Spectral molecular imaging - a new modality

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Learning Objectives

1. Spectral molecular imaging uses an XRay photon processing detector and a polychromatic Xray source.

2. Spectral molecular imaging can specifically identify and distinguish between substances in tissues, such as iodine, gadolinium, calcium, lipid even when they are mixed together.

3. Spectral molecular imaging can quantify these substances in mgm/ml.

4. Spectral molecular imaging is different from all other imaging modalities including dual-energy CT.

5. Spectral molecular imaging can image new specific contrast agents that target specific cell types and biomarkers.

Main

Introduction

Spectral molecular imaging(1-3) is a new 3D quantitative colour imaging modality that provides molecular imaging at the histological scale. It measures x-ray attenuation of the tissues at different energies (known as spectral imaging). The advantage of spectral molecular imaging over current molecular imaging techniques is to differentiate and quantify multiple biomarkers and drug penetration into the target tissue at the same time. Other names for spectral molecular imaging include multi-energy CT, or spectral CT, but these names misrepresent the novel nature and applications of this new imaging modality.

"Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems. To elaborate; Molecular imaging typically includes 2- or 3-dimensional imaging as well as quantification over time. The techniques used include radiotracer imaging/nuclear medicine, MR imaging, MR spectroscopy, optical imaging, ultrasound, and others."(4)

The potential applications for spectral molecular imaging are diverse. From the image it should be possible to measure the biomarkers of vulnerable atherosclerotic plaque; diagnose the microbe responsible for an infection; simultaneously measure drug delivery to tumour and the inflammatory response. This would accelerate drug discovery. Spectral
molecular imaging is likely to accelerate the development of new, safer, tissue specific contrast agents or molecular imaging probes.

**Basis of spectral molecular imaging**

Spectral molecular imaging is based on a photon-processing chip detector assembly (5,6) which measures the energy of each incoming photon from a standard polychromatic Xray source. Measuring the attenuation profile of each photon from multiple energy bands allows identification of the tissue component; counting the number of photons with that energy profile allows quantification.

The potential applications and benefits of spectral imaging are in part dependent on the specifications of the photon-processing detector. Detector designers are faced with a complex trade-off between spatial resolution and energy resolution and spectroscopic capability. A key need is to measure multiple biomarkers simultaneously, at biological concentrations for intrinsic biomarkers, and as low a concentration as possible for introduced biomarker labels. Finding the ideal combinations of pixel pitch, semiconductor sensor layer and thickness, detector size and tiling methods are major challenges for the detector designers. Small pixel detectors (which have excellent spatial resolution) suffer most from charge sharing, whereby the energy of the photon is shared between two neighboring pixels. The detector records two separate events of lesser energy rather than a single event of the actual energy. This can be overcome by operating the detector in charge summing mode (such as in Medipix-RX(7)). In this mode, the charge sharing artifact is removed by summing charge over several neighboring pixels(8).

The modality of spectral molecular imaging differs from all others including dual-energy CT because each step in the chain from detector to data acquisition, to image reconstruction, to image display is different. The energy resolving photon detector acquires energy specific information, image processing requires algebraic reconstruction techniques, compressed sensing to deal with sparse data sets, development of novel material decomposition methods, then sophisticated tools for image display so that the user can interrogate the volumetric image quantitatively. Filtered back projection is not fit for the purpose of spectral molecular imaging (9).

**Applications of Spectral molecular Imaging**

Atherosclerosis: In order to influence clinical outcome in atherosclerosis, imaging needs to determine the composition of the plaque rather than plaque burden or luminal stenosis(10). The potential of spectral molecular imaging is to identify disease activity in individual plaques by measuring lipid content, inflammatory markers(11,12), and possibly the fibrous cap. This could be a basis for monitoring the individual during to prevent stroke and cardiac events and accelerate the development of appropriate treatments - personalised medicine. So far, spectral imaging has been able to image gold-labeled
macrophages in plaque(11), and gold-labeled platelets in excised human plaque(13) - k-edge imaging. We have used spectral imaging to measure the lipid component of excised human atheroma(3) - soft tissue imaging.

**Infection and Inflammation:** Markers of the inflammatory response tagged with high Z nanoparticles such as gold have been imaged with spectral CT(2,11,12). There is the potential to label the infective microorganism with gold-labeled antibodies to enable microbiological diagnosis from the spectral molecular imaging scan. The host immunological response could be quantified on the same scan if labeled macrophages or other markers of the inflammatory response were present.

