

Applying CERN's detector technology to health: MARS Biomedical 3D spectroscopic x-ray imaging

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ABSTRACT

New Zealand has benefited considerably from our links with the European Centre for Nuclear Research (CERN). We have been an associate member of CERN for 8 years, with projects in high energy physics theory, in the high energy physics Compact Muon Solenoid (CMS) experiment, and in technology development. In 2006 we joined the Medipix-3 Collaboration. We have installed Medipix detectors in the CMS Cavern for monitoring neutrons and ionising radiation. Our major effort has been to build Medipix detectors into a 3D x-ray scanner of our design. The scanner is dubbed Desktop MARS (Medipix All Resolution system) and provides energy selective images of small biological and pathology specimens.

This paper reviews several matters. We look at the support given by the NZ government who have seen benefits in our involvement, including skill development, economic and commercial opportunities, and in overcoming the isolation of distance. We review NZ's particular role in CMS where particle physics is a driver of new technology; We explore the opportunities arising from Medipix as the first photon processing detector. We first summarise the design of the Medipix detector and discuss likely benefits of spectroscopic imaging in clinical radiology. CERN and the Medpiox-3 Collaboration have licensed us to commercialise the technology for biomedical imaging of small animals and humans using the Medipix detector as the key tool for obtaining 3D computed tomography spectroscopic x-ray CT images. Finally we present some images of biological specimens taken with the MARS scanner, including initial spectroscopic images of mice.

Keywords: Medipix, spectroscopy, medical imaging, x-ray, neutron, radiology, computed tomography, MARS.

1 INTRODUCTION

New Zealand has been involved with CERN (the European Organisation for Nuclear Research) since 2001, predominantly in detector research for ionising particles. Despite New Zealand's nuclear free policy we have been able to develop these skills. One particular focus has been to strengthen the tertiary education system's capability for teaching and research in image acquisition and image processing. Another has been to establish a start-up company that seeks to create a market for spectroscopic x-ray computed tomography scanners. This talk will review progress we have made and touch on some of the issues that we have had to address.

At the time of writing CERN is a matter of weeks away from injecting the first protons into the Large Hadron Collider. The LHC has captured the imagination of people as diverse as British TV (the BBC), mystery novelist Dan Brown (Angels and Demons), and most importantly from my viewpoint, numerous young people who will be our future physicists. The LHC is searching for discoveries that

will extend our understanding of sub atomic matter beyond the so-called standard model. It will do this by creating the most energetic proton collisions ever, at twice 14 GeV. There are good reasons to expect it will discover the Higgs boson. Nobel Prize-winning physicist Leon Lederman has dubbed Peter Higgs' boson the 'god particle' as it believed to bestow mass on all other particles. Endeavours of this kind inspire humans to reach beyond themselves.

Experiments such as the LHC also inspire ingenuity in technology. Large numbers of physicists and engineers of diverse backgrounds are brought together to solve novel problems, and given the money and freedom to do so. The results are always unpredictable, often surprising, and frequently useful.

We set out to move these technological advances accessible under a formal collaboration between the NZ Government and CERN into the research laboratories and into the academic fabric of the universities and polytechnics of NZ. Our particular interest is in strengthening links between the basic science of imaging and its medical applications. We are linking the basic physics, engineering and computer science to clinical projects in Christchurch Hospital and the Christchurch Medical School. Our Ministry of Education funding is, in part, to ensure that the teaching of medical physics registrars, radiology registrars and radiographers is up to date and world class. Four of NZ's eight universities and several of NZ's polytechnics are involved.

CERN is a Swiss based collaboration of 20 European states, with 65 other countries as associate members [1]. The driving force for the research is a series of collaborations, some like CMS, the Compact Muon Solenoid collaboration, consist of hundreds of universities and 3,500 scientists, engineers and students. CERN has developed a range of new technologies in recent years. It continues to develop computing technologies beyond their invention of the World Wide Web [2]. Much CERN effort is in distributed computing, and CERN is a leader in GRID technology. They have built the largest superconducting magnets, the largest detector systems and the largest vacuum systems. Many groups, both scientific and commercial, have accessed the new technologies associated with these achievements. The focus of our group has been to contribute to, and share the benefits of, the very best detectors of ionising particles, especially those referred to as silicon pixel detectors.

