum signal-to-noise ratio (depends on x-ray source spectrum).

The existing technique to select the appropriate width of energy range for capturing the K-edge feature of an element is based on signal difference to noise ratio (SDNR) where the signal difference is defined between reconstructed target region values on either sides of the K-edge feature [He et al., 2012]. The limitation of this technique is that it has only been studied using an ideal detector within simulation framework. Moreover, the subtraction of signal increases the uncertainty which reduces the energy information.

In this study, I have introduced the “K-factor” as an indicator of energy information provided by the K-edge of an element which is defined as below:

\[
K\text{-factor} = \frac{\text{X-ray attenuation at K-edge energy range}}{\text{X-ray attenuation at preceding energy range}} \times 100\% \quad (8.1)
\]

In contrast to signal difference to noise ratio technique, using K-factor reduces the uncertainty of energy information as we are calculating the ratio of x-ray signal on either side of the K-edge feature. The higher the K-factor, the better the energy (spectroscopic) information.
8.2. Materials and methods

Table 8.2: Determination of ranks for various potential combination of energy thresholds based on K-factor and x-ray intensity performance in K-edge containing energy range for I, Gd and Au based contrast agents.

<table>
<thead>
<tr>
<th>Element</th>
<th>Scheme</th>
<th>Energy range</th>
<th>K-factor Value (%)</th>
<th>X-ray intensity Value (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td>19-32, 32-52</td>
<td>204</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>25-35, 35-55</td>
<td>248</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>21-35, 35-54</td>
<td>161</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>27-33, 33-49</td>
<td>668</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>20-35, 35-60</td>
<td>167</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32-52, 52-83</td>
<td>185</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35-55, 55-82</td>
<td>139</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35-54, 54-85</td>
<td>172</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>33-49, 49-81</td>
<td>287</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35-60, 60-85</td>
<td>79</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>52-83, 83-118</td>
<td>146</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>55-82, 82-118</td>
<td>193</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>54-85, 85-118</td>
<td>130</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>49-81, 81-118</td>
<td>204</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>60-85, 85-118</td>
<td>170</td>
<td>10</td>
</tr>
</tbody>
</table>

Higher K-factor implies that higher energy information has been restored by reducing the wash out effect of K-edge feature. Similarly, the higher the intensity of x-ray photons results better QSNR for a system which follows the Poisson distribution. Figure 8.2 shows the x-ray spectrum (120 kVp and 3.8 mm Al thickness), and mass attenuation coefficient of I, Gd and Au as a function of photon energy. K-edges of I, Gd and Au are apparent at 33.2, 50.2 and 80.7 keV respectively.

When Medipix3RX is operated in Charge Summing Mode, four adjustable energy thresholds that correct the charge sharing effect are available in each pixel [Ballabriga et al., 2013b]. These energy thresholds need to be selected judiciously to allow simultaneous discrimination of the K-edge features of each of three elements I, Gd and Au. Table 8.2 shows examples of five different energy threshold schemes for each element. In Table 8.2, the trade-off between
Table 8.3: Determination of best energy threshold scheme for simultaneous discriminating the K-edge features of I, Gd and Au based on ranking. Overall rank for various schemes of energy thresholds were determined based on K-factor and x-ray intensity performance as shown in Table 8.2. Top two rated schemes (Scheme B and Scheme D) are selected for evaluating their spectral imaging performance to discriminate all three contrast agents (I, Gd and Au) simultaneously.

