Quantitative Imaging With a Pinhole Cardiac SPECT CZT Camera

by

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Abstract

This work develops methods to quantify absolute activity measurements with a multi-head pinhole cardiac SPECT camera that uses cadmium-zinc-telluride (CZT) detectors (Discovery NM530c, GE Healthcare). A central component of absolute activity quantification is the correction for Compton scattered photons. A modified Dual Energy Window (DEW) scatter correction (SC) method was developed that compensates for the presence of unscattered photons in the lower-energy window used to measure scatter. The DEW-SC method was validated using phantom experiments. The mean error in absolute activity measurement was $5 \pm 4 \%$ when correcting for attenuation, scatter and the partial volume effects. Clinical accuracy was assessed using ^{99m}Tc -tetrofosmin myocardial perfusion images obtained on the NM530c and compared to DEW scatter-corrected images acquired on a conventional SPECT camera for the same patient. DEW-SC images acquired on the NM530c had increased noise but had summed perfusion scores that were not significantly different from those acquired on the conventional SPECT camera. To reduce noise in scatter corrected images and provide a more accurate estimate of scatter, a model-based SC method was developed based on the analytical photon distribution (APD) approach. Using physical phantom experiments and a set of five clinical studies, the accuracy of APD-SC was evaluated and compared to DEW-SC. Images generated using the model-based method agreed well with acquired data. APD-SC images had lower noise than DEW-SC images and provided a more accurate measure of cardiac activity in high-scatter scenarios. The developed methods

provide an accurate means of correcting for scatter and thereby allow the absolute quantification of pinhole cardiac SPECT images.

Statement of Originality

This thesis is the summary of the most significant portion of the author's research during the course of his Ph.D. studies at Carleton University. It is based on peer-reviewed publications and conference abstracts listed below in order of appearance in the thesis. Dr. R. Glenn Wells supervised the project and provided guidance on all its components, including the publications. He also contributed code for the iterative reconstruction algorithm, forward projector and system matrix calculations. Specifically, the $F(\xi) \frac{\cos \xi}{4\pi r_{i_k \rightarrow n_i}^2}$ factor referenced in chapter 5 was taken from his calculations. Otherwise, the author of this thesis designed and carried out all experiments and all the computational work and drafted and revised all the manuscripts.

Peer-reviewed papers

1. Pourmoghaddas, A. and Wells, R. G. (2016). "Quantitatively accurate activity measurements with a dedicated cardiac SPECT camera: Physical phantom experiments." *Medical Physics* 43(1): 44-51.
2. Pourmoghaddas, A., Vanderwerf, K., Ruddy, T. and Wells, R. G. (2015). "Scatter correction improves concordance in SPECT MPI with a dedicated cardiac SPECT solid-state camera." *Journal of Nuclear Cardiology* 22(2): 334-343.
3. Pourmoghaddas, A. and Wells, R. G. (2016). *Analytically-Based Photon Scatter Modeling For A Multi-pinhole Cardiac SPECT Camera* (submitted for publication).

Conference abstracts

1. Pourmoghaddas, A. and Wells, R. G. (2015). *Quantitative accuracy of SPECT imaging with a dedicated cardiac camera: Physical phantom experiments. World Congress on Medical Physics and Biomedical Engineering, June 7-12, 2015, Toronto, Canada. Oral presentation and IFMBE proceedings pp 147-149.*
2. Pourmoghaddas, A. and Wells, R. G. (2013). "Activity measured as a function of MLEM iterations for a dedicated cardiac SPECT camera." *J Nucl Med Meeting Abstracts* 54 (2): 2076.

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Abbreviations and Notation

AC	Attenuation Correction
ACPVC	Attenuation Correction and Partial Volume Correction
ACSC	Attenuation Correction and Scatter Correction
ACSCPVC	Attenuation Correction, Scatter Correction and Partial Volume Correction
APD	Analytic Photon Distribution
APDI	Analytic Photon Distribution Interpolation
ASNC	American Society of Nuclear Cardiology
CAD	Coronary Artery Disease
CTAC	CT-based Attenuation Correction
CT	Computed Tomography
CZT	Cadmium Zinc Telluride
DEW	Dual Energy Window
ESSE	Effective Scatter Source Estimation
FBP	Filtered Back-Projection
FOV	Field of View
FWHM	Full Width at Half Maximum
INF	Infinia Hawkeye SPECT/CT Scanner
IR	Iterative Reconstruction
ISF	Incoherent Scattering Function
keV	kiloelectron-Volts
LSF	Line Spread Function
LV	Left Ventricle
LW	Lower Window
MBF	Myocardial Blood Flow
MBq	Mega Becquerel
MC	Monte Carlo
mCi	milliCurie
MeV	Mega electron-Volt
MLEM	Maximum-Likelihood Expectation Maximization
MPI	Myocardial Perfusion Imaging
MRI	Magnetic Resonance Imaging
NaI	Sodium Iodide
PE	Photoelectric Effect
PET	Positron Emission Tomography
PDF	Primary Distribution Function
PSF	Point Spread Function
PV	Partial Volume
PVC	Partial Volume Correction
PVE	Partial Volume Effect
PW	Photopeak Window
RMSE	Root Mean Squared Error
ROI	Region of Interest
SD	Standard Deviation

SDF	Scatter Distribution Function
SDS	Summed Difference Score
SDSE	Slab Derived Scatter Estimation
SPECT	Single Photon Emission Computed Tomography
SPS	Summed Perfusion Score
SRS	Summed Rest Score
SSS	Summed Stress Score
SUV	Standardized Uptake Value
TDCS	Transmission-Dependent Convolution Subtraction
UOHI	University of Ottawa Heart Institute
VOI	Volume of Interest

Chapter 1 Introduction

1.1 Cardiac Imaging With SPECT

Heart disease continues to be a major cause of death and disability in Canada, accounting for close to 20% of all deaths in Canada in 2011 [1]. A commonly used method to diagnose heart disease is by imaging the heart using Single Photon Emission Computed Tomography (SPECT). SPECT is a medical imaging modality that allows for three dimensional visualization of organ function in the body. In North America, over 9 million cardiac SPECT studies are performed annually [2]. In SPECT imaging, a drug is chemically attached to a photon-emitting radioisotope and injected into the blood stream. This radio-labeled compound is commonly referred to as a tracer (or radiotracer) and is designed to follow a particular physiological pathway in the body. The radioisotope emits gamma-ray photons when it decays which are detected from outside the body, revealing the location of the drug and characterizing the physiological pathway under study. A SPECT scanner, or gamma camera, is used to detect these photons, each detector acquiring a view or *projection* of the radiotracer distribution from a specific angle (Figure 1.1). Computers are used to calculate three-dimensional visualizations from the measured projections.

Figure 1.1 A general model of 2D projections of a 3D object. In conventional SPECT scanners, the camera head rotates around the patient, acquiring projections whose elements are given by line-integrals of the activity distribution through the patient

SPECT is a functional imaging modality. While other modalities such as X-ray computed tomography (CT) and magnetic resonance imaging (MRI) provide non-invasive visualization of patient anatomy, SPECT tracer distributions provide information as to how well the organ is functioning. SPECT imaging is a non-invasive procedure, that is, it provides information about the state of the disease of the patient without the need of a scalpel.

The use of SPECT imaging has garnered widespread clinical acceptance and is used to diagnose a variety of disorders and diseases such as cancer, brain disorders,

heart disease and kidney dysfunction. Cardiac SPECT is a popular diagnosis tool for detecting blockages in coronary arteries and for measuring reduced pumping efficiency of the heart. The most common type of cardiac scan is myocardial perfusion imaging (MPI) which measures blood flow in the heart muscle. This scan can be done using a ^{99m}Tc -labeled drug called tetrofosmin. Tetrofosmin is a lipophilic cation which accumulates in normal heart muscle (myocardium) in proportion to myocardial blood flow after injection. Since undersupplied and dead muscle tissues do not take up tetrofosmin, a tetrofosmin scan indicates which areas of the heart which are still supplied adequately with blood and are functioning properly. Cardiac SPECT scans are usually repeated in rest and stress conditions. A stressed condition can be achieved by having the patient exercise on a treadmill or stationary bicycle. Alternatively, the patient can also be stressed pharmacologically. The two sets of images (rest vs stress) are compared to distinguish between healthy, undersupplied, and dead tissue – the blood supply can often be restored to undersupplied tissues by reopening the obstructed arteries that are causing the reduction in blood flow. Such interventions can improve heart function and improve the prognosis of the patient [3].

1.2 SPECT Camera Instrumentation

1.2.1 The Anger Camera

The first SPECT scanner was designed by Hal Anger in 1958, which consisted of a single scintillation crystal plane optically coupled to an array of photomultiplier tubes[4]. The early version of Anger's camera used a pinhole aperture or collimator

(a lead sheet with a single small hole). This was later changed in 1964 to a parallel-hole collimator to increase efficiency [5]. Gamma-ray photons are emitted by the radio-isotope, leave the body, pass through the collimator, strike the scintillator crystal and are absorbed. The scintillator then re-emits this radiation in the form of lower-energy light photons. The most common scintillation crystal used in SPECT is sodium iodide (NaI) due to its high light output. The scintillation light photons are translated into an electronic signal by photomultiplier tubes (PMTs) that are positioned behind the scintillator crystal. The camera electronics process the signal and determine the location of the detected gamma-ray photon. The energy of the incident gamma-ray is proportional to the number of light photons produced by the PMT and is digitized by the multichannel analyzer for the PMT's. The detected location of each gamma-ray is then stored on a computer (Figure 1.2).

While many innovations have been made since Anger's original design, today's clinical gamma cameras are often called *Anger cameras* because the essential features have remained unchanged in conventional SPECT cameras to this day. Small modifications have occurred such as the move to dual-head systems, but conventional SPECT cameras generally have continued to be based on a NaI scintillation detector coupled with PMTs, fronted by a general-purpose parallel-hole collimator and mounted on a rotating gantry.

Figure 1.2. A schematic of fundamental components of the conventional SPECT camera.

Figure 1.3. The Infinia-Hawkeye 4 SPECT/CT camera, a conventional SPECT camera with parallel-hole collimators.

1.2.2 Data Acquisition

In most SPECT scanners gamma-rays that exhibit energies that are outside of the energy window boundaries are rejected upon detection. Energy window boundaries are specified prior to the start of the scan and are generally set with two parameters: a window median value and a window range specified as a percentage thereof. For instance, for imaging ^{99m}Tc tracers that emit 140 keV gamma-rays, a window may be specified as $140 \text{ keV} \pm 10\%$ (a 20%-wide window accepting gamma-rays with energies between 126 and 154 keV). The location of the gamma-rays accepted by the energy window are histogrammed additively in real-time for each projection and recorded on a computer.

With the advancement in detector technology and electronics, more recent cameras are able to record every single detected gamma-ray and their deposited energy in a time-stamped list. This type of data-storage is called *list-mode* acquisition. This format requires large amounts of memory storage ($\sim 300 \text{ MB}$ for a typical SPECT scan) but allows post-acquisition division of the data, enabling energy windows to be applied retrospectively and multiple images to be produced from a single acquisition or temporal manipulation of the scan.

1.2.3 Collimators

As described above, SPECT images are formed from gamma-photons projected onto the detector surface. Since gamma photons cannot be focused the way light photons are by optical lenses, an *absorptive collimator* is needed. Absorptive collimators mechanically select for photons traveling in specific directions by

absorbing the photons traveling in directions other than those specified by the collimator. Absorptive collimation is inefficient; most photons emitted in the direction of the detector are absorbed by the collimator. This is one of the main reasons for the relatively poor sensitivity of SPECT imaging compared to modalities like positron emission tomography (PET).

Parallel-hole collimators are the most commonly used collimator type in SPECT cameras. These collimators are essentially a large sheet of lead with many holes through it. These holes are aligned parallel to one another and also parallel to the normal of the detector crystal surface and so ideally will only accept photons which are travelling perpendicular to the detector plane (Figure 1.4(b)).