Some 15 years ago the first Medipix Collaboration was formed to transfer the ideas generated in designing detectors to characterise the jets of particles created in 14GeV proton on proton collisions, to medical and industrial applications. The Medipix-2 detectors are in commercial use for materials analysis [3]. The University of Canterbury is a foundation member of the Medipix-3 collaboration [4].

The University of Canterbury brings special skills and interest to the Medipix-3 collaboration. Of key relevance to the main topic of this paper are the close interactions between University of Canterbury physicists, engineers and computer scientists, with hospital clinicians, and with University of Otago medical school radiologists and medical researchers. These lead to a unique link between fundamental research and its clinical application.

Some of these qualities arise from our history and location. The city of Christchurch was the last planned colony of the era of English settlement. It is close to being the antipodes of London. With a population of 400,000 it is the largest city of the South Island of New Zealand. The nearest larger city is Auckland, 1,000km away, while Sydney, Australia is 2,000km across the ocean.

The University of Canterbury was established in 1873. Among its first graduates was the first female honours graduate in the British Empire, and Ernest Rutherford, perhaps the greatest experimental physicist the world has known. There is an attitude that if you cannot do it, or find it, in Christchurch, then you need to search the specialists of the world.

Being part of the Medipix collaboration brings us close to the researchers from 17 institutes worldwide who are working together to further explore the unique abilities of spectral imaging.

2 THE MEDIPIX DETECTOR

When Ernest Rutherford wanted to measure the directions that alpha particles were scattering off gold foil, he looked for scintillations on a screen, in a darkened room. The alternative at the time was photographic film. Since then particle physicists have invented better and better detectors for ionising radiation: Geiger Mueller counters, cloud, bubble and spark-gap chambers, and most recently silicon

pixel detectors. Medipix is a silicon pixel detector. An ionising particle creates an electron-hole cloud in a silicon sensor layer, and the timing and size of this cloud is measured by a CMOS logic layer bump-bonded to the sensor layer. Each Medipix pixel is 55 μm square, giving a spatial resolution comparable to mammographic film—the film with the smallest grain size that is in regular use in medical imaging. Each Medipix pixel can be seen as an individual spectral detector. The logic circuits for each pixel (some 1300 transistors) can analyse incoming events at megahertz rates, comparing the charge of the electron-hole cloud with preset levels, giving a resolution of about 2 keV across the range of 8 - 140keV.

X-rays create an electron-hole cloud of small spatial dimensions in the sensor layer of the Medipix detector. Charged particles, e.g. energetic electrons, muons and protons leave tracks, with the sensor layer acting as a “silicon bubble chamber”, while alpha particles create a characteristic blob spreading over several pixels, the size related to the alpha particle’s energy. It is possible to replace the silicon sensor layer with a range of materials in order to alter the sensitivity of the detector. E.g. GaAs and CdTe can be used to provide good efficiency for higher energy particles [5].

In summary, the Medipix detector is a hybrid ionizing particle detector designed to provide energy selective images at high spatial and temporal resolutions. It is one of the first, if not the first, photon processing, imaging detector capable of processing single events at the high flux rates in the CMS and ATLAS experiments at CERN and in medical imaging applications. In the next section we summarise the use we are making of the Medipix detector to characterise and monitor the background radiation in the CMS cavern. In the following sections give some of our preliminary research results that use this spectroscopic capability for biomedical imaging.

3 MEDIPIX in CMS and ATLAS

The Medipix detectors have been designed by teams who designed the large detectors at CERN, but while the design of many aspects of the ATLAS and CMS detectors was fixed some years ago due the long construction times, the Medipix team has had the flexibility to continue with developments. It is with some wry amusement, in a somewhat “coals to Newcastle” or “sand to Arabia” reversal, that a small number of Medipix detectors were installed in the ATLAS and CMS caverns in the final months before LHC turn-on [6].

The readout systems in the caverns are slow, but the Medipix detectors will give real time measurements of many particles, some of these are not readily obtained by other means. For example by covering part of the 14mm x 14mm Medipix sensor with plastic, fast neutrons create knock-on protons which give characteristic tracks. Likewise a thin layer that contains boron over another section absorbs slow neutrons and the emitted alpha particles can be detected.

This work is an important aspect of our research programme using Medipix because it [6]:

- 1) Demonstrates the flexibility of Medipix, e.g. detection of fast and slow neutrons.
- 2) Provides early measurement of what is happening inside the ATLAS and CMS caverns, thus allowing confirmation of models.
- 3) Further develops NZ’s detector skills and speeds progression of flow-on benefits into NZ.