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Energy ranges</th>
<th>Overall rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>19-32, 32-52, 52-83, 83-118</td>
<td>3</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td><strong>25-35, 35-55, 55-82, 82-118</strong></td>
<td><strong>2</strong></td>
</tr>
<tr>
<td>C</td>
<td>21-35, 35-54, 54-85, 85-118</td>
<td>5</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td><strong>27-33, 33-49, 49-81, 81-118</strong></td>
<td><strong>1</strong></td>
</tr>
<tr>
<td>E</td>
<td>20-35, 35-60, 60-85, 85-118</td>
<td>4</td>
</tr>
</tbody>
</table>

energy information (K-factor) and QSNR ($\propto \sqrt{x\text{-ray intensity}}$) with the width of the energy range has been illustrated. For example, in Scheme D the selection of energy ranges of 27-33 keV and 33-49 keV provides a maximum K-factor (668 %), however, x-ray intensity (29 %) in K-edge containing energy range is the poorest of five schemes for iodine. Based on K-factor and and x-ray intensity in the K-edge containing energy range, a rank was assigned to each of these schemes as shown in Table 8.2.

Based on the combination of individual rank of each scheme for all elements (I, Gd and Au), an overall rank was determined as shown in Table 8.3. For example, Scheme D has the highest rank (1) because the combined rank based on the K-factor and x-ray intensity ranks for all three elements is better than that of the schemes (A, B, C & E).

### 8.2.3 Spectral data acquisition

For evaluating the effectiveness of spectral performance of various combinations of energy thresholds, top two rated energy threshold schemes (scheme B (ranked 2) and scheme D (ranked 1)) as shown in Table 8.3 were selected. Energy calibration was performed using
8.2. Materials and methods

Table 8.4: Technical settings for spectral imaging

<table>
<thead>
<tr>
<th>Scanner</th>
<th>MARS scanner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phantom inserts</td>
<td>I (9, 18, 36 mg/ml), Gd (2, 4, 8 mg/ml), Au (2, 4, 8 mg/ml), Water, Ca(140, 180 mg/ml)</td>
</tr>
<tr>
<td>X-ray detector</td>
<td>CdTe-Medipix3RX</td>
</tr>
<tr>
<td>Camera mode of operation</td>
<td>Spectroscopic CSM</td>
</tr>
<tr>
<td>Magnification factor</td>
<td>1.34</td>
</tr>
<tr>
<td>Detector pixel pitch (µm)</td>
<td>110</td>
</tr>
<tr>
<td>X-ray exposure</td>
<td>118 kVp, 27 µA, 120 ms</td>
</tr>
<tr>
<td>Total filtration (Al)</td>
<td>(1.8 mm (inherent) + 2 mm (added))</td>
</tr>
</tbody>
</table>

**Energy ranges (keV) for Scheme B** 25-35, 35-55, 55-82, 82-118

**Energy ranges (keV) for Scheme D** 27-33, 33-49, 49-81, 81-118

<table>
<thead>
<tr>
<th>Focal spot size (µm)</th>
<th>≈ 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconstruction algorithm</td>
<td>Ordered Subset Expectation Maximization (OSEM)</td>
</tr>
<tr>
<td>Reconstruction voxel size (µm³)</td>
<td>180 × 180 × 180</td>
</tr>
<tr>
<td>Slice thickness at isocenter (µm)</td>
<td>241</td>
</tr>
</tbody>
</table>

x-ray tube voltage (kVp) as described in Chapters 3. Spectral CT images of a multi-contrast phantom were acquired using a MARS scanner equipped with an energy-resolving detector (CdTe-Medipix3RX). The settings used for spectral imaging are summarised in Table 8.4. The x-ray tube was operated at 118 kVp and MARS camera was operated in spectroscopic Charge Summing Mode.

The projection data in each energy range was flat field corrected, processed, and reconstructed simultaneously using in-house built Ordered Subset Expectation Maximization (OSEM) technique with voxel dimensions of 180 × 180 × 180 µm³. The slice thickness at isocenter was 241 µm.

Spectral imaging performance of Scheme B and Scheme D were evaluated by comparing the energy information (K-factor) and signal-to-noise ratio for each element individually. Mass attenuation coefficient for each element was calculated for estimating the K-factor of both schemes. Similarly, 720 flat field images for each scheme were averaged to calculate the
SNR at K-edge containing energy ranges for each element individually.