Figure 1.4. Top row: schematics of a pinhole (a) and a parallel-hole (b) collimator. The solid-colored arrow represents the source distribution being projected onto a planar detector and the shaded arrow is the image of that source. In the case where the distance from the pinhole opening to the detector is smaller than the source-pinhole distance, the image is minified. The parallel-hole collimator preserves the dimensions of the source. Bottom row: the parallel-hole collimator (right) absorbs photons not travelling straight through the collimator while the pinhole collimator (left) allows photons coming from different directions.

In parallel-hole collimators, the walls between the holes are called *septa*. Collimators with thicker septa prevent photons from penetrating through from one hole to the other, improving spatial resolution. Smaller and longer holes provide better spatial resolution, by reducing the angle at which gamma-rays can pass through the collimator, but do so at the price of reduced efficiency. Alternatively, wider, shorter holes allow more photons entering at a broader range of incident

angles to reach the detector, increasing collection efficiency, but degrading the accuracy of directional information and hence spatial resolution.

A *pinhole* collimator is created by piercing a small pinhole aperture in a slab of a heavy metal absorber, such as lead, tungsten or platinum. The principle of a pinhole-collimator is the same as in an inexpensive “box camera”: an upside-down image of the activity source is projected onto the detector surface (Figure 1.4). The image is smaller than the source when the distance from the source to the pinhole is larger than the distance from the pinhole to the detector surface, and vice-versa. In some cameras, the magnification property of the pinhole collimator is used for imaging small organs, such as the thyroid, as well as for small-animal imaging [6]. The pinhole opening diameter for clinical cameras is typically a few millimeters and can be widened in some collimator designs, increasing photon through-put efficiency (sensitivity), while decreasing spatial resolution, or vice-versa.

1.2.4 Discovery NM530c: A Dedicated Cardiac SPECT Camera

Recently, there has been a revolutionary improvement in the technology available for SPECT cardiac cameras. The new designs use solid-state detectors which are able to convert the incident radiation directly into an electric signal without the need for an intermediate high-gain amplification stage (the PMT’s in conventional cameras, Figure 1.2)[7]. Removing the PMT’s from the design makes for compact detectors which operate at low voltage. Inside the solid-state crystal, the absorbed energy of an incident gamma-ray liberates charge carriers (electrons and holes) which induce charge on the terminals, generating an electronic pulse

(Figure 1.5). The direct conversion of the gamma-rays also produces a larger electronic signal with correspondingly decreased uncertainty compared to that from a scintillator-PMT combination, resulting in considerably better energy resolution (5.5% for CZT vs 9.5% for conventional SPECT scanners, at 140 keV [8])(Figure 1.6). Some solid-state detectors such as high- purity Germanium need to be cooled down to low temperatures (-150°C) whereas others such as cadmium telluride and Cadmium Zinc Telluride (CZT) operate at room temperature. The main disadvantages of solid-state detectors are lower efficiency for higher energy incident photons, and higher fabrication costs [9].

Figure 1.5. A schematic of the detection of a gamma-ray photon by a solid-state detector.

The excellent energy resolution of CZT detectors is counterbalanced by some effects that prevent complete signal formation: (1) electron and hole trapping inside the crystal creates a depth-of-interaction dependence on the generated signal, (2) the finite size of the signal contact results in an induced signal that depends more on the relatively slow hole drift speed for signals generated closer to the anode and (3) pixilation of the detector results in lower sensitivity of detection at the pixel

boundaries [10]. These effects combine to create a tail of events on the low-energy side of the photopeak (Figure 1.6) which is commonly referred to as the *low-energy tail*. As seen in Figure 1.6, imaging a point source in the absence of a scattering medium results in the detection of a relatively large number of counts with lower energies.

Figure 1.6 The normalized extrinsic energy spectrum for a ^{99m}Tc point-source in air as recorded by the Discovery NM530c (CZT) and the Infinia Hawkeye4 SPECT cameras. The CZT camera shows improved energy resolution compared to the Infinia, as measured by the FWHM. The CZT spectrum also shows a large number of unscattered photons detected below the photopeak. This effect is commonly referred to as the *low-energy tail*. The small broad peaks in the Infinia spectrum that are centered at 80 keV and approximately 100keV reflect interactions with the collimator and likely backscatter from the camera head.

In addition to using CZT detectors, dedicated cardiac SPECT scanners such as the DSPECT (Spectrum Dynamics Medical Inc.) [11] or the Discovery NM530c [8] (GE

Healthcare, Milwaukee, WI, USA) have been redesigned to greatly increase count sensitivity (a 4 to 8 fold increase over conventional cameras [7]) for imaging the heart. The improved sensitivity offers the potential for reduced patient radiation exposures [12, 13] or shortened scan times[14-16] compared to conventional scanners with parallel-hole collimators.

A NM530c dedicated cardiac SPECT camera (CZT camera; GE Healthcare) has been in use at the University of Ottawa Heart Institute (UOHI) since 2009 (Figure 1.7). This camera uses a multi-pinhole design in which an array of pixelated CZT detectors is positioned on a stationary gantry and is focused on the heart. The compact design of the CZT detectors allows for nineteen detectors to be positioned around the patient and thereby removes the need to rotate the camera during image acquisition.

The use of pinhole-collimated CZT detectors also improves the energy and spatial resolution over conventional SPECT cameras, and the use of simultaneously acquired views improves the overall sensitivity of the system. A study characterizing the NM530c reported a resolution of 7 mm at the centre of the FOV, compared to 11 mm for a conventional SPECT scanner, for ^{99m}Tc sources [8, 17]. The same study reported a 4.1x increase in sensitivity, when using the NM530c. The added sensitivity reduces the scan times from 15 min down to 3 min or less [8, 16]. Furthermore, the capability of having simultaneously acquired views improves the temporal resolution, allowing for dynamic imaging and the absolute measurement of myocardial blood flow (MBF) and coronary flow reserve (CFR) [8, 18].

Figure 1.7. (A) The Discovery NM530c (GE Healthcare) installed at the University of Ottawa Heart Institute, (B) alternate view of the camera and (C) a schematic of the pinhole-collimators and the detector array focusing on the heart.

1.3 Isotopes

The isotopes used in SPECT imaging decay through the emission of gamma ray photons. The photon energies are specific to the isotope. Some isotopes have a single prominent decay energy ($^{99\text{m}}\text{Tc}$: 140 keV), while others may decay through a variety of pathways (^{67}Ga : 93 keV, 184 keV, and 296 keV). Isotopes frequently used in SPECT are listed in Table 1.1.

Table 1.1 Common SPECT tracers and their indicators.

Tracer	Half-life	Photon energy	Source	Indications
^{201}Tl	73 hours	70-80 keV	Nuclear Reactor	Myocardial perfusion
$^{99\text{m}}\text{Tc}$	6 hours	140 keV	Generator (^{99}Mo)	$^{99\text{m}}\text{Tc}$ -sestamibi and $^{99\text{m}}\text{Tc}$ -tetrofosmin for Myocardial perfusion, $^{99\text{m}}\text{Tc}$ -pertechnetate for cardiac ejection fraction
^{123}I	13 hours	159 keV	Nuclear Reactor	^{123}I -(BMIPP) for Fatty-acid metabolism, ^{123}I -(MIBG) for Sympathetic innervation
^{111}In	2.8 days	171 keV, 245 keV	Nuclear Reactor	^{111}In -octreotide for neuroendocrine tumour imaging, ^{111}In -oxime for white blood cell infection studies
^{67}Ga	3.26 days	93 keV, 185 keV, 296 keV	Nuclear Reactor	Gallium citrate produces free $^{67}\text{Ga}^{3+}$ ions which are used to image inflammation and tumor growth

Note: ^{123}I -(BMIPP), beta-methyl-p- ^{123}I -iodophenyl-pentadecanoic acid; ^{123}I -(MIBG), ^{123}I -metaiodobenzylguanidine;

1.4 Photon Interactions With Matter

To fully understand the imaging process, it is important to understand the interactions that photons can have inside the patient or phantom and within the SPECT camera. Photons emitted from the decay of SPECT tracers inside the patient may interact with body matter one or more times prior to exiting (Compton or Rayleigh scattering), or they may be absorbed within the body (photoelectric effect), or they may exit the body with no change in energy or direction. A brief description of these interactions is provided in the following sections. A more complete description can be found, for example, in [19].

1.4.1 Compton Scattering

Compton (incoherent) scattering is the most prevalent form of scatter at the energies used in nuclear medicine (70-511 keV) [19]. In Compton scattering, a

photon interacts with an electron, transferring a portion of its energy to the electron and liberating it from its host atom. The energy of the scattered photon (E') is given by the following equation:

$$E' = \frac{E}{1 + \alpha(1 - \cos \theta)} \quad (1)$$

where α is the energy of the photon divided by the rest mass of the electron, E is the initial energy of the photon, and θ is the angle of deviation. If the incident photon scatters only once within the scattering medium, a 'first-order' Compton scatter has occurred. However, a photon can scatter more than once in the medium. A photon which has scattered twice is referred to as second-order scatter, one that scattered three times as third-order scatter, and so on. As a result of Compton scattering, the scattered photon (E') always emerges with reduced energy. Compton scattering accounts for 97.4% of the total cross section for 140 keV photons in water [20] (Figure 1.8). The differential cross-section for Compton scattering ($\frac{d\sigma(\theta)}{d\Omega}$) is given by the Klein-Nishina formula:

$$\frac{d\sigma(\theta)}{d\Omega} = \frac{r_0^2}{2} (1 + \cos^2 \theta) \left(\frac{1}{1 + \alpha(1 - \cos \alpha)} \right)^2 \left(1 + \frac{\alpha^2(1 - \cos \alpha)^2}{(1 + \alpha(1 - \cos \alpha))(\alpha(1 + \cos^2 \theta))} \right) \quad (2)$$

where Ω is the solid angle of the scattering cone and r_0 is the classical electron radius. Because α depends on the energy of the incident photon, the cross-section decreases with increasing photon energy. Figure 1.9 shows the relative probability of Compton scatter per unit solid angle as a function of the angle of scatter. The probability of Compton scatter is highest for small deflection angles and drops rapidly as the angle of deviation increases, while increasing again as the scattering angle approaches 180°.

Figure 1.8. Relative importance of the three main modes of photon interaction in water, for the energy range common to SPECT imaging [20](adapted with permission (Appendix C)).

The Klein-Nishina formula assumes that the electron is stationary and not electromagnetically bound to any nucleus. As a result, the Compton cross-section per electron is relatively constant as a function of the atomic number of the scattering medium. However, for most scattering media the scattering electrons are not free and so a correction factor, the *incoherent scattering function* (ISF), can be applied to include binding effects from the nucleus. The ISF is a function of the scattering angle (θ), the wavelength of the scattered photon (λ) and the atomic number of the scattering medium (Z). The ISF is also sometimes referred to as the incoherent scattering form factor. The ISF is calculated using quantum mechanics and is applied as a multiplicative correction to the Klein-Nishina differential cross section to obtain the incoherent scattering differential cross section. Tabulated values for the ISF can be found in [21, 22].

Figure 1.9 Angular dependence of the Klein-Nishina function $d\sigma(\theta)/d\Omega$ for various photon energies, normalized to the value at 0° , plotted as a function of scattering angle (θ)

1.4.2 Rayleigh Scattering

Rayleigh (coherent) scattering occurs when the electric field associated with an incident photon sets the electrons in the atom into momentary vibration. The oscillating electrons in turn retransmit the photon at the same wave-length as the incident radiation. With Rayleigh scattering, no energy is converted into kinetic energy of the electron therefore the energy of the photon does not change but the direction does. Rayleigh scattering probability increases with higher atomic number of the scattering medium Z and decreases rapidly with increased photon energy. In SPECT imaging, the contribution of Rayleigh scatter to the total scattering cross-section is small (Figure 1.8) and so is often ignored.

1.4.3 Photoelectric Effect

In the photoelectric effect (PE), a photon collides with an atom resulting in the ejection of a bound electron. This effect is most likely to occur when the energy of the incident photon is *just* larger than the binding energy of the electron. The probability of occurrence of the cross-section per electron of the photoelectric effect decreases with increased photon energy as $\frac{1}{E^3}$ and increases proportional to Z^3 where Z is the atomic number of the atom for high- Z materials and as approximately $Z^{3.8}$ for low- Z materials. The effective atomic number of biologically relevant material is relatively small ($Z_{\text{water}} = 7.4$, $Z_{\text{bone}} = 12.3$, compared to $Z_{\text{lead}} = 82$) thereby reducing the contribution of the photoelectric effect at energies used in SPECT imaging (1.9% in water at 140 keV (Figure 1.8)).