**Cancer:** Personalised cancer treatment becomes possible when the amount of drug entering a tumour can be measured, and the response to treatment assessed noninvasively. The next goals of cancer imaging are to: detect physiological changes signaling the presence of cancer when it is still at a curable stage; evaluate the molecular response of cancer to treatment; and to streamline the development of anticancer drugs(14). Spectral imaging is theoretically well placed to do this, as it could monitor multiple biomarkers simultaneously. The specificity achievable in molecular imaging is a key advantage. Nanoparticles labeled with different high-Z atoms are the obvious choice, but the challenge is to achieve sufficient payload of the high-Z atom to allow quantification within the tumour.

Gold nanoparticles (AuNP) can be bound to drugs or targeted to tumour biomarkers or attached to antibodies. The rate of penetration of nanoparticles into tumours, and their retention within tumours is improved by using macromolecules (15). Gold achieves better contrast than iodine at a lower X-ray dose(16). In nanoparticle form, gold is less toxic, has lower osmolality, and delivers more gold atoms per molecule than iodine, and is better suited to k-edge imaging(11,17).

**Drug Discovery:** Molecular imaging methods are particularly useful for accelerating the assessment of developmental drugs in animal models, rapidly revealing that a drug is a poor candidate (18)). Fewer experimental animals might be needed in preclinical drug testing, and more rapid transition to human drug trials achieved. If drugs are incorporated in macromolecules, selective drug delivery to the tumour is enabled, reducing toxicity to normal tissue(19). Toxic drugs, if incorporated into micelles(20), can be transported safely to the target site where the drug becomes active after endocytosis. Spectral molecular imaging could monitor and measure this.

**Bone Densitometry:** Dual-Xray absorptiometry scanning has the disadvantage of being 2D, and it has difficulty compensating for non-standard bone size(21). Quantitative CT (22) is a research tool which can measure bone densitometry but relies on converting
bone content into bone mineral equivalents by calibration with an hydroxyapatite calibration phantom - using a weighted average Hounsfield unit. This incorrectly assumes that a Hounsfield unit is a constant: it is not, Hounsfield units are very much energy dependent (23). Spectral molecular imaging could overcome these disadvantages as the calcium content could be measured directly from the spectral data.

**Lipid:** Measurement of lipid content of the liver is possible with MR and $^1$H-MRS(24-26). Spectral molecular imaging has the potential to measure lipid content directly and noninvasively in the liver(9) and elsewhere in the body.

**Comparison with other spectroscopic and molecular imaging techniques**

MR spectroscopy(27) has found most use in the brain and prostate. As imaging time is lengthy, the area of interest needs to be motion-less. MR spectroscopy has found limited application elsewhere in the body - apart from breast(28) and liver(29). In spectral molecular imaging, the spectroscopic information is specific to the tissue component, particularly for k-edge imaging(17) of higher Z substances such as iodine, barium, gadolinium, gold, yttrium (1,12,30-32) etc. These metals can be directed to specific biomarkers either as nanoparticles or nanorods or attached to antibodies, micelles, liposomes, and ligands. As they can be distinguished from each other, multiple biomarkers can be measured simultaneously.

The advantage of spectral molecular imaging over other molecular imaging modalities is its ability to specifically identifying the substance, and potential translation to human imaging. Its disadvantage is that the detectable level of the label is at a greater concentration than can be achieved with radiopharmaceuticals in PET and SPECT(33). Spectral molecular imaging will work well for identifying and measuring biomarkers that are macromolecules (34) but it is not appropriate on its own for imaging the small molecules better imaged with fluorescence(35), or PET or SPECT(36,37). PET is the molecular imaging modality with greatest sensitivity but FDG-PET is non-specific. PET has poor spatial resolution. Combining spectral molecular imaging with PET would provide a powerful molecular imaging tool.

**What is needed for Translation to Human imaging?**

Spectral molecular imaging is currently a research tool used in small animal and specimen imaging. To translate it to human imaging, the ASIC sensor assembly needs to be efficient in the human energy range (30-100 keV). The technology for bonding GaAs or CdTe or CZT to the required ASIC is under intense development; new image processing software is required to deal with the data, new software for material decomposition (quantification of multiple different materials within the same voxel) is in development, and new image display methods are required. All these factors are expected to lead to
X-ray dose that is 10-50% of current CT dose. New molecular imaging probes (contrast agents), which are specific to cell types and other biomarkers, are being developed - such as gold-labeled anti-platelet antibodies, and iodine labeled anti-monocyte antibodies.(38).