For further data analysis, voxel values (absolute x-ray attenuation or linear attenuation coefficient (cm$^{-1}$) of the reconstructed CT image were transformed to relative x-ray attenuation in Hounsfield Units (HU) using Equation 8.2:

\[
HU_{\text{voxel}} = \frac{\mu_{\text{voxel}} - \mu_{\text{water}}}{\mu_{\text{water}} - \mu_{\text{air}}} \times 1000
\]

where $HU_{\text{voxel}}$ is the HU of the voxel, the $\mu_{\text{voxel}}$, $\mu_{\text{water}}$, $\mu_{\text{air}}$ are linear attenuation coefficient of the voxel, water and air in reconstructed image, respectively.

For the measurement of the relative x-ray attenuation (HU) of different regions of interest (ROIs) containing contrast agents, the mean value and standard deviation ($\sigma$) within a circular ROI comprising $\approx 300$ voxels (N) were measured. The standard error of x-ray attenuation was calculated as $\frac{\sigma}{\sqrt{N}}$.

### 8.2.4 Material decomposition

Material decomposition (MD) in spectral CT exploits the energy dependence of x-ray attenuation of each voxel inside the object from multiple energy ranges to determine the basis materials in the reconstructed material volume. Material decomposition based on the MARS constrained linear least square algorithm [Bateman, 2015] was used on reconstructed images using the subtracted energy ranges. The basis image was generated by expressing the energy-dependent x-ray attenuation in each image voxel as a linear combination of the x-ray attenuation of several predefined basis materials. MD was applied on a voxel-by-voxel basis based using the energy-dependent x-ray attenuation.
8.3 Results

8.3.1 Evaluation of spectral imaging performance

K-factor and SNR were used as matrices to compare the spectral imaging performance of Scheme B and Scheme D. Figure 8.3(a) shows that K-factor of Scheme D is higher for all elements. Similarly, figure 8.3(b) shows that SNR of Scheme D is slightly higher than that of Scheme B for K-edge containing energy ranges of gadolinium and gold. But SNR of Scheme B is higher at K-edge contain energy range of iodine. The practical spectral imaging performance of both schemes are consistent with theoretical spectral imaging performance as presented in Table 8.3. This shows that spectral imaging performance of Scheme D is marginally better than Scheme B. Further data analysis comprises only the spectral data acquired using Scheme D.
8.3.2 Discrimination of multiple K-edges

Spectral CT images acquired using Scheme D are shown in Figure 8.4. The images acquired in four distinct energy ranges of 27-33 keV, 33-49 keV, 49-81 keV and 81-118 keV are shown. The multi-contrast phantom including iodine (9, 18 & 36 mg/ml), gadolinium (2, 4 & 8 mg/ml) and gold (2, 4 & 8 mg/ml) based contrast agents, and bone-like material (calcium-chloride of 140 & 280 mg/ml), and soft tissue-like (water) material are shown. Each CT image in each energy range possesses unique energy-dependent x-ray attenuation (HU) values. The presence of ring artifacts is visible, these are due to inconsistency of signal collection in some pixels during scanning.
8.3. Results

<table>
<thead>
<tr>
<th>Energy range (keV)</th>
<th>Relative x-ray attenuation (HU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-33</td>
<td>0</td>
</tr>
<tr>
<td>33-49</td>
<td>50</td>
</tr>
<tr>
<td>49-81</td>
<td>100</td>
</tr>
<tr>
<td>81-118</td>
<td>150</td>
</tr>
</tbody>
</table>

(a) Iodine (K-edge at 33.2 keV)

(b) Gadolinium (K-edge at 50.2 keV)

(c) Gold (K-edge at 80.7 keV)

(d) Material decomposed basis image based on MARS constrained linear least square algorithm to differentiate water, iodine, gadolinium, gold and calcium contrast agents. The material decomposed image is based on the same energy ranges selection as in 8.5(a)-8.5(c). Purple: iodine at 9, 18, 36 mg/ml; Green: gadolinium at 2, 4, 8 mg/ml; Yellow: gold at 2, 4, 8 mg/ml and White: calcium at 140, 180 mg/ml.