1.5 Partial Volume Effect

There are two distinct phenomena that are commonly referred-to as the *Partial Volume Effect* (PVE). The first effect is the blurring of the image by the finite spatial resolution of the SPECT camera. The spatial resolution of a pinhole-collimated camera is influenced by factors such as the size of the pinhole opening, the intrinsic resolution of the detector and the reconstruction process. As a result of this blurring, the image of a small source appears as a larger but dimmer source (Figure 1.10). The blurring can be mathematically described by a 3D convolution operation of the original image with the point spread function (PSF) of the imaging system. The PSF essentially corresponds to the image of a point-source, as imaged by the camera. The PSF of SPECT scanners is spatially-variant and worsens as a function of

depth inside the body.

The second cause for PVE is the sampling of the image onto a discretized voxel grid. The edges of the voxelized source will not perfectly match the actual edges of the tracer activity distribution. As a result, voxels in the reconstructed image will represent a mixture of different tissue types. The intensity of the image voxel will be the average of the signal intensities of the underlying tissues included in that voxel. This effect is called the *tissue fraction effect* and would still be present in the case where the imaging system has perfect resolution.

Figure 1.10. A diagrammatic representation of the spillover of measured activity from the myocardium to the blood and vice versa. (A) Shows schematically a short axis cut through the LV myocardium (B) Depicts an activity profile of the cross section shown in (A). (C) Shows an activity profile from the same cross section when the blood activity is high and the myocardial tracer uptake is low.

The PVE is important for quantitative and qualitative interpretation of SPECT images. For activity structures that only partially fill a reconstructed voxel element,

the intensity of the voxel no longer accurately reflects the concentration of activity within the structure because the measured activity is distributed over a volume that is larger than the actual size of the source. Also, the activity concentration at the edge of organ boundaries is influenced by the activity spill over from neighboring organs.

For instance, in cardiac imaging, the thickness of the heart wall is typically on the same order of the resolution of the system (a thickness of 9 mm [23] compared to a resolution of 7 mm full width at half maximum (FWHM) for the NM530c [17], or 1 cm for a conventional SPECT scanner). As a result of the PVE, photons originating in the heart wall are blurred into surrounding organs such as the liver, stomach, lung and the blood pool. In addition, photons originating in these organs, that are in close proximity to the heart, blur into the myocardium.

Nuclear cardiac imaging can therefore benefit from partial volume correction (PVC) and a variety of methods have been proposed to diminish the impact of PVE. Strategies for correcting for the PVE are given in section 2.3.

1.6 Attenuation Correction

Photons generated from the radiotracer injected into the body pass through varying thicknesses of attenuating media before reaching the SPECT detectors. Some photons are absorbed in the body as a result of PE, and others are scattered through Compton or Rayleigh scattering, and are displaced from their original path. As shown in section 1.4, Compton scatter is the most likely interaction for photons in the energy range of most SPECT radiotracers, but both Compton scattering and

the PE lead to a loss of detected photons and therefore contribute to attenuation. Also, Compton (and Rayleigh) scattered photons may still be detected and can be difficult to distinguish from primary photons. A review of scatter correction techniques follows in section 2.2.

Due to photon attenuation, the probability of photons exiting the body decreases exponentially as a function of the distance travelled through the body:

$$I(x) = I_0 e^{-\int \mu(E,x) dx} \quad (3)$$

where μ is the linear attenuation coefficient of the material the photon is travelling through, x is the position along the photon's path, E is the photon energy and I_0 and I are the original and exiting photon fluxes, respectively. As a consequence of photon attenuation, photons originating from deep inside the body have a lower likelihood of detection, resulting in depressed values in the reconstructed image – also known as an *attenuation artifact*. The total amount of attenuation also depends on the composition of the body along the path travelled by the photon – denser regions of the body have larger μ values.

Various methods have been suggested for attenuation correction (AC) [24-27]. To correct for attenuation with iterative reconstruction (IR), a map of the linear attenuation coefficients for the SPECT isotope is used as an input to the reconstruction algorithm. These maps can be generated using radioisotope transmission scans [28] or using CT images [26, 29]. More details on AC with IR follow in section 1.7.2.

1.7 SPECT Reconstruction

In SPECT, the data acquired by the detector represents a set of line integrals through the activity distribution inside the body of the patient (Figure 1.1). Traditional SPECT cameras capture projections from various angles by rotating one or two planar detector panels around the patient. In the CZT camera, 19 detectors are arranged on a stationary gantry and all of the projections are acquired simultaneously. Once the projections are acquired, it is necessary for the data to be reconstructed into a useful format for viewing by physicians. Image reconstruction is the process of calculating a three dimensional tomographic image using the measured projections.

1.7.1 Filtered Back-Projection

Filtered Back-Projection (FBP) is an analytic method for reconstruction of SPECT projections [30]. A back-projection image is generated by spreading the value recorded in each pixel of each projection along the line from which the photon came. Where lines intersect the projection values are added, reinforcing each other and indicating the true source location (Figure 1.11-B).

Figure 1.11 (a) A schematic diagram of the forward-projection operation of a simple source distribution for three projection angles. (b) Back-projection of these data. Intersections of the shaded areas correspond to possible source locations and converge towards the actual distribution with additional projection angles.

The density of the intersecting lines decreases with increasing distance from the position of the source, giving a spike or star-like appearance for each reconstructed source. To correct for this effect, a ramp filter is applied to the projection prior to back-projection which sharpens the appearance of the source. A more thorough treatment of reconstruction by FBP can be found in [29]. Image reconstruction using FBP is computationally fast, which is important for implementation in the clinic, however, the ramp filter used in FBP tends to amplify noise in the image, reducing image quality. In order to reduce noise levels, a low-pass filter is often applied. However, this adjustment reduces the high-frequency structure in the image that is associated with sharp changes in the activity distribution, reducing image resolution. Additionally, with FBP it is difficult to accurately account for physical effects such as the system point spread function (PSF) and photon attenuation. While exact analytic inversions of the attenuated Radon transform operation have been developed for non-uniform attenuation [31, 32], the presence of Poisson noise

in the projection data degrades the quality of the final result. Other approaches to attenuation correction with FBP rely on approximations [25] and may not provide as accurate a correction as can be achieved with an iterative reconstruction algorithm. While the use of iterative reconstruction is currently common-place in clinical practice, FBP continues to be used in instances where computation time is a critical factor.

1.7.2 Iterative reconstruction

In contrast to FBP which analytically calculates the final reconstruction directly from the measured projections, iterative reconstruction (IR) starts by guessing an estimate of the reconstructed image, then repeatedly modifies that guess to conform more closely to the measured projections (Figure 1.12).

Figure 1.12. Flow-chart of an iterative reconstruction algorithm.

To better understand IR, the SPECT image acquisition process can be summarized by the following equation:

$$P_i = \sum_{k=1}^M S_{i,k} A_k \quad (4)$$

where P_i is the number of counts detected in detector bin i , A_k is the amount of activity in voxel k of the object and M is the total number of voxels in the object which contains activity. The term $S_{i,k}$ refers to element (i,k) of the system matrix which represents the probability that a photon emitted from voxel k in the object will be detected in bin i of the detector. The system matrix aims to model the relationship between the activity in the object and the detected projections. At the minimum, the system matrix can be calculated analytically using geometrical ray-

tracing of the photon propagation [33, 34]. This only incorporates the geometrical contributions of the detection probability. Other effects such as the intrinsic detector response, septal penetration and collimator aperture effects also affect the detection probability and require laborious characterization of the system using Monte Carlo calculations, [35] modeling efforts [36] or experiments [37]. The size of the system matrix is given by the product of total number of object voxels and the total number of projection bins, and hence is very large. Thus, most commonly, the system matrix elements are not calculated directly. However, with the NM530c camera, there are only 19 projections each with 32×32 projection bins and so the total number of projection bins is smaller than with traditional cameras, allowing the system matrix elements to be calculated and stored as a pre-calculated look-up table. Patient-specific effects such as attenuation and scatter can also be taken into account in the system matrix calculations, enabling accurate AC and SC for SPECT image-reconstruction.

Several algorithms have been proposed for iterative reconstruction [38-41]. One of the most commonly used iterative algorithms is that of Maximum Likelihood Expectation Maximization (MLEM) [42, 43]. Through iterative calculations, the likelihood function is maximized when the difference between calculated and measured projections is minimized. The MLEM algorithm is given by the following equation:

$$f_j^{n+1} = \frac{f_j^n}{\sum_{i=1}^N S_{i,j}} \sum_{i=1}^N \frac{S_{i,j} P_i}{\sum_{k=1}^M S_{i,k} f_k^n} \quad (5)$$

where f_j^n is the n^{th} iterative estimate of the object activity in voxel j , the subscript

k spans all activity voxels in the reconstructed image, P_i represents the measured number of counts in detector bin i and N is the total number of projection bins. The term $\sum_{k=1}^M S_{i,k} f_k^n$ is commonly referred-to as the *forward-projection* of estimate f^n for detector pixel i (equation (4)). The forward-projection of f^n effectively calculates the projections as measured by the detectors, given an activity distribution (f^n) (Figure 1.11).

The reconstructed image produced by IR improves with each iteration as it converges to an acceptable solution, but it's not always clear how many iterations should be used and the final solution is not necessarily unique. The optimal number of iterations cannot be known prior to reconstruction since it is dependent on the spatial frequencies, the activity distribution in the object and the accuracy of the system matrix. IR requires much more computing power than FBP, however the ability to model physical effects with IR makes it a more accurate option for image reconstruction in SPECT.

1.8 Structure of the Thesis

1.8.1 Goal and Hypothesis

The goal of this thesis is to evaluate the quantitative accuracy and precision of a pinhole cardiac SPECT CZT camera. As scatter estimation and correction is central to accurate absolute quantification of images, the thesis focuses on methods of scatter correction for the new cardiac system. To this end, we develop a modified dual-energy-window scatter correction method. We hypothesize that (1) correcting for attenuation, scatter and the PVE will enable quantitatively accurate measurements

of activity with the NM530c SPECT camera and (2), we hypothesize that a model-based scatter correction method will provide as good a correction as an energy-based method but with less noise in the images.

1.8.2 Thesis Organization

Chapter 2 is a review of the previous work on the subject of quantitative imaging in SPECT and the various approaches taken to address scatter and partial volume correction. In chapter 3, the quantitative accuracy and reproducibility of activity measurements with the CZT camera is assessed, an energy-based scatter correction method is proposed and its quantitative accuracy is verified by way of physical phantom measurements. Chapter 4 evaluates the accuracy of the verified method as applied to clinically acquired ^{99m}Tc -tetrofosmin myocardial perfusion images obtained on the CZT camera. The CZT images are compared to DEW scatter-corrected images from a conventional camera. In chapter 5 the accuracy of an analytically-based scatter estimation method is verified and its performance is compared to the energy-based method studied in chapters 3 and 4. Chapter 6 summarizes the results and proposes some possible avenues of further research.

Chapter 2 Background and Literature Review

2.1 Quantitative Imaging With The NM530c

In nuclear medicine, *quantitative imaging* refers to the measurement of activity in units of activity per unit volume. Three main features are needed in order to generate quantitatively accurate images: (1) minimizing image-degrading factors: physical factors such as photon attenuation and scatter, patient factors such as heart and breathing motion and factors in the instrumentation such as the collimator-detector response [44-47], (2) a reconstruction algorithm that behaves in a linear fashion in terms of the reconstructed activity concentration and (3) the ability to calibrate the reconstructed data in units of activity per unit volume (e.g. $\text{kBq} \times \text{cm}^{-3}$). Historically, quantitative imaging has been easier with PET than with SPECT, mostly because AC is a simpler problem in PET and it has been more accessible. PET scanners have always been sold with some form of transmission imaging, either radioisotope or CT based. Hybrid SPECT/CT scanners are available but a very large percentage of SPECT scanners are still sold without any form of transmission imaging capability [48]. Finally, due to the superior image resolution of PET compared to SPECT, PVE is less of a problem in PET.