4 CLINICAL APPLICATIONS of SPECTROSCOPIC DETECTORS

Spectroscopic x-ray detectors, such as Medipix, are opening the door to the widespread use of energy selective biomedical x-ray imaging. With dual energy computed tomography quickly becoming the clinical standard, spectroscopic imaging is a likely next step. However to confirm the utility of spectroscopic x-ray detectors there needs to be a clearer indication of the clinical benefits of the technology.

In order to identify possible applications of spectroscopic imaging we conducted a brief literature review of clinical applications of dual energy systems. In addition we analysed simulation results from our own group, our collaborating partners, and industry [7, 8, 9].

Broadly, we group the benefits of spectroscopic x-ray imaging into three areas.

- 1) Improved image quality, in particular reduction in beam hardening artefact [10].

2) K-edge imaging, the identification of high Z-number contrast agents based on their k-edge. This technique will lead to better use of contrast agents. E.g. a) less contrast agent required in high risk patients such as in renal impairment, diabetes, and elderly, b) separation of several contrast agents allowing for multiphase studies to be performed with less x-ray dose and less time on the scanner. [7, 8, 9, 10]

3) Improved soft tissue contrast from differences in mass attenuation coefficients of different tissues. The diagnoses of several diseases, such as breast cancer, are known to be improved by dual energy systems. In addition, there is improved soft tissue contrast of normal structures [11,12,13,14].

This information was coupled with information regarding the clinical significance of diseases and radiology work practices. It was decided that our research should focus on two main areas;

- 1) Improved used of contrast agents as these are used in vascular imaging and tumour imaging. This is initially being investigated on mice models.
- 2) Soft tissue imaging will be investigated using mammography. This has been chosen due to the easy access to excised surgical breast specimens containing both normal and abnormal tissue. In addition it is the leading cause of cancer death in our society [15].

The review suggested there will be significant clinical benefits from spectroscopic imaging across a wide range of radiological problems. In addition, technologies like Medipix are rapidly developing and full body spectroscopic imaging is likely to be technically possible in the near future. However, there exists a “chicken and egg” problem in which the clinical applications can not be developed or confirmed without a working spectroscopic system, but full body spectroscopic systems are unlikely to be built without confirmation of clinical benefits. Construction of the desktop MARS scanner solves this chicken and egg problem by enabling research to confirm clinical applications while the underling technology matures.

5 MARS: A 3 DIMENSIONAL X-RAY SPECTROSCOPE USING MEDIPIX

A desktop x-ray CT scanner was designed that would enable us to image small (up to 80mm diameter and 200mm length) animals and biological samples to demonstrate the novel spectral information that Medipix can deliver. The scanner (Fig. 1) was designed to take full advantage of the high spatial resolution that Medipix offers (55µm pixels) and to access the most energy information possible within the limits set by detector material and low energy charge-sharing effects. This was a prototype scanner, built to prove both the detector’s abilities and the scanner design; it had to be safe, robust, architecturally flexible, transportable and affordable.

The scanner is built around a very stable steel frame made of 50x25mm welded box-section steel to reduce any twisting or vibration to a minimum. The scanner gantry is constructed from two solid steel endplates attached to each other by four steel rods to form a very strong and rigid rotating unit. The endplates rotate on large diameter bearings, leaving a 106mm hole for sample tubes to pass through, giving a maximum sample size of 100mm. One side of the gantry is formed by a solid steel base plate, which provides support for the X-ray tube and detector. All sides can be covered by stainless panels, one of which has a primary 3mm lead barrier attached to reduce radiation.

The scanner is housed in a lead shielded box which consists of 1.8mm lead sandwiched between 0.5mm aluminium and 0.5mm stainless. The box has interlocked access on sample doors, and shielded ports for cable entry and ventilation. The box has been subjected to a radiation survey and there was no measurable radiation above background. Cables going to the rotating gantry are arranged to accommodate a half twist as they leave the scanner through a port in line with the centre of rotation.

Detector Mount:

The Medipix detector is mounted on a plate that allows fine angular adjustment to ensure the detector pixels are aligned with the direction of vertical travel. Since the detectors are small (either a single detector chip at 14x14mm, or a quad detector assembly at 28x28mm) they must be translated vertically to build a complete projection radiograph. The mounting plate is connected to a screw drive which accurately translates the detector to each imaging position. The screw drive is supported by the

steel base plate and can be translated perpendicular to the access of rotation to accommodate different sample sizes, which range from 25 to 80 mm.