Figure 8.5: (a) Relative x-ray attenuation of various concentrations of iodine based contrast agent showing K-edge enhancement at 33-49 keV (b) Relative x-ray attenuation of various concentrations of gadolinium based contrast agent showing K-edge enhancement at 49-81 keV (c) Relative x-ray attenuation of various concentrations of gold based contrast agent showing K-edge enhancement at 81-118 keV. The standard error in the measurement of relative x-ray attenuation of various concentrations of contrast agents is ± 7-35 HU. (d) Material decomposed basis image based on MARS constrained linear least square algorithm to differentiate water, iodine, gadolinium, gold and calcium contrast agents. The material decomposed image is based on the same energy ranges selection as in 8.5(a)-8.5(c). Purple: iodine at 9, 18, 36 mg/ml; Green: gadolinium at 2, 4, 8 mg/ml; Yellow: gold at 2, 4, 8 mg/ml and White: calcium at 140, 180 mg/ml.
Figures 8.5(a) - 8.5(c) present the mean relative x-ray attenuation (HU) within different concentrations of I, Gd and Au contrast agents. The mean values were calculated over ≈ 300 voxels in each ROI. The standard error of x-ray attenuation within different ROIs was ± 7-35 HU. X-ray attenuation of all contrast agents of all concentration increases as energy increases only for the energy range containing the K-edge relative to the adjacent lower energy range or higher energy range. X-ray attenuation is maximum for all concentrations of iodine, gadolinium and gold at 33-49 keV, 49-81 keV and 81-118 keV respectively. This is because of the K-edge effect of the corresponding element. The maximum K-factors for I, Gd and Au were 157 %, 153 % and 125 % respectively. These results show that multiple K-edges for I, Gd and Au can be discriminated in a single scan using spectral CT.

8.3.3 Material decomposition

The basis image was generated by expressing the energy-dependent x-ray attenuation in each image voxel as a linear combination of the x-ray attenuation of several predefined basis materials. Figure 8.5(d) shows the basis image which decomposes: water, iodine, gadolinium, gold and calcium based contrast agents based on their energy-dependent x-ray attenuation properties.

8.3.4 K-edge hiding effect

Figures 8.6(a) and 8.6(b) show the absolute x-ray attenuation and relative x-ray attenuation within 300 voxels of Gd contrast agent (2 mg/ml). Both mean and median of absolute x-ray attenuation values in energy range of 49-81 keV (as shown in Figure 8.6(a)) hide the K-edge feature of Gd. However, both mean and median of relative x-ray attenuation in energy range of 49-81 keV (as shown in Figure 8.6(b)) able to discriminate the K-edge feature of Gd. Similar effects were observed in other concentrations of Gd and Au.

Total absolute x-ray attenuation coefficient based on NIST database [Berger et al., 2010] incorporates the x-ray attenuation coefficient contributed from photo-electric effect, Compton effect and coherent scattering within the human diagnostic energy range. However, the measured x-ray attenuation values using spectral CT is affected by secondary photons reaching...
the detectors. Secondary photons which contribute to the x-ray attenuation with spectral CT arise from scattering of incident photons by absorbing media and air path, and x-ray fluorescence (XRF) produced in the absorber by the incident x-ray beam. Moreover, high-Z sensor CdTe which was used in this experiment is itself a potential source of XRF. The magnitude of the contribution of x-ray attenuation by secondary photons depends on different experimental conditions such as x-ray beam geometry (cone beam or fan beam or parallel beam), collimation, photon energy, detector response function, atomic number of sensor, reconstruction software, the quality and the thickness of the absorbing media.

To measure the absolute x-ray attenuation accurately, the magnitude of contribution of scattering and XRF needs to be subtracted from total measured x-ray attenuation in spectral CT. This requires in-depth knowledge of the magnitude of the scattering and XRF components.