There are many potential benefits of quantitative imaging. In general, the correction for physical degrading factors results in improved diagnostic ability [49]. Specifically, quantitative imaging provides the ability to extract specific physiological parameters of interest which in some cases is not possible with relative imaging. For instance, quantitative PET imaging (and recently, SPECT) has

emerged as a tool for determining biological target volumes for radiotherapy or to retrospectively determine the absorbed dose delivered during targeted radionuclide therapy treatments [50]. Quantitative measurement of ^{99m}Tc -MDP uptake is an essential diagnostic test for bone abnormalities [51]. Imaging of ^{123}I -labeled neuroreceptor tracers are used to investigate receptor density and occupancy in the brain [52, 53]. A list of other potential uses for quantitative SPECT can be found in [54].

Among the physical sources of image degradation, photon attenuation is perhaps the most prominent image-degrading factor in SPECT [45]. The variable effect of attenuation in tissues surrounding the heart such as lung, breast, bone and soft tissue (muscle and blood) can lead to a regional decrease in myocardial count density that can be mistaken as a perfusion defect [46, 55]. Additionally, attenuation effects are complicated by the presence of breathing and gross patient movement. If a transmission map is available, accurate AC is possible for SPECT via an iterative reconstruction algorithm (Section 1.7). In cardiac SPECT, AC has been shown to greatly improve the specificity of MPI [56].

With dedicated solid state SPECT cameras such as the CZT camera, attenuation effects present with different patterns from those seen with conventional NaI-based systems and have been shown to be less prevalent overall [14]. Nevertheless, attenuation is still present and attenuation correction (AC) is still beneficial at removing image artifacts [16, 17, 57]. Without correction for scatter, studies that were acquired on a dedicated-cardiac system were shown to have similar performance to attenuation corrected images acquired with a conventional camera

[16].

While photon attenuation and collimator blurring can now be corrected in clinically acceptable times, accurate and efficient scatter correction (SC) is a more difficult problem [48]. Attenuation correction based on narrow-beam attenuation coefficients can lead to apparent overcorrection unless compensated for the presence of scatter [26], which can substantially affect quantitative accuracy [58]. Photon scatter within the myocardium reduces image contrast [59] and scatter from extra-cardiac activity can interfere with uniformity [26]. The design of the dedicated cameras can alter the sensitivity profile of the system. For example, cameras with multi-pinhole collimators have decreased sensitivity for distant structures like liver and gall-bladder, which may alter the pattern of scatter in the projection data. However, photons from the liver that scatter in the heart can still be detected and contribute significantly to the magnitude of the detected signal. The impact of scatter and scatter compensation (SC) on pinhole-based dedicated cardiac images has not previously been evaluated.

The quantitative accuracy of SPECT images can be evaluated by comparing activities measured in those images to the true activity distribution used to create the images. While the true activity in a patient study can be difficult to determine, it can be easily established with *phantom* experiments. A phantom is a plastic model which mimics the patient habitus and often includes fillable organ compartments with known shapes and volumes. Phantom studies provide a means to measure the quantitative imaging accuracy and reproducibility that can be achieved in a controlled experimental setting. The DataSpectrum anthropomorphic torso

phantom with cardiac insert (Data Spectrum Corporation, Durham, NC, USA) is a phantom that is commonly used in cardiac imaging research. This phantom has organ compartments for the heart, lungs, liver and soft tissue (Figure 2.1) which can all be filled with differing amounts of radioactivity.

Figure 2.1 Top:an anthropomorphic torso phantom with cardiac insert (Data Spectrum Corporation, Durham, NC, USA). Bottom: the torso phantom positioned in the GE-Discovery NM530c dedicated cardiac SPECT scanner.

Accurate SPECT quantification has been shown to be possible for conventional cameras, for example in Shcherbinin *et. al.* [60]. In this study, an extensive analysis of quantitative accuracy with four radiotracers (^{99m}Tc , ^{111}In , ^{123}I and ^{131}I) was performed using parallel-hole cameras with NaI detectors. Their experimental set-up consisted of placing cylindrical bottles containing radioactivity inside a thorax phantom to resemble tumors. Imaging was done using a conventional clinical SPECT camera with parallel-hole collimators. Corrections for attenuation, scatter and collimator septal penetration effects were applied and they reported error levels of 3-5% for all isotopes.

2.2 Scatter Estimation and Correction

The presence of scattered photons is perhaps one of the most complicated physical factors affecting image quality in cardiac SPECT. Detection of scattered photons results in the loss of image contrast in the acquired projections and significantly degrades one's ability to accurately estimate the underlying activity distribution [44, 61]. Scattered photons can originate from the organ itself or from adjacent organs. The effect of scatter is influenced by the activity in adjacent organs, their shapes and relative positions, and different tissue densities. In cardiac imaging, scattered photons can originate from adjacent activity structures such as the right ventricle (RV), and in some patients a raised diaphragm can push the liver and other abdominal organs into close proximity with the inferior wall of the myocardium [62].

In clinical scenarios, the scatter fraction (ratio of scattered to unscattered

photons) has been reported to be approximately 30%-40% in the photopeak energy window [63]. Due to the finite energy resolution of the camera, it is impossible to avoid the detection of some scattered photons. Detection of scattered photons can be reduced, but not eliminated, by using energy discrimination wherein the inclusion of the detected photons in the image depends on whether their energy falls within a specific pre-defined energy window (Figure 2.2).

Various methods have been proposed to estimate and correct for scatter, ranging from those that are simple and approximate to others that are theoretically correct but complex and computationally expensive. Methods that estimate scatter can be split into two categories – methods that directly measure the scatter, and others that model the scatter. Correction involves either a direct subtraction of the scatter estimate before- or after image reconstruction (irrespective of whether direct measurement or modeling was used) or incorporation of the scatter information into the image reconstruction. The disadvantage with direct subtraction of scatter is the added noise introduced by pixel-by-pixel subtraction. Additionally, direct subtraction has the possibility of introducing negative values in the scatter-corrected projections. Incorporating the scatter image into the IR alleviates these concerns, while preserving the Poisson distribution of counts in the projection data which is an assumption that is inherent in maximum likelihood algorithms [64]. The limitation of reconstruction-based corrections is the added execution time since scatter calculations tend to be computationally expensive and have to be repeated several times during the IR process.

A few of the more common SC methods are reviewed here, with a focus on dual

energy window (DEW) and analytic photon distribution (APD) methods which are implemented and validated with experiments in chapters 3, 4 and 5. A good review of scatter correction (SC) methods can be found in [63, 65].

2.2.1 Scatter Correction Based on Direct Measurements

2.2.1.1 The Dual Energy Window Method

The earliest SC methods rely on using a lower energy window to measure a scatter image. The dual-energy window (DEW) method [66] estimates scatter in the projections by recording the photons detected in a lower energy window placed below the photopeak window (Figure 2.2).

Figure 2.2. Normalized energy spectrum and typical energy windows for a $^{99\text{m}}\text{Tc}$ clinical scan acquired on the CZT camera. The photopeak window is marked in grey ($140 \text{ keV} \pm 10\%$) and the lower energy window is marked in black ($120 \text{ keV} \pm 5\%$).

The photons detected in the lower energy window are assumed to be purely scattered photons. The distribution of scattered photons in the photopeak window

is assumed to be the same as that in the lower energy window, multiplied by a scaling parameter, k . The scaling parameter can be calculated by dividing the number of scattered photons in the photopeak window by the number of photons measured in the lower energy window. The estimated scattered distribution is then subtracted from the measured photopeak energy window distribution.

Unfortunately, the parameter k is not a fixed value and it has been shown that it depends on the activity distribution, geometry and composition of the scattering medium, the width and location of the energy windows, the size of the region of interest (ROI) and the type of reconstruction (FBP or IR) [67-69]. The landmark article introducing the DEW method heuristically determined k to be 0.5 [66] and this value is often used as a constant [68, 69]. Later work involving imaging of spheres of activity in a uniform background showed that k was not sensitive to sphere location or sphere activity-to-background ratio [70]. However, the k value calculated in this study did depend slightly on the scatter correction procedure – whether scatter was subtracted in projection space or subtracted post reconstruction, and the size of the scattering media. Methods for calculating k range from Monte Carlo simulations [58, 68, 69], analytical calculations [71] and physical measurements [66, 67, 70].

While the DEW method is popular and simple to implement, it incorrectly assumes that the spatial distribution of scattered photons in the lower energy window is the same as the scattered photons in the photopeak window. As evident in equation (1), the energy of the scattered photon is inversely proportional to the Compton scattering angle. Therefore, scattered photons detected in the photopeak

energy window tend to have higher energy, smaller deflections and thus a narrower spatial distribution, compared to those which are measured in the lower-energy scatter window which have scattered through larger angles and hence have a broader distribution. Also, photons which have undergone multiple scatters will most likely have lower energies than those which have not. Consequently, the DEW correction removes too many photons far from the actual source location and not enough from near to the source location. This discrepancy between spatial distributions has been shown previously [69, 72].

2.2.1.2 The Triple Energy Window Method

The triple energy window (TEW) correction [73] is similar to the DEW method. In many respects however, it is advantageous for situations where there is down-scatter from high-energy sources as well as scatter from the identified photopeak. For example, TEW is most useful for dual gamma emitting isotopes such as ^{111}In or when imaging two isotopes at once [74, 75]. In this method, two relatively narrow energy windows are placed on either side of the photopeak window. An estimate of scatter in the photopeak window is calculated based on the average of the projections measured in the higher and lower energy windows and normalized by each respective energy-window width – effectively a linear interpolation between the two side windows. This makes TEW practical to implement, since it does not rely on a pre-calculated and variable k value. In the case where a single-gamma emission isotope is imaged, counts detected in the higher side window are negligible and the TEW method reduces to the DEW method and a k -value of 0.5 (though the

TEW scatter window is usually much narrower than a DEW scatter window).

Since the amount of scatter in the identified photopeak window does not vary linearly with energy, the accuracy of the TEW method will depend on the location and width of the two side windows. Also, since the width of the side windows is relatively narrow (≈ 2 keV), this method is susceptible to statistical fluctuations due to the small number of photons detected in them [65].

2.2.1.3 Other methods

Several other groups have also investigated corrections for scatter by using two or more energy windows. The dual photopeak window method [76, 77] splits the photopeak into two non-overlapping windows and is based on the fact that Compton scattered photons contribute more to the lower energy portion of the photopeak than the higher energy side. Therefore, a regression relationship could be obtained between the ratio of counts within these two windows, and the fraction of scattered-to-non-scattered counts in the total photopeak window. Other methods which employ multiple energy-windows, such as in [77, 78] express the scatter image detected in the photopeak window as a linear combination of scatter images detected in multiple energy windows. These methods suffer from low count statistics in the multiple energy window estimates and assume that the shape of the scatter distribution does not change from pixel to pixel. These methods perform similarly to DEW and TEW and thus, over time, they have not demonstrated any clear advantage over the simplest measurement-based SC methods (DEW and TEW) [63].

2.2.2 Scatter Correction Based on Modeling the Scatter Distribution

As noted above, SC methods that rely on activity measured in energy windows other than the photopeak window are plagued by statistical uncertainty and make inaccurate assumptions with regards to the spatial distribution of scatter. In addition, these techniques require data to be acquired simultaneously in multiple energy windows. Although 2 or 3 energy windows are usually available with modern cameras, multiple energy windows are not always available, especially with older SPECT cameras. Model-based methods aim to model the scatter distribution using parameters developed by experimental observations from controlled test studies. Accurate modeling of the full spatial scatter response is much more complex than the direct-measurement methods introduced above, however these methods have shown to be superior to energy-window-based SC [35, 79-83]. What follows is a review of the more popular model-based SC techniques.

2.2.2.1 Convolution Methods

Convolution methods aim to model the scatter distribution based on the assumption that the acquired image can be represented by a convolution of the photopeak window image with a stationary mono-exponential blurring (or scattering) kernel [84, 85]. This kernel directly models the point spread function (PSF) of the camera and can be decomposed into scattered and un-scattered components. After the scattered component is calculated, it can be subtracted from the actual data (Convolution Subtraction or CS) [86, 87], or de-convolved from the measured data [84, 88, 89]. In de-convolution methods the compensated true data

are calculated by de-convolving a mono-exponential function from the measured (scatter + non-scatter) data. The parameter values for the exponential function can be determined using Monte Carlo simulations [90] or physical experiments [84]. Alternatively, the scattered component can be incorporated into the IR [91-93].