**Conclusion**

Spectral molecular imaging is a new modality able to discriminate and quantify different components of tissue simultaneously at high spatial and energy resolution, yet at low X-ray dose. It is currently being used for small animal and specimen imaging. The pathway to human imaging is likely to be achieved within the next few years. By then, it may be possible to quantify drug delivery to target tissues, measure the inflammatory response, make microbiological diagnoses directly from the image, and greatly accelerate drug discovery. The world of personalised medicine is within sight.

**Acknowledgements**

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**Images for this section:**
Fig. 1: examples of MARS spectral images of titanium scaffold, scaffold with bony ingrowth, atheroma, mouse spine, gold-labeled anti-platelet antibodies on atheroma, mouse chest with barium and iodine distinguished
Fig. 2: CT images of THR showing fracture, cement displaced, but of similar HU. Example of CT head with probable bleed (courtesy of K Taguchi, John Hopkins).
Fig. 3: Spectral images of phantom containing fat, water, calcium, iodine, gold. Can distinguish each material on material decomposition image (right) using all 6 energy bins, but not from a single energy bin.
Fig. 4: Barium and iodine in mouse chest distinguished at MARS spectral imaging
Fig. 5: Beam hardening artefact at CT, metal artefact at MR. Right image is MARS spectral 3d image of neck of a femoral component of THR in air - no beam hardening
**Fig. 6:** Beam hardening - streak artefacts in metal scaffold at full energy range, artefact eliminated using a narrow energy range. Cupping artefact at full energy range eliminated in narrow energy range - no special post-processing required.
Fig. 7
Xray dose reduction in Spectral Imaging

30% due to improved detector fill factor
30% due to noise reduction
30% due to energy reduction

Standard CT

MARS spectral

Reasonable to expect over 50% dose reduction in clinical conditions

Fig. 8
Fig. 9: Attenuation profile of semiconductor layers (courtesy of Betina Mikulec)
Fig. 10: Material decomposition of carotid atheroma plaque into fat, water and calcium images at MARS spectral

Zainon et al Eur Radiol 2012; 22: 2581
### Spectral molecular Imaging (MARS)

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<th>high-Z element</th>
<th>carrier</th>
<th>target</th>
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**Fig. 11:** Table of multiple high Z materials, carriers, targets and diseases that can be assessed at spectral molecular imaging. 4-6 materials, carriers and targets could be imaged in one imaging data set.
Fig. 12: Attenuation profile with energy for Fe, fat, water, calcium, Iodine. Each profile is different. HU is energy dependent.
Fig. 13: Gold nanoparticles with HDL targeting macrophages in inflamed aortic plaque of rabbit imaged with spectral imaging
Fig. 14: MARS spectral images of excised atherosclerotic plaque compared with histological stains
Fig. 15: Material decomposition of MARS spectral 3D images of carotid plaque. Quantifiable MARS spectral image of carotid plaque with gold labeled anti-platelet antibody (yellow) distinguished from calcium (pink).
Fig. 16: Gold nanoparticles in mouse model of breast cancer
Fig. 17: Drug delivery using macromolecules
New bone formation

Strontium (Sr) can show where new bone is laid down

Osteoporosis treatment
Metabolic bone disease monitoring and treatment

Volumetric renders of a rat vertebral sample using synchrotron and k-edge subtraction showing bone remodelling. Cooper DLM Phys Med Biol 2012; 57:5777

**Fig. 18:** Quantification of Strontium as marker of new bone using synchrotron
Fig. 19: MARS spectral images of metal scaffolds without and with bony ingrowth
Further information

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http://www.marsbioimaging.com/

http://www.otago.ac.nz/bioengineering/christchurch/index.html

**Fig. 20:** How to obtain further information about MARS Spectral
Personal Information

I hold positions as an academic radiologist in the Centre for Bioengineering, Academic Department of Radiology, University of Otago, Christchurch

http://www.otago.ac.nz/bioengineering/research/otago037899.html

and as a clinical radiologist at Royal Hobart Hospital.

I have always enjoyed interdisciplinary research. My current main research interest is in Spectral Molecular Imaging, and how to develop applications for it, and translate it from small animal and specimen imaging, to human spectral imaging. The interdisciplinary nature of this research encompasses physics, mathematics, engineering, biological sciences, computer science, and imaging sciences. I get great pleasure from such a diversity of academic interactions both local and international. Previously, I had a long research interest in ultrasound particularly Ob Gyn, fetal and neonatal ultrasound. My clinical radiology used to be at Christchurch Women's Hospital and Christchurch hospital, but now I commute between Royal Hobart Hospital for clinical work, and University of Otago, Christchurch for research work.

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