The contribution of secondary photons produces the systematic effect in measured abso-

![Figure 8.6](image_url)

**Figure 8.6:** Standard box plots showing (a) absolute x-ray attenuation in term of linear attenuation coefficient (cm$^{-1}$) across 300 pixels within the region of interest containing 2 mg/ml of Gd contrast agent and (b) relative x-ray attenuation in term of Hounsfield Unit (HU) across 300 voxels within the region of interest containing 2 mg/ml Gd contrast agent. Absolute x-ray attenuation (both mean and median values) in term of linear attenuation coefficient hides the K-edge feature of Gd in 49-81 keV energy range. But relative x-ray attenuation (both mean and median values) in term of Hounsfield Unit able to discriminate the K-edge of Gd in 49-81 keV energy range.
lute x-ray attenuation. I think this is the reason why absolute x-ray attenuation data presented in Figure 8.6(a) hide the K-edge feature of Gd. However, when calculating the relative x-ray attenuation (HU), the absolute attenuation of the voxel is normalised with that of water, as shown in Equation 8.2. As the relative x-ray attenuation (HU) is calculated as a ratio, the systematic effect from the secondary photon is cancelled out. This enables the discrimination of K-edge in Figure 8.6(b) in terms of relative x-ray attenuation (HU). The K-edge hiding effect has not been described previously in the literature and requires further investigation.

8.4 Discussion

The work reported in this chapter has demonstrated the feasibility of element-specific spectral imaging by discriminating the K-edge features of iodine, gadolinium and gold based contrast agents simultaneously using a photon counting spectral CT. One exciting possibility of spectral imaging is its ability to discriminate and quantify multiple contrast agents targeting different biological sites or functional activities in a single scan.

Immediate applications of imaging multiple K-edges of high-Z contrast agents can be found in in-vivo molecular imaging of atherosclerosis or cancer in a mouse model within human energy range. The importance of multiple K-edges imaging which provides element-specific information lies in the possibility to simultaneously identify the disease (by using specific functionalised nano-particle to target the bio-markers of a disease), the immune response using nano-particles specific to the immune cell (e.g. macrophages), and drug delivery. Furthermore, the ability to differentiate more than one high-Z contrast agent may have clinical relevance in simultaneous selective enhancement of different regions such as cardio-vascular system by using blood-pool contrast agent and nano-particles targeted to bio-markers (e.g. lipid core or intra-plaque haemorrhage) of atherosclerotic plaque in a single scan.

To readily identify a specific element by using its K-edge in spectral imaging, the energy ranges should be sufficiently narrow and well separated. Each energy range should be narrow enough to preserve energy information (or K-factor) and it should be wide enough to provide adequate quantum signal-to-noise ratio. Moreover, the global spectral resolution of a detector is also a limiting factor for the minimal practical energy width of an energy range. The finite global spectral resolution of a detector broadens the energy borders and increases the
cross-talk effect between adjacent energy ranges. So, for K-edge imaging, selecting the right energy thresholds or width of an energy range is a trade-off between energy information and quantum signal-to-noise ratio. This study was able to optimise both for discriminating multiple K-edges.

High-Z contrast agents are used to increase the x-ray attenuation of a lesion relative to the surrounding soft tissue in pre-clinical or clinical x-ray imaging. High resolution spectral imaging integrated with selective contrast agents can exploit the difference in blood supply (vessel size, resistance, leakiness, flow rate) between normal and pathological tissues to visualise and characterise them non-invasively. A contrast agent should possess high x-ray attenuation property with lower concentration to produce sufficient image contrast within imaging energy range.

However, in human diagnostic energy range with 120-140 kVp, iodine is not a suitable contrast agent because of photon starvation (poor quantum signal-to-noise ratio). Photon starvation is caused because of (1) beam hardening (absorption of lower energy photon) (2) relatively lower energy photon available in the human diagnostic energy range and (3) isotropic x-ray scattering. Because of this drawback of widely used iodinated contrast agent, there will be more interest in the development of high-Z element based contrast agent with higher K-edge for spectral imaging. Apart from spectral characteristic, bio-compatibility and cost of a contrast agent also need to be taken into account. Au is considered to be an excellent bio-compatible contrast agent but is costly.