Iterative methods have also been used to optimize the scatter estimate, introduced by Bailey *et. al.* [94]. Later, the same group incorporated transmission measurement data that improved the scatter estimation process, named *transmission-dependent convolution subtraction* or TDCS [95-99]. The TDCS method uses opposing projections and their geometric mean in order to minimize depth-dependence, thereby necessitating a modification of the standard reconstruction algorithm. The blurring kernels are found either by using a point source or by phantom images. Implementation of TDCS does require measured transmission data, which has become less of a problem with the availability of dual modality systems. Also, the method requires having the geometric mean of opposing projections, which requires a modification of standard reconstruction algorithms [63]

Recently, a model-based technique was proposed by Fan *et. al.* [75] for cross-talk correction in dual-isotope studies, on a CZT-based dedicated SPECT camera. In dual-isotope studies, two different radio-tracers are imaged simultaneously. Cross-talk occurs when the photons of the tracer emitting higher-energy photons scatter in the subject and are detected within the energy window designated for the lower-energy tracer. With CZT detectors, due to the detection of non-scattered photons in the low-energy-tail, application of a conventional energy-window based SC method for

cross-talk correction would lead to an overestimation of scatter. In this study, the low-energy-tail was modeled using Monte Carlo simulations to aid with the extraction of scattered and non-scattered projections through an MLEM approach. An iterative de-convolution technique was then used for cross-talk correction. This approach could equally well be applied to scatter correction in single-isotope studies.

2.2.2.2 Slab Derived Scatter Estimation

The slab derived scatter estimation method (SDSE) is more complex than convolution-based techniques [92, 100-102]. This method improves upon de-convolution methods by modeling scatter assuming a spatially invariant PSF and employing a database of scatter distribution functions for line sources at various distances from the detector surface and various depths behind a “slab” of water. These functions can be extended to uniform objects of various shapes [92, 102]. This enables the calculation of camera-specific and object-dependent line spread functions (LSFs) which are parameterized by fitting to a combination of Gaussian and/or exponential functions, via experimental or Monte Carlo methods. This allows for fitted functions to account for both the peaked central regions and exponential “tails” of a typical, scatter-inclusive PSF or LSF (profiles such as in Figure 2.3). Implementation of SDSE for inhomogeneous scattering media has been shown to have errors estimating the scatter-to-primary ratio to be as high as 15% for line sources in a simple inhomogeneous water slabs (with air gaps) [103]. Additionally, this method is error-prone for lower energy ^{201}Tl photons when the source is

situated close to the edge of a homogenous scattering medium [91].

Figure 2.3. A line-profile through the centre of a measured projection for a point source immersed in water, acquired on the GE Discovery NM530c dedicated cardiac SPECT scanner. The effect of photon scatter is visible in the form of broadening of the acquired PSF.

2.2.2.3 Effective Scatter Source Estimation

The problems associated with SDSE led to the development of the effective scatter source estimation method (ESSE) [80, 91, 104]. This method is based on the idea that the scatter component of the projection data could be estimated from the

attenuated projection of an effective scatter source. The scatter source is estimated by convolving the activity distribution with a pre-calculated scatter “kernel”. The estimated component of scatter is then obtained by forward-projecting the effective scatter source. The ESSE method is intended to be used in an iterative reconstruction algorithm as part of the attenuated projection operation. The scatter kernels used in the ESSE method can be calculated using computer simulations of water slab phantoms, similar to the SDSE method.

Application of ESSE has shown to be promising in a range of applications [105, 106], although since its implementation requires three image space convolutions (or alternatively several multiplications in the frequency domain), it can be computationally intensive [80].

2.2.2.4 Analytical Scatter Calculations

Direct evaluation of the photon interaction equations allow for analytical calculation of the scatter distribution [80, 107-110]. These approaches incorporate transport of photons from the point of emission to the detector using the Klein-Nishina probabilities for Compton scattering, or other types of interactions at any point. These probabilities are weighted by the electron density of the patient tissues at the point(s) of scatter and attenuation factors which depend on the path travelled from the source location to the point of detection. These methods are very computationally intensive since they involve calculation of high dimensional integrals, but have become possible due to the continual improvements in computer technology. Since these methods model the same processes as MC simulations, they

are as accurate but may be faster than MC as it is no longer necessary to use stochastic techniques in the calculation process.

Analytical methods have several advantages. In addition to being theoretically accurate, they can model any camera and are only limited by the accuracy of the photon interaction models and the precision of its numerical calculations. Since these calculations do not rely on direct measurements in projection space, they can be essentially noise-free and so the scatter estimate does not include the additional noise inherent in a separate scatter measurement. These methods have been successfully validated against MC and physical experiments [108, 110, 111]. In the earliest implementation, the numerical integrations were solved “on the fly” i.e. without using pre-calculated values and were capable of accurately determining all orders of Compton scatter [107]. However, the calculation times were extremely long for anything higher than first order scatter (16-58 hours).

The analytic photon distribution method (APD) [109] is the scatter estimation method on which the work in chapter 5 is based. This method successfully modeled first and second order Compton scatter as well as an estimate of the Rayleigh scatter in heterogeneous scattering media. To accelerate calculations, *Wells et al.* [109] pre-calculated parameters that were independent of the patient and only needed to be calculated once for each different imaging protocol on a given camera. These parameters were organized into look-up tables and the geometric parameters exploited symmetries in the response of the detector and translations of the source location to reduce look-up table size. The main scatter calculation relied on patient specific parameters such as the distribution of activity and attenuating material in

the body, while using the look-up tables. A more detailed description of the APD method as it was originally developed is in [109], and some of those details are described briefly in section 5.2.1.

In order to further reduce calculation times with the APD approach, *Vandervoort et al.* [110] proposed limiting the scatter calculation to a subset of the activity distribution voxels and subsequently, calculate the scatter contribution for the remaining voxels using tri-linear interpolation [110]. This method was named the analytic photon distribution interpolation (APDI) method. The interpolation was done on the basis that the SDF for individual source voxels that are separated by small spatial distances show little variation. Results showed that on average, the scatter projections calculated using the APDI method were very close to those determined using APD and calculation times took 3-4 hours for a typical cardiac imaging study. The authors also implemented scatter correction by adding the calculated scatter distribution to the IR and showed that scatter corrected images had similar image noise and contrast to the ideal scatter-free reconstructions.

2.2.3 Conclusion

While most of the scatter correction methods discussed in this chapter have shown to be effective at improving the image quality, in practice only basic methods for correction are routinely used in the clinic. It is the opinion of many practitioners that simple SC algorithms such as the DEW or TEW subtraction techniques provide sufficient correction given that the magnitude of errors caused by scatter is secondary to other factors such as attenuation and motion artifacts [63].

A review of a variety of SC methods for cardiac ^{99m}Tc -perfusion imaging was performed in [82]. This study compared the performance of SC for 4 categories: 1) modification of the energy window; 2) use of effective values of attenuation coefficients; 3) estimating the scatter distribution from energy spectrum information; and 4) estimating the scatter using a model-based method. The study concluded that while all methods were successful at significantly reducing the effects of scatter on the images, model-based methods gave the best results. Other authors have also shown model-based corrections to perform better than energy window-based SC, even if the window based scatter estimate is noise-free [79, 80].

2.3 Partial volume corrections

The PVE (section 1.5) is well known as one of the main degrading factors affecting the accuracy of both the activity concentration in organs and tumors, as well as the distribution of activity. In clinical practice, this degrades the accuracy with which clinicians can analyze quantitative values in reconstructed images. Functional brain imaging as well as measurements of cerebral blood flow, glucose metabolism and receptor binding are all affected by spillover of activity from neighboring regions [112-114]. In cancer imaging, staging of tumors is directly related to the quantitative measurement of tracer uptake inside tumors and lymph-nodes, commonly referred to as the standardized uptake value or SUV. The SUV values are underestimated as a result of PV spill-out [115-117]. In the context of myocardial perfusion imaging, spatial variations of the PVE can lead to an apparent non-uniformity in myocardial perfusion due to a variation in wall thickness [118].

This effect can result in false positive perfusion studies [47, 119, 120]. The PVE can also reduce apparent perfusion in the apical region of the heart where the myocardial wall is thinner [47, 119, 120]. Additionally, spill-over of activity from organs close to the heart can significantly increase myocardial perfusion values [55, 121, 122].

A variety of methods have been proposed to correct for PVE in cardiac perfusion imaging. These methods generally aim to model and correct for the overall imaging PSF in projection space [123, 124], or recover spatial resolution during the reconstruction process [46, 125], or use anatomical information to apply corrections in the image domain [113, 117, 125-129]. A thorough review of partial volume correction techniques can be found in [115, 130]. Since partial volume effects are dependent on factors such as the type and resolution of the scanner, organ size and the activity distribution, each method is optimal in a particular imaging scenario. Alternatively, approaches can be combined to optimize performance. For instance, the IR used with the NM530c at UOHI incorporates the PSF into the system matrix, which is effective in reducing PV effects, but does not completely remove them and thus applying additional partial-volume corrections would further improve the quantitative accuracy of the images.

To further reduce the effect of PV in the phantom study described in chapter 3, the *template-based partial-volume correction* method [113, 117, 126] was used. This method relies on high-resolution anatomical imaging (such as CT or MRI) over-laid on the reconstructed SPECT image to determine the boundaries of the activity structures being investigated in the PVC. For example, in myocardial perfusion

imaging with SPECT, these structures might include the LV blood pool, the RV blood pool, liver, lungs, stomach and soft tissue. A 'template' is created by assigning a uniform activity value to all voxels within that structure – assuming uniform activity within each structure. The assigned value can be estimated by averaging ROI values placed inside each structure on a regular (non-partial volume corrected) reconstruction. The template-image is then forward-projected and reconstructed to model the PVE-caused degradation of the actual image that occurs during data acquisition and reconstruction. This image is subtracted from the regular reconstructed image to remove these structures and hence their spill-over influence, and thereby produce a PVE-corrected activity distribution. Note that this corrects for spill-in from the template structures but not spill-out from the remaining structures (e.g. the myocardium).

With the assumption that all structures investigated in the PVC have uniform activity distribution, a partial-volume-corrected image is generated by subtracting the forward-projected – and reconstructed – template from the regular reconstructed image [112, 113, 124, 126, 128, 131, 132]. On the other hand and more realistically, the template regions have non-uniform activity distributions, leading to template value estimates which are affected by PVE themselves. To address this issue, a study in [133] updated template values using the partial-volume corrected image and repeating the forward-projection and reconstruction process. This method has been called the 'iterative PVE correction' and was shown to perform better than the non-iterative technique in situations with severe spill-in/spill-out effects.

The main challenge in implementing template-based PVC is creating a template image that is a realistic representation of the true activity distribution. A good way to obtain a template image is with high-resolution anatomical imaging (such as CT or MRI), but that may not always be available. Also, a limitation of using CT images is that not all structures can be distinguished within the CT image. For example, with a non-contrast CT, the endomyocardial surface of the heart may not be available because the ventricular blood pool cannot be distinguished from the myocardial wall. In this case, the addition of a contrast-agent would help distinguish areas that otherwise have similar CT numbers, but other situations may not have such simple solutions. Furthermore, the activity in template regions is assumed to be constant however, this might not be the case in actual patient studies. Nevertheless, the template method is appropriate for use in the phantom study in Chapter 3 in which uniform activity distributions are inserted into all organ compartments and compartment boundaries were accurately delineated by obtaining CT-scans of the empty phantom.

Chapter 3 Quantitatively Accurate Activity Measurements With A Dedicated Cardiac SPECT Camera: Physical Phantom Experiments

This chapter, in a slightly modified form has been published as Pourmoghaddas, A. and Wells, R. G. (2016). "Quantitatively accurate activity measurements with a dedicated cardiac SPECT camera: Physical phantom experiments." Med Phys 43(1): 44. The modifications are in formatting and that the scatter correction method developed in this chapter was first introduced in [134].