X-ray Tube Mounting:

The X-ray tube is also attached to the base plate and can be moved in or out to give the most efficient position ensuring complete coverage of the sample object. A fan has been mounted to cool the X-ray tube and allow continuous operation at full current.

Scanner Operation:

To simplify cable and data management, the scanner is designed to complete one revolution and then return. Projection data is gathered at each specified angle for both gantry rotation directions and the sub-images subsequently reordered and spliced together. A small overlap of a few pixels is acquired at each image location to help check alignment and to ensure consistent exposures. All scanner control and image triggering is performed via Matlab™ routines. In particular the x-ray tube, steppers motors are controlled via separate serial interfaces.

The Medipix detector is read using the Pixelman software and custom readout electronics which are called from the Matlab control routines

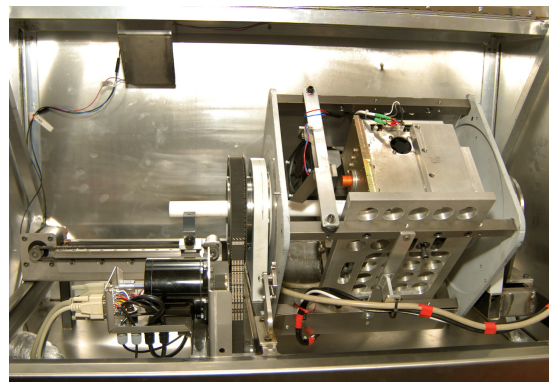
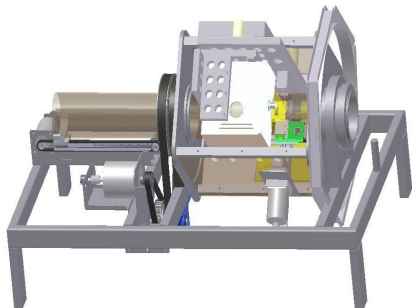


Fig 1: MARS Scanner design and the completed scanner.

6 FIRST RESULTS FROM THE MARS SCANNER

The scanner performed well, in that it gave acceptable image quality and demonstrated that spectral CT yields additional information through variations in mass attenuation. We are in the process of making numerous minor changes to the scanner design and operation. These will improve image quality and reduce imaging time.

Mouse 1: non contrast.

Following imaging of phantoms, a mouse was imaged. The mouse was euthanised and imaged soon after death. Images were obtained with the detector set to measure a broad range of energies. Images were reconstructed using cone beam filtered back projection to create a 3D volume of data where

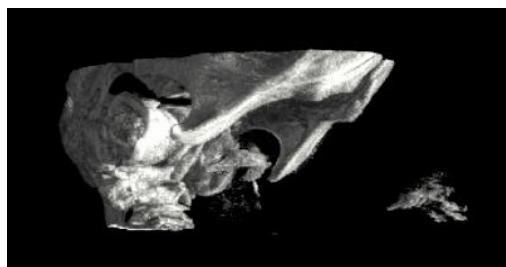


Fig 2 Volume rendering of the jaw and skull base of a mouse.

each voxel is a 32micron isovolumetric element. Fig. 2 is a 3D volume rendering of the mouse's skull base and front paws.

Mouse 2: with contrast

Following the success with the non-contrast mouse we imaged a mouse's abdomen containing iodine contrast. Such contrast is routinely used in medical imaging studies of cancers and blood vessels. On conventional CT scans it is highly attenuating and, depending of concentration, looks similar to bone. However, iodine has a k-edge at 33 keV and therefore should be identifiable as a separate material with our multi-energy MARS scanner.

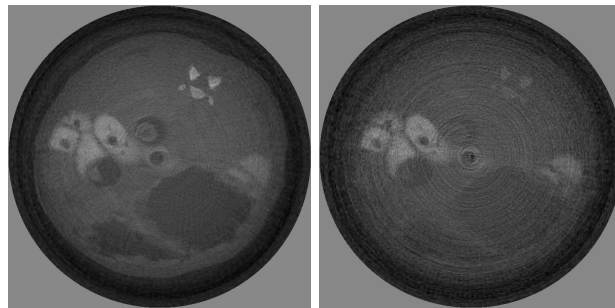


Fig 3. Transverse slice through the abdomen of a mouse obtained at different energies. In the left image (>12 keV), the iodine contrast in the bowel and the bone of the spinal column (upper right) are both white, implying they have similar attenuations at this energy. The right image (>33 keV) shows that iodine contrast is more attenuating than the bone at this energy,

Following successful phantom studies, a mouse was anaesthetised and iodine contrast placed into bowel via gastric lavage. The mouse was then euthanised and imaged on the MARS scanner. We choose 4 separate energy bins, 12 keV, 17 keV, 33 keV, 42 keV. Each bin had low threshold and no upper threshold, e.g. the 33 keV bin counted all photons above 33keV.