K-edge hiding effect was observed in absolute x-ray attenuation (cm$^{-1}$). There are several potential sources of error affecting the absolute x-ray attenuation in spectral CT. One of them is secondary photons arising from scattering of incident photons by absorbing media and air path, and x-ray fluorescence emitted from the absorber or high-Z sensor (CdTe). The magnitude of the contribution of x-ray attenuation by secondary photons depends on different experimental conditions such as x-ray beam geometry (cone beam or fan beam or parallel beam), collimation, photon energy, detector response function, atomic number of sensor, reconstruction software, the quality and the thickness of the absorbing media. Other potential sources that introduce inaccuracy of absolute x-ray attenuation are beam hardening effect, finite spectral resolution of the detector, and uncertainty in energy calibration, and concentration of contrast agents used. This systematic error may hide the K-edge of an element.
8.5 Summary

1. The study reported in this chapter has demonstrated a methodology for determining the appropriate energy thresholds to balance the trade-off between energy information (k-factor) and signal-to-noise ratio (x-ray intensity). I introduced a methodology to evaluate the effectiveness of spectral performance of various combination of energy thresholds in spectral imaging. The work reported in this chapter has demonstrated the feasibility of discriminating the K-edges of I, Gd and Au simultaneously using spectral CT based on energy-resolving detector.

2. The ability to perform element-specific spectral imaging may open up several possibilities for new medical applications such as simultaneous quantification of bio-markers of a disease. It may have clinical relevance in simultaneous selective enhancement of different regions such as cardio-vascular system by using blood-pool contrast agent and nano-particles targeted to bio-markers (eg. lipid core or intra-plaque haemorrhage) of atherosclerotic plaque in a single scan.

3. Spectral data presented in terms of absolute x-ray attenuation (i.e linear attenuation coefficient (cm\(^{-1}\)) hides the K-edge feature of a high-Z contrast agent at lower concentration. This could be due to systematic effect contributed from secondary photons such as scattering and x-ray fluorescence from an absorber.
The objective of my research was to improve the spectral performance for soft tissue imaging. It was realised through (1) development of novel energy calibration techniques and characterisation of the energy response of individual pixels of an energy-resolving photon-counting detector (2) measurement of count rate capability and imaging performance of a MARS scanner, and (3) ex-vivo characterisation of the composition of human carotid atherosclerotic plaque and element-specific spectral imaging of the high-Z contrast agents iodine, gadolinium and gold within the human diagnostic energy range.

The major achievement of this research was to demonstrate that low-Z soft tissue components lipid, water and calcium in an ex-vivo human carotid atherosclerotic plaque have sufficiently measurable distinctive energy information within the human diagnostic energy range (30-120 keV). As soft tissue components do not have K-edges available within the human diagnostic energy range and the intrinsic spectral separation (difference in x-ray attenuation) between multiple soft tissue components diminishes with the energy of photons, soft tissue imaging is challenging. Despite this, spectral imaging with energy-resolving detectors is able to detect the subtle x-ray attenuation differences among multiple components of soft tissue.

These findings potentially have high clinical impact when spectral imaging is translated into human imaging by non-invasive detection of vulnerable plaques within patients before their disruption or rupture. This should allow clinicians to identify and diagnose the vulner-
able plaques which cause adverse cardiovascular events (stroke, myocardial infarction and peripheral vascular diseases). The major limitation of this study was that it was conducted in an ex-vivo specimen. The immediate extension of this study will be in-vivo atherosclerosis imaging in a mouse model prior to a human MARS scanner.