3.1 Introduction

Myocardial perfusion imaging with Single Photon Emission Computed Tomography (SPECT) is a valuable tool in the diagnosis and management of heart disease. Dedicated cardiac SPECT scanners such as the DSPECT (Spectrum Dynamics Medical Inc., Palo Alto, CA, USA)[11] or the Discovery NM530c [8] (GE Healthcare, Milwaukee, WI, USA) have greatly increased count sensitivity (a 4 to 8 fold increase over conventional cameras) without a loss in spatial resolution due to improved detector technology and novel collimator designs. These improved features offer the potential for reduced patient radiation exposures [12, 13] or shortened scan times [14-16] compared to conventional scanners with parallel-hole collimators. However, although the prevalence of and appearance of artifacts are reduced [14], images from the new cameras are still degraded by physical effects like attenuation, scatter and resolution losses. As such, correction for these factors remains important.

The design of the Discovery NM530c camera uses multiple heads each with a

single pinhole collimator. The pinhole-collimator design can lead to position-dependent attenuation[57], noise[135], sensitivity and resolution[17] variations, but an accurate system model and CT-based attenuation correction can accurately compensate for many of these effects [16, 17, 57, 134]. For scatter compensation, energy-based approaches are fast and easily implemented and, therefore, often used in the clinic with standard gamma cameras. The cadmium-zinc-telluride (CZT) detectors used by the NM530c camera have a low-energy tail, that is a large fraction of unscattered photons detected with reduced energy [10]. The presence of unscattered photons in a scatter window leads to an over-estimate of the scatter, but a modified dual-energy window (DEW) approach can correct for this and has shown promise in clinical studies [134]. In these studies, the quantitative accuracy of the modified DEW method could not be directly assessed because the true activity concentrations in the heart were unknown. The quantitative accuracy of SPECT imaging is more easily evaluated using physical phantom experiments.

In this study we validate the quantitative accuracy and reproducibility of a modified DEW scatter correction method for ^{99m}Tc myocardial imaging with a CZT-detector-based dedicated cardiac gamma camera using an anthropomorphic cardiac-torso phantom.

3.2 Methods

3.2.1 Modified Dual-Energy Window Scatter Estimation

In CZT detectors, a low energy tail is seen in the photon energy spectrum below the photopeak (Figure 3.1) that occurs mostly due to incomplete charge collection

and inter-pixel scatter [10, 89]. Therefore, the standard DEW correction [66] is not directly applicable since there are a non-negligible number of primary photons detected in the lower energy window (LW). Therefore, a modified approach should be considered, as shown in the following equation:

$$\begin{cases} Meas_{LW} = k \times Prim_{PW} + Scatter_{LW} \\ Meas_{PW} = Prim_{PW} + k' \times Scatter_{LW} \end{cases} \quad (6)$$

Figure 3.1. Energy spectra for a ^{99m}Tc point source in air (solid line) and a patient Tc-Sestamibi scan (dashed line) as measured by the Discovery NM530c SPECT scanner (GE Healthcare). PW refers to the photopeak energy window ($140 \text{ keV} \pm 10\%$) and LW to the lower-energy window ($120 \text{ keV} \pm 5\%$). The point source energy spectrum shows a large number of unscattered photons detected in the lower energy window (LW). The energy spectrum from the patient scan shows a large number of photons detected in the photopeak window, due to photon scatter.

where the photons measured in the LW ($Meas_{LW}$) are expressed as the combination of a fraction (k) of primary photons detected in the PW ($Prim_{PW}$) plus the scattered photons in the LW ($Scatter_{LW}$). Similarly, the factor k' represents the

fraction of scattered photons detected in the PW .

As with the standard DEW method, the spatial distribution of the scattered photons is assumed to be the same in both energy windows, as is the distribution of primary photons. DEW scatter subtraction then can be applied assuming a constant value for k and k' , solving equation (6) for $Prim_{PW}$ and $Scatter_{LW}$. This gives a modified DEW correction of: $Prim_{PW} = \frac{Meas_{PW} - k' \cdot Meas_{LW}}{1 - k \cdot k'}$. The $\frac{1}{1 - k \cdot k'}$ factor shows the degree to which noise is amplified over a standard DEW method. This difference between this modification and the standard DEW is simply a scaling factor that corrects the magnitude of the primary signal.

3.2.2 Calibration

To calibrate counts measured by the SPECT camera to absolute activity, known amounts of ^{99m}Tc tracer were measured using a dose calibrator (CRC-25R, Capintec Inc.) and then placed in the centre of the FOV of the camera. To avoid losses due to self-attenuation and partial volume losses, a small but distributed point source with high activity concentration was created by placing a few drops (75-150 MBq; 2-4 mCi) of ^{99m}Tc onto a cotton ball. The experiment was repeated 6 times on different days to assess the stability of the calibration coefficient. Data were acquired for 10 minutes to provide low-noise counting statistics. Images were reconstructed using 100 iterations of maximum-likelihood expectation maximization (MLEM) iterative reconstruction with no attenuation correction or post filtering. The number of iterations was chosen based on previous phantom studies which showed that images converged to within 95% of their final value after 100 iterations of the

reconstruction algorithm [136]. The total number of counts was measured in each reconstructed image by calculating the summation of activity in a spherical volume of interest (VOI) with an 8 cm diameter, drawn at the centre of the FOV, and corrected for physical decay of the radioactivity. The size of the VOI was selected so that no activity was lost, due to blurring by the system PSF, while avoiding reconstruction artifacts at the edges of the FOV. A calibration coefficient was calculated for each experiment by dividing the activity measured in the dose calibrator by the count rate recovered from the reconstructed images.

To assess the statistical uncertainty in the measurements, the 10-min acquisition for each experiment was split into ten 1-minute intervals and each interval was reconstructed individually. A calibration coefficient was calculated for each 1-minute interval and the mean of 10 values for each experiment were averaged over the 6 experiments to return the final calibration coefficient. The standard deviation of the 6 mean values was used to measure the variation about the mean.

3.2.3 Physical Phantom Experiments

To determine the quantitative accuracy of images acquired with the CZT camera, fifteen ^{99m}Tc -SPECT phantom experiments (with 7 unique fill conditions) were conducted using an Anthropomorphic Torso phantom with a cardiac insert (Data Spectrum Corporation, Durham, NC, USA), an image of which is shown in Figure 2.1. The experiments were divided into three groups: ‘cold’ for experiments without activity in the soft-tissue compartment, ‘hot’ for experiments with activity in the soft-tissue compartment, and ‘enhanced liver’ for experiments with activity in the

soft-tissue compartment and additional activity in a saline bag positioned adjacent to the heart wall. Prior to each imaging session, the true activity inserted into each organ compartment in the phantom was measured using the dose calibrator. The activity ratios in each organ compartment were selected to be representative of a typical ^{99m}Tc -sestamibi scan in our clinic. The obtained concentrations were as follows: 10:1 heart to background, 1.2:1 heart to liver and 1.5:1 heart to lung. Here background refers to the activity in the 'soft-tissue' compartment of the phantom (Figure 2.1). This heart to lung ratio is somewhat low compared to values reported in the literature, which suggest a 2.2:1 ratio instead [137, 138] and, therefore, increase the scatter contribution from the lungs. Left ventricular blood activity matched the background activity in each experiment. The measured activity concentration ratios are seen in Table 3.1. The uncertainty in these concentrations is influenced by the tracer adhering to the syringe at the time of the filling. A plastic 'lesion' was placed inside the septal wall of the myocardial insert to simulate the presence of a region with no tracer uptake. Care was taken to position the heart in the centre of the field of view (FOV) of the scanner and place the phantom in the same position for all experiments.

Table 3.1. Activity concentration ratios for phantom organ compartments, decay corrected to the beginning of scan time. Symbols seen alongside the scan numbers show fill-conditions shared between datasets (Cold, Hot and Enhanced liver).

	Scan number	Myo /liver	Myo /lungs	Myo /Background	Myo /salinebag
Cold	1	1.37	1.79	N/A	N/A
	2*	1.00	0.82		
	3§	1.51	2.17		
	4‡	1.16	1.81		
	5°	1.14	1.26		
Hot	1†	1.45	1.76	13.77	N/A
	2*	1.00	0.82	13.18	
	3§	1.51	2.17	15.20	
	4‡	1.16	1.81	15.15	
	5°	1.14	1.26	7.77	
Enhanced liver	1	1.04	1.28	5.98	0.21
	2§	1.51	2.17	15.2	0.76
	3‡	1.16	1.81	15.2	1.07
	4°	1.14	1.26	7.77	0.72
	5†	1.45	1.76	13.8	0.68
	Mean of uniques	1.24	1.56	11.8	0.85
	SD	0.21	0.46	4.31	0.19

In order to assess the accuracy of the correction methods used in this study over different levels of photon scatter, experiments were repeated with- (hot) and without activity (cold) in the soft tissue compartment. The ‘hot’ dataset represented the most clinically applicable scenario. Also, a case of enhanced extra-cardiac activity spill-in was produced by taping a saline-bag containing the same activity concentration as the liver adjacent to the posterior wall of the heart compartment (enhanced liver). For each acquisition, the scan duration was 10 minutes.

3.2.4 Image reconstruction

The acquired SPECT projections and co-registered CT images were then off-loaded for MLEM image reconstruction, developed in-house. Ray tracing through the aperture was used to calculate the system matrix of the scanner, based on

specifications provided by the manufacturer under a research agreement. Each object voxel was subdivided into a $5 \times 5 \times 5$ array and each projection pixel into an 11×11 array generating 125×121 rays that were used to estimate each system matrix element. The contribution of each ray that passed through the aperture was weighted by $\cos(\theta) \times sp / d^2$ where θ is the angle between the detector normal and the ray, sp is the sub-pixel area and d is the distance between source and detector elements [139]. Edge penetration of the collimator was modeled with an effective pinhole diameter [139]. The ray was not considered to have passed through the aperture if the angle between the ray and the normal of the pinhole aperture plane was greater than the opening angle of the pinhole. Images reconstructed using this code agree with the vendor reconstructions to within a few percent, with and without AC, and this code has been successfully used in previous studies [57]. Images were reconstructed into $70 \times 70 \times 50$ image volumes with a voxel size of 4 mm^3 . The MLEM algorithm ran for 100 iterations and no post-filtering was applied to reduce partial volume blurring [136].

For each phantom experiment, separate images were created including reconstruction with no corrections (NC); with attenuation correction (AC); with attenuation and dual energy window (DEW) scatter correction (ACSC) [134]; with attenuation and partial volume correction (PVC) applied (ACPVC); and with attenuation, scatter and PVC applied (ACSCPVC). The traditional DEW SC method assumes that all counts detected in the lower energy window are from scattered photons. However, the CZT detectors measure a large fraction of unscattered photons with reduced energy, which are impossible to separate from scattered

photons in the lower energy window. In order to apply the DEW method accurately, these unscattered photons will need to be accounted by applying a modified version of the correction which multiplies the scatter subtracted counts in the photopeak window by 1.176. This approach has been shown to prove effective in reducing the effects of scatter in clinical images even though it leads to an increase in noise beyond what is obtained with the DEW method in standard NaI detectors. [134]

In order to apply DEW scatter correction (SC), list mode files were re-binned into a photopeak ($140.5 \pm 10\%$) and a lower energy window ($120 \text{ keV} \pm 5\%$) on the clinical workstation before being exported off-line for subtraction and image reconstruction. Off-line reconstruction was used because the vendor-supplied software on the CZT camera did not provide on-line PVC.

3.3 Results

The mean calibration coefficient and relative standard error were 2.16 ± 0.02

$\frac{\text{MBq}}{\frac{\text{Summed activity}}{\text{Scan duration}}}$ (Figure 3.2).

Figure 3.2 Variation in the measured coefficient across experiments conducted over 6 days. Each data point represents the average of 10 values, each corresponding to a 1 min acquisition of a point source, scanned at the centre of the field of view (FOV) of the scanner.

Table 3.2. Percentage errors between activity measured using reconstructed images vs true activity inserted into the cardiac compartment of the phantom. 'Hot' and 'Cold' refer to acquisitions with- and without activity in the soft-tissue compartment of the phantom, respectively. All errors were significantly different from the NC dataset ($p < 0.0001$).