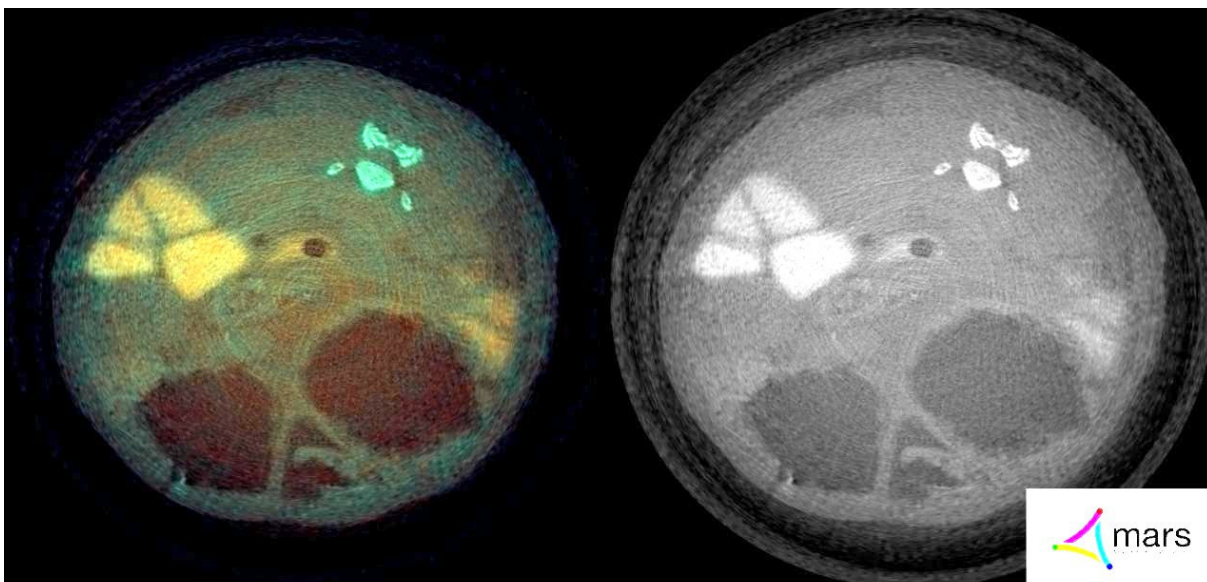


Fig 4. CT slice of mouse abdomen. The right image was obtained with a wide energy window on the Medipix detector. This is equivalent to a conventional non-energy selective CT. The left hand image is colored based on PCA analysis of the spectral information. The spine is shown greenish, iodine contrast agent in bowel as yellowish, air dark, etc.

Projection images were obtained over 2 hours using 180 angular projections each of 3 sensor locations. Tube voltage was 75 keV, with 0.7 mm of aluminium beam filtration. Tube current was nominally 79 uA. Projection images were corrected for intensity fluctuations and inhomogeneous behaviour of individual pixels. Each energy bin was separately reconstructed into a 3D volume using a cone beam filtered back projection,

Using this spectral CT data we are now investigating ways to maximise the amount of information available to people viewing spectral data. In particular we are studying the application of Principal Components Analysis to the data. Fig 4 displays a non-energy selective image (equivalent to a conventional broad spectrum CT) beside MARS image in which colour has been added based on PCA analysis of the spectral information. The technique highlights that the materials within the mouse attenuate the x-ray beam differently over the range of energies.

7 CONCLUSION

NZ has benefited in a number of important ways from our collaborative research at CERN. From an educational perspective, the links to the leading international physics research laboratory has inspired many students and university staff. From a commercial perspective we have been able to use our special skills to bring one of the new technologies to market. This has had the side effect of giving NZ the very latest spectroscopic x-ray CT system for our biomedical research. We are actively seeking further research partners in these three areas.

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