The other exciting achievement of this research was element-specific spectral imaging using MARS scanner. K-edges of high-Z contrast agents lie within the human diagnostic energy range. K-edges of iodine, gadolinium and gold contrast agents were discriminated simultaneously. This study was performed using CdTe-Medipix3RX operated in Charge Summing Mode. The experiment was designed to determine the optimal imaging energy thresholds to investigate the discrimination of K-edges of various concentrations of iodine, gadolinium and gold contrast agents. The ability to identify and quantify several contrast agents simultaneously means that multiple bio-markers (which are biological hallmarks of a disease) can be targeted in a single scan. The limitation of this study was that it was a proof-of-concept study performed in a physical phantom, not in a biological specimen. The immediate extension of this work will be targeting multiple bio-markers in atherosclerosis (such as lipid core, macrophages, and micro-haemorrhage) or cancer in a mouse model.

The global energy calibration technique based on reference x-ray tube voltage (kVp) developed in this research is an accurate and effective technique which runs with minimal resources and user intervention in a pre-clinical environment. This is a fast technique that does not require any monochromatic x-ray sources such as synchrotron and radioisotopes.

In order to improve the spectral resolution of the spectral detector, my research has developed a technique to measure the energy response of individual pixels using γ-ray source and x-ray fluorescence emitted from metallic targets bombarded with a polychromatic x-ray beam. This new technique measures the energy response of individual pixels using high-x-ray flux from an x-ray tube which is much faster (21 times) than using a high radioactive radioisotope (241Am of 1.56 GBq).

The measurement of threshold dispersion across the pixel matrix at different energies shows that threshold dispersion increases with energy (I measured threshold dispersion of 5 threshold DAC at 24.2 keV and 10 threshold DAC at 59.5 keV). The measured threshold dispersion is directly related to CMOS manufacturing variation and effectiveness of threshold equalisation. Similarly, the gain variation (energy response variation i.e threshold DAC/keV) across the whole pixel matrix is 6.1 - 6.5% for 4 counters in Charge Summing Mode.
Spectral resolution measured with x-ray fluorescence underestimates the true spectral resolution of the detector as there are many accompanying x-ray fluorescence lines (such as K-series or L-series) at different energies which overlap and broaden the x-ray fluorescence peak. However, x-ray fluorescence peak can be used to compare spectral resolution (relative) performance of different energy-resolving detectors. Spectral resolution of a pixel in CdTe-Medipix3RX was found to be 8.9 keV at 59.5 keV ($\gamma$-ray source). This spectral broadening could be due to high electronic noise, leakage current, low charge collection efficiency, and threshold dispersion across the pixel matrix. Moreover, the spectral resolution across the pixel matrix varies widely by 10-30% which could be due to the inhomogeneous nature of CdTe crystals.

The count rate capability of CdTe-Medipix3RX in Charge Summing Mode (CSM) is notably lower than in Single Pixel Mode (SPM), especially at higher x-ray flux. CSM and SPM show deviation in count rate from linear fit beyond 40 and 80 $\mu$A of tube current respectively. To avoid count loss or saturation of the detector, we need to operate an x-ray tube with sufficiently low tube current in CSM. The experiments with CdTe-Medipix3RX in Charge Summing Mode presented in this thesis were performed under conditions of low x-ray flux accommodating the fact that state-of-the-art, high-rate photon-counting detectors cannot cope with count rates as high as those present in human CT. New ASIC design should address this issue by designing faster readout.

Future ASIC readout design should reduce the electronic noise and make finer resolution (steps) and a wider range in threshold equalisation to reduce the residual threshold dispersion across the pixel matrix. The threshold dispersion can be reduced with higher transistor matching enabled through the miniaturisation of CMOS technology. Other potential sources of random fluctuations that cause threshold dispersion include variable concentration and size of the doping material in the sensor.