Hot (n=5)					
	NC	AC	ACSC	ACPVC	ACSCPVC
mean	-75.7	22.2	8.5†	10.0†*	5.2†*
SD	1.9	4.0	4.4	5.0	3.6
Cold (n=5)					
mean	-78.2	15.7	5.4†	10.7†*	5.2†
SD	1.2	4.6	3.2	4.9	3.2

NC, No corrections; AC, attenuation correction; ACSC, attenuation and scatter correction; ACPVC, attenuation and partial volume correction; ACSCPVC, attenuation, scatter and partial volume correction; SD, standard deviation. The dagger sign indicates statistical significance compared to AC for each set ($p < 0.01$). Asterisk indicates significant improvement due to PVC (Hot: $p < 0.04$, Cold: $p < 0.001$).

A representative short-axis slice through the phantom is shown in Figure 3.3 for

all of the reconstruction approaches and both the hot and cold soft-tissue background.

Figure 3.3. An example of Short Axis (SA) views of the myocardial compartment of the phantom, scanned in cold (top) and hot (bottom) backgrounds. The ‘hot’ dataset show an elevation in extra-cardiac activity. The defect inserted into the septal wall is seen in each image. Images corrected with ACSC show improved contrast and a reduction in photon scatter detected in the myocardial wall and defect. Images corrected for partial volume further improve spillover of activity into the myocardium.

Mean errors in the absolute quantification over all the experiments ($n=5$) are shown in Table 3.2 for the hot and cold torso datasets. T-test comparisons showed no significant mean differences between the hot- and cold datasets ($p>0.05$) for images reconstructed with the same method except for NC ($p=0.01$). This suggests

that adding activity in the soft-tissue compartment at a concentration of $1/10^{\text{th}}$ that of the heart did not significantly increase the activity measured in the myocardium. T-tests did show that the mean error in the absolute activity was significantly reduced for AC and ACSC compared to NC, for both hot- and cold datasets ($p < 0.001$). Also, ACSC and ACSCPVC show significant reductions in mean differences compared to AC ($p \leq 0.001$) without increasing the uncertainty ($p > 0.4$). The comparison between AC and ACPVC values for the hot dataset were not significant after Bonferroni correction ($p = 0.0092$), but are suggestive of a change. While AC, scatter subtraction and PVC are known to increase noise in SPECT images, the increase was not significant in these experiments, except for the AC vs NC results in the 'Cold torso' dataset ($p = 0.025$), not significantly different after Bonferroni correction. The effect of SC was significant in reducing errors over AC in 'Hot', 'Cold' datasets ($p < 0.001$). Partial volume corrections significantly improved errors for AC images in both hot and cold datasets ($p < 0.01$). In the 'Hot' images, PVC suggests improved differences in ACSC images ($p = 0.053$), but not in the 'Cold' images ($p = 0.36$).

For the case of the enhanced extra-cardiac activity (Figure 3.4), the boundary between the liver and the heart is less well defined. The percentage errors in the quantification of absolute activity in the heart for the case of enhanced extra-cardiac activity spill-in (Table 3.3) show that SC significantly reduces the error compared to AC ($p = 0.0001$) which is significantly different from NC. The error with ACSC is significantly higher than in the hot dataset suggesting a large contribution of counts due to spill-in from the adjacent activity.

Table 3.3. Percentage errors in the quantification of absolute activity in the heart for the 'enhanced liver' dataset.

Enhanced liver (n=5)			
	NC	AC	ACSC
mean	-77.0	68.6*	31.0†*
SD	3.3	17.1*	12.5

NC, No corrections; AC, attenuation correction; ACSC, attenuation and scatter correction; SD, standard deviation. The dagger sign indicates statistical significance compared to AC ($p < 0.0001$). Asterisk indicates significant difference compared to NC ($p < 0.025$)

Figure 3.4. An extreme case of extra-cardiac activity spill-in was produced by taping a saline-bag containing the same activity concentration as the liver, adjacent to the posterior wall of the heart compartment (enhanced liver). These images show high spillover of activity into the inferior wall of the myocardium which do not completely normalize after correcting for scatter. The reduction in activity values in the inferior region due to photon attenuation (NC) is normalized after attenuation correction (AC).

Mean and standard deviation of contrast values calculated for a 100% 'lesion' placed in the septal wall of the myocardium are shown in Table 3.4. Our results show that SC and PVC both significantly increased the contrast in the lesion for the 'Hot' dataset ($p < 0.03$) over AC alone and the combination (ACSCPVC) is significantly better ($p < 0.033$) than either ACSC or ACPVC. For the cold dataset, scatter correction and PVC alone do not significantly increase contrast, but the combination (ACSCPVC vs AC) was significantly better ($p < 0.001$). T-test comparisons between hot- and cold datasets showed no significant differences in the mean contrast for all five reconstruction methods (NC, AC, ACSC, ACPVC and ACSCPVC) ($p > 0.053$). The uncertainties in contrast values were also not significantly different for any of the

reconstruction approaches ($p>0.05$). These results demonstrate both PVC and SC improve lesion contrast and the corrections do not significantly increase noise over images with AC only.

Table 3.4. Contrast values for a 100% lesion in the septal wall of the myocardium. ‘Hot’ and ‘Cold’ refer to acquisitions with- and without activity in the soft-tissue compartment of the phantom, respectively.

Hot (n=5)					
	NC	AC	ACSC	ACPVC	ACSCPVC
mean	0.787†	0.683*	0.832†	0.772†	0.871†*
SD	0.125	0.177	0.134	0.148	0.112
Cold (n=5)					
	NC	AC	ACSC	ACPVC	ACSCPVC
mean	0.817†	0.893*	0.888	0.839*	0.967†*
SD	0.071	0.069	0.151	0.096	0.050

NC, No corrections; AC, attenuation correction; ACSC, attenuation and scatter correction; ACPVC, attenuation and partial volume correction; ACSCPVC, attenuation, scatter and partial volume correction; SD, standard deviation. The dagger sign indicates statistical significance compared to AC ($p\leq 0.01$). Asterisk indicates significant differences compared to NC (Hot: $p<0.013$, Cold: $p<0.006$).

3.4 Discussion

Various methods have been suggested to correct for scatter in conventional cardiac SPECT imaging [63]. The DEW-SC method is an easily implemented and attractive option as it only requires the acquisition of two energy-window images simultaneously. Also, since it is a simple subtraction in projection space, it is very fast and therefore it can be used with most cameras. These positive features allow for easy clinical implementation compared to more complex (but potentially more accurate) modeling methods.

Although CZT detectors have better energy resolution and dead-time performance than conventional scintillator crystals, factors such as incomplete charge collection on detector boundaries, the finite size of the signal contact, and

depth of interaction dependence on the generated signal combine to create a low-energy tail in the energy spectrum below the photopeak. [10, 134] Consequently, application of the DEW-SC approach in these cameras leads to a higher increase in noise than with standard cameras due to the subtraction of true counts detected in the low-energy tail. Our results show that, although SC can lead to an increase in noise compared to AC images, the increase was not statistically significant when recovering measured activity or lesion contrast.

The stability of count sensitivity with the camera was also assessed using data from daily quality control (QC) flood source measurements with a single Co-57 plane-source. Results showed that the mean count-rate of the camera during daily QC was $14.6 \text{ Bq/s} \pm 0.550 \%$, $n=322$ samples over the course 500 days (Jan 2, 2014-May 13, 2015). Given the high level of stability in the sensitivity of this camera, the largest sources of error in quantification are the uncertainty in the dose-calibrator measurements as well as human error.

Partial volume corrections have been shown to be effective in improving quantitative accuracy of clinical studies in SPECT [131, 140]. The high performance of the template based approach used in this study is reliant on having precise anatomical information (CT) to determine the boundaries of the investigated organ and uniform activity distributions in all organ compartments in the phantom [133]. In clinical studies, if the activity in background structures cannot be approximated as uniform, alternate PVC approaches may be needed [116]. The template-based PVC approach used in this study forward-projects and reconstructs scaled binary masks of the extra-cardiac activities, which leads to a mean estimate of the activity

spill-in to the heart region. Subtraction of the mean spill-in does not substantially change the noise in the estimate of the total heart activity (Table 3.2). If other PVC approaches are used [116], such as those that do not assume uniform extra-cardiac regions or simultaneously correct for spill-out and spill-in to all regions, this may lead to increases in image noise. A limitation of CT-based PVC is that not all structures can be distinguished within the CT image. For example, with a non-contrast CT, there is very little difference in the Hounsfield units of the myocardial wall and the blood in the ventricle. While this particular issue can be solved by acquiring an additional contrast CT, in other scenarios like our ‘enhanced liver’ images, an easy solution may not be available. In the ‘Enhanced liver’ images, the boundaries of the activity-filled saline-bag were not recognizable on the CT images, therefore PVC could not be accurately applied to these images. In this case since structural information was not available, partial volume correction factors would need to be calculated solely using emission data. Doing so is not trivial, and segmentation of activity structures is a topic of ongoing discussion in oncology [141-143]. The extent of spill-out depends on the type of the segmentation method[144] and also on the reconstruction settings, making any correction scan specific. A final limitation of this study is that the phantom was static and thus did not exhibit the physiological motion present in clinical scans. While application of PVC have shown promise in brain studies, clinical application of this PVC technique in cardiac imaging is challenging due to the amount of physiological motion [140]. Therefore, the gains seen for PVC in this study do not account for motion, and implementation of PVC in clinical studies may need incorporation of motion

blurring into the organ templates or application of motion-correction to the images.

Our study shows that CT-AC and an easily implemented DEW-SC approach significantly reduce errors in quantitative ^{99m}Tc cardiac SPECT imaging, producing a mean error of 5 ± 4 %. One possible concern with this camera design is that the limited FOV leads to inconsistencies in the projection data – activity in organs outside of the FOV are seen by some detectors and not by others, leading to artifacts in the image [145]. The hot-background results demonstrate that, for clinically reasonable distributions of activity, the bias in the activity in the heart is small (8.5% for ACSC, 5.2% for ACSCPVC). Results show that AC is imperative for accurate activity and contrast measurements. DEW scatter correction was effective in reducing errors and PVC also improved results, although when PVC was added to ACSC images the improvement was not statistically significant. These correction methods did not significantly increase uncertainty in the quantitative measures in these experiments, although there is a suggestion that AC and SC may do so in clinical images [134].

3.5 Conclusions

Quantitative measurements of cardiac ^{99m}Tc activity are achievable using attenuation and scatter correction, with our dedicated cardiac SPECT camera. Partial volume corrections offer improvements in measurement accuracy in AC images and ACSC images with elevated background activity, however these improvements are not significant in ACSC images with low background activity.

Chapter 4 Improving clinical SPECT MPI with scatter and attenuation correction

This chapter, in a slightly modified form has been published as Pourmoghaddas, A., Vanderwerf, K., Ruddy, T. and Glenn Wells, R. (2015). "Scatter correction improves concordance in SPECT MPI with a dedicated cardiac SPECT solid-state camera." Journal of Nuclear Cardiology 22(2): 334-343. The introduction and methods sections have been modified in the interest of avoiding repetition. The description of the modified DEW method was relocated to chapter 3.

4.1 Introduction

In chapter 3 we developed a modified dual energy window (DEW) scatter correction method and verified its use with physical phantom experiments. In this chapter, we evaluate the accuracy of dual-energy-window scatter correction applied to clinically acquired ^{99m}Tc -tetrofosmin myocardial perfusion images obtained on a dedicated multi-pinhole camera by comparing them to DEW scatter-corrected images from a conventional camera.