Apart from technical development of spectral CT, its potential role needs to be demonstrated in a number of clinical avenues to clarify its clinical impact. The wide adoption of spectral CT based on the energy-resolving detector will only be possible if there is overwhelming clinical recognition of its utility. Spectral CT integrated with high-Z nano-particle contrast agents shows huge clinical promise in the fields of cardio-vascular diseases, cancer, orthopaedics and infectious diseases. Spectral imaging needs to explore new potential roles, as well as expanding its existing clinical utilities.
Appendix A

Search of novel contrast agent for human imaging

Spectral x-ray imaging provides the capability to decompose images into basis-set constituents and can thus be used for material characterisation and quantification. The material decomposition methods exploit the differences in energy dependence of x-ray attenuation of the various materials. To enhance the soft tissue contrast, exogenous contrast agent is introduced.

Since there are different contrast agents with different elements, it is hard to decide which is the best high-Z element to use in the contrast agent for a given energy range. In this appendix, I have demonstrated a theoretical framework to help choose the best high Z-element to be used for a given energy range. This is illustrated in Figure A.1(a) and A.1(b).

First, it is assumed that there is a lesion within soft tissue and it is also assumed that the lesion and the surrounding background (B) of soft tissue possess the same x-ray attenuation properties and physical density ($\rho_B$). Secondly, it is also assumed that the contrast agent (CA) does not alter the tumour volume ($V_T$).

From the mixture rule, the mass attenuation of the combination of tissue and contrast agent is calculated as
(a) similar x-ray attenuation between lesion and surrounding soft tissue (b) Contrast enhancement by 5% between lesion and surrounding soft tissue after introducing high-Z contrast agent. The model derived in this appendix aims to find out the concentration of various high-Z contrast agents needed to enhance the contrast (differential x-ray attenuation) between the lesion and the surrounding soft tissue at different energies under ideal conditions.

\[
\frac{\mu}{\rho_{B+CA}} = \left[ \frac{\mu}{\rho_B} f_B + \frac{\mu}{\rho_{CA}} f_{CA} \right]
\]  
(A.1)

where \( f_B \) and \( f_{CA} \) are the mass fractions of \( B \) and \( CA \) in the mixture. The mass fractions of the tumour and contrast agent in the mixture can be written as

\[
f_B = \frac{m_B - m_{CA}}{m_{B+CA}} = \frac{\rho_B V_T - C_{CA} V_T}{V_T \rho_{B+CA}} = \frac{\rho_B - C_{CA}}{\rho_{B+CA}}
\]  
(A.2)

\[
f_{CA} = \frac{m_{CA}}{m_{B+CA}} = \frac{C_{CA} V_T}{V_T \rho_{B+CA}} = \frac{C_{CA}}{\rho_{B+CA}}
\]  
(A.3)

where \( c_{CA} \) is the contrast agent concentration and \( \rho_{B+CA} \) is the density of tissue with contrast agent.

Writing out the equations for x-ray transmission through these materials,

\[
I_B = I_0 e^{-\left( \frac{\mu_B}{\rho_B} \rho_B T \right)}
\]  
(A.4)
Appendix A. Search of novel contrast agent for human imaging

\[ I_{B+CA} = I_0 e^{-\left[ \frac{\rho_B}{\rho_B} (\rho_B - C_{CA}) + \frac{\mu}{\rho_{CA}} C_{CA} \right] T} \] (A.5)

where \( T \) is the lesion thickness.

Note that the image contrast could be defined in terms of the difference of the number of transmitted x-rays, or it could be defined after a log-transformation of the image. When contrast is defined in terms of log-transformation it has a linear relationship with the material attenuation coefficients.

For an image contrast of 5\%, (100\% detector efficiency and no scatter) we now have:

\[
\log(I_B - I_{B+CA}) = \log\left( I_0 e^{\left[ \frac{\mu}{\rho_B} \rho_B T \right]} - I_0 e^{\left[ \frac{\mu}{\rho_B} (\rho_B + \frac{\mu}{\rho_{CA}} C_{CA}) T \right]} \right) = 0.05 \quad (A.6)
\]

Simplifying, and re-arranging Equation A.6 for the contrast agent concentration we have

\[
C_{CA} = \frac{0.05}{\frac{\mu}{\rho_{CA}} T} \quad (A.7)
\]
Bibliography


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