4.2 Methods

Patients for this study were selected retrospectively from those patients who had a clinical rest/stress ^{99m}Tc -tetrofosmin (Myoview; GE Healthcare) myocardial perfusion test acquired on a conventional SPECT/CT camera (INF; Infinia Hawkeye 4, GE Healthcare) at the University of Ottawa Heart Institute between April 3rd, 2009 and December 2nd, 2010 and who had consented to a second set of images acquired

on the same day with the CZT-based dedicated cardiac SPECT camera (CZT; Discovery NM530c, GE Healthcare). The study was approved by the Ottawa Health Science Network Research Ethics Board and informed and signed consent was obtained from all patients (Appendix B). There were 203 patients who met the initial inclusion criteria. From this set of 203 patients, 54 patients were identified as having an abnormal summed stress score (as defined below) based on the results from the conventional INF camera images reconstructed without corrections. To have a balanced set of normal and abnormal studies for evaluation, the first 54 normal patients from the set of 203 patients were also included for a total of 108 patients. The order of the camera used for imaging for each patient differed based on availability of the camera and the clinical workload on the day of the study. Scans on the INF camera preceded the CZT scans of 65 patients (60%) for stress imaging and 87 (80%) patients for rest imaging. A total of 5 of the 108 patients had rest and stress studies done on different days; the rest of the patients had a 1-day protocol. Patient demographics are shown in Table 4.1.

Table 4.1. Patient Demographics	
Male Gender	73%
Age (years)	58±13
BMI (kg/m ²)	29±6
Previous CABG	21%
Previous PTCA/PCI	36%
Family History	43%
Current Smoker	12%
Ex Smoker	58%
Hypertension	74%
Hyperlipidemia	72%

4.2.1 Image Acquisition

The 1-day rest/stress protocol used was in accordance with ASNC

recommendations [146] where the injected activity at rest was 346 ± 31 MBq (9.4 ± 0.8 mCi) and the stress activity was 1086 ± 94 MBq (29.4 ± 2.6 mCi), injected 3 minutes after stress infusion. Pharmacologic stress with dipyridamole (0.142 μ g/minute/kg over 5 minutes) was used in 57 % of cases, 43% of cases underwent exercise stressing. For INF-imaging, thirty projections/head were obtained over a 90° rotation (total 60 projections over 180°). Projections were acquired for 25 seconds/projection at rest and 20 seconds/ projection at stress using a 64×64 matrix with a pixel size of $6.8 \text{ mm} \times 6.8 \text{ mm}$. A CT scan was obtained immediately following both rest and stress for attenuation correction (120 kVp, 1.0 mAs, 2.0 rpm), giving a CT patient exposure of approximately 0.4 mSv / scan. For CZT-imaging, 19 projections with a matrix size of 32×32 were acquired in list-mode. The projection pixel size was $2.46 \times 2.46 \text{ mm}$. CZT images were acquired immediately prior to or following the INF images.

4.2.2 Scatter Correction and Image Reconstruction

For the INF datasets, vendor supplied software on an Xeleris workstation (GE Healthcare) was used. Images were reconstructed according to our standard clinical protocol for full-dose studies: 2 iterations of ordered-subset expectation maximization (OSEM) with 10 subsets and no resolution recovery, a voxel size of 6.8 mm, and a Butterworth post-filter with an order of 10 and cutoff of 0.3 cycles/cm. Separate images were created that included reconstruction with no-corrections (INF-NC), with AC (INF-AC), and with AC and SC (INF-ACSC). Scatter correction was performed as a pre-correction to the projection data using the DEW method with

vendor recommended settings. Images reconstructed with AC and without SC were evaluated because vendor-supplied reconstruction software for the CZT camera did not provide on-line SC. For the CZT datasets, images were reconstructed using vendor-supplied software on an Xeleris workstation (GE Healthcare). The maximum-likelihood expectation maximization (MLEM) algorithm was used and included modeling of the system point-spread function and a noise-suppression prior. Reconstruction parameters were those used clinically: 60 iterations of MLEM with a post-reconstruction Butterworth filter (order 7, cut-off frequency of 0.37 cycles/cm), voxel size of 4 mm, and one-step-late regularization ($\alpha=0.7$, $\beta=0.3$). Similar to INF imaging, CZT-NC, CZT-AC, and CZT-ACSC datasets were generated for each patient. Attenuation correction was performed using the attenuation map generated from the CT image acquired on the INF. The CT scan was imported into an Xeleris processing workstation (GE Healthcare) and manually registered to the SPECT image using vendor-supplied quality assurance tools as has been done previously [12, 16, 147, 148]. The modified DEW energy window approach developed in chapter 3 was used for CZT scatter correction. CZT list files were rebinned into a photopeak energy window (140.5 keV $\pm$ 10%) and a lower energy window (120 keV $\pm$ 5%) and were exported offline for processing. Scatter corrected projections were created as described above and then loaded back into the camera for iterative image reconstruction on an Xeleris workstation (CZT-ACSC dataset).

4.2.3 Data Analysis

All reconstructed images were processed using the 4DM software package (Invia)

for cardiac analysis. This software is the clinical standard for review and reporting of cardiac perfusion and function. For each patient image, the software automatically detected the location of the heart, reoriented the heart into the cardiac short-axis, vertical- and horizontal long-axis views and converted the 3D image of the heart into a 2D polar map. The software was then used to apply a standard 17-segment heart model to the 2D polar maps and return 17 values that are normalized to the maximum uptake in the heart (Appendix A). This process was repeated for rest and stress scans. To compare the images from the two cameras, summed stress (SSS), rest (SRS), and difference (SDS) scores were estimated as indicated below:

$$SSS / SRS = \sum_{i=1}^{17} \begin{cases} 0, & P_i \geq 75 \\ (75 - P_i)/10, & 35 < P_i < 75 \\ 4, & P_i \leq 35 \end{cases} \quad (7)$$

where P_i is the normalized uptake in a single segment of the polar map. The SSS, SRS and SDS scores were used to classify the severity of the disease for each patient as seen across the processed datasets. Normally in the clinic, an integer SSS is used, so for the purposes of classification, the SSS was rounded to the nearest integer. Patients were then classified based on SSS into 5 categories: low-normal (0-1), high-normal (2,3), mild disease (4-8), moderate disease (9-13), severe disease (>13) [149, 150]. Of the 203 patients included in the study, 54 were identified to be abnormal based on the INF-NC scans.

4.2.4 Statistical Analysis

Correlations between the cameras for the different reconstruction approaches

were measured using an intraclass correlation coefficient. A Shapiro-Wilks test for normality showed that all score datasets followed a non-normal distribution. Details on the Shapiro-Wilks test and the other statistical tests used in this chapter can be found in *Sheskin, et. al.* [151]. Therefore, a non-parametric two-way analysis of variance (Friedman's analysis of variance by ranks) test was used to assess the differences in the 6 reconstruction methods separately for SSS, SRS and SDS. When the Friedman test showed there was a significant difference, the means and standard deviations (SD) of the datasets were then compared using Wilcoxon's signed rank test and the Ansari-Bradley test, respectively. Marginal inhomogenities in the classification of disease severity were assessed using a McNemar's test. Concordance was assessed using a Cohen's kappa test. In all tests, p -values less than 0.05 were considered significant.

4.3 Results

An example set of images is shown for one patient in Figure 4.1. The effects of AC and SC were similar for both cameras. On the stress images, AC reduces the magnitude of the inferior wall defect while ACSC increased the contrast in this region. We note that in this patient, there was activity apparent inferior to the heart in the CZT image that was not present in the INF image. The presence of activity was confirmed in the projection data and was likely due to physiological movement of activity in the gut in the interval between the two image acquisitions.

Scatter plots of the SSS and SRS along with their corresponding Bland-Altman plots are shown in Figure 4.2 comparing NC, AC and ACSC images from the INF and

CZT cameras.

Figure 4.1 Example images. The reconstruction methods shown are no correction (NC), attenuation correction (AC) and attenuation correction with DEW-based scatter correction for scans acquired on the Infinia Hawkeye4 (INF) and the Discovery NM530c (CZT) cameras. Summed stress/rest scores are also shown for each reconstruction. The extra-cardiac activity seen in the resting CZT images which is inferior to the heart is seen in the projection data and thus likely corresponds to the moving of the activity within the sub-diaphragmatic structures in the interval between the CZT and INF acquisitions. The effects of AC and SC were similar for both cameras. On the stress images, AC reduces the magnitude of the inferior wall defect while ACSC increased the contrast in this region. We note that in this patient, there was activity apparent inferior to the heart in the CZT image that was not present in the INF image. The presence of activity was confirmed in the projection data and was likely due to physiological movement of activity in the gut in the interval between the two image acquisitions. The white arrows indicate the improvement in lesion contrast in the inferior wall when correcting for scatter that is evident for both cameras.

Figure 4.2. Correlation plots and corresponding Bland-Altman plots comparing datasets for all patients. The red data points correspond to SSS, blue points correspond to SRS.

The scatter plots all showed correlations of $r^2 > 0.88$ between the two cameras. The intraclass correlation coefficients for the SSS, SRS and SDS between INF-ACSC and CZT-ACSC images were 94%, 94% and 35% respectively Table 4.2. Correlations for AC and NC were similar and are also shown in Table 4.2.

Table 4.2. Comparison of intraclass correlation coefficients for reconstructed datasets.

	CZT NC - INF NC	CZT AC - INF AC	CZT AC - INF ACSC	CZTACSC-INFACSC
SSS	97%	98%	93%	94%
SRS	96%	95%	90%	94%
SDS	57%	41%	41%	35%†

NC, No corrections; AC, attenuation correction; ACSC, AC with scatter correction, SRS, summed rest score; SSS, summed stress score; SDS, summed difference score.

† Significantly different vs NC ($p=0.04$). No other significantly different data-pairs were seen across each row.

Histograms of the SSS/SRS/SDS differences are shown in Figure 4.3. These figures show that ACSC on the CZT camera with DEW SC resulted in SSS/SRS/SDS that were very similar to those from the conventional SPECT camera; the mean difference between the cameras are <0.4 for the SSS/SRS/SDS scores (Table 4.3).

Figure 4.3. Histogram of differences in the summed stress/rest/difference scores (SSS/SRS/SDS) between using the INF versus CZT camera for various correction schemes: no corrections (NC), attenuation correction alone (AC) and attenuation plus scatter correction (ACSC)

Table 4.3. Mean differences in SSS, SRS and SDS values for comparisons of different reconstruction methods shown in Figure 4.3.

		CZTNC- INFNC	CZTAC- INFAC	CZTAC- INFACSC	CZTACSC- INFACSC
SSS	Mean (SD)	-1.3 (2.6)	-0.43 (2)†	-1.9 (3.2)	0.24 (3.7)§
	Friedman p-value	S ($p<0.001$)			
SRS	Mean (SD)	-1.2 (3)	0.18 (3.1)†	-2.4 (3.8)	-0.12 (3.8)§
	Friedman p-value	S ($p<0.001$)			
SDS	Mean (SD)	-0.091 (3.6)	-0.61 (3.4)	0.52 (4.1)*	0.36 (5)§
	Friedman p-value	S ($p<0.01$)			

NC, No corrections; AC, attenuation correction; ACSC, AC with scatter correction, SRS, summed rest score; SSS, summed stress score; SDS, summed difference score.

†There was a statistically significant difference in mean values for SSS and SRS compared to those in the CZTNC-INFNC column ($P=0.0012$ and $P<0.001$, respectively) while the SD values are not significantly different ($P=0.50$ and $P=0.72$). The SDS mean and SD for the AC column ($P=0.27$ and $P=0.48$) are not significantly different than the NC column ($P=0.2$ and $P=0.45$).

§There was a statistically significant difference in mean values for SSS and SDS compared to CZT AC-INF AC column ($P=0.008$, $P=0.001$ respectively), but not for SRS ($P=0.20$). The SD values are different ($P=0.0003$, $P=0.04$, $P=0.004$).

*There was a statistically significant difference in mean and SD values for SDS compared to CZT AC-INFAC ($P=0.0001$, $P<0.02$), but not for SSS and SRS.

When CZT-AC is compared to INF-ACSC the differences are significantly greater ($p<0.001$) than those between CZT-AC and INF-AC, which are not significantly different from those between CZT-ACSC and INF-ACSC ($p\geq 0.20$). The mean differences between the cameras for AC was also significantly less than that for NC ($p<0.001$). The standard deviation in the differences increases for ACSC compared to AC ($p<0.04$), reflecting the increase in noise with scatter correction. A Wilcoxon's signed rank test on the SSS, SRS or SDS scores for the ACSC images did not show any significant difference between the two cameras ($p>0.3$). The same test repeated for AC showed significant differences for SRS ($p=0.8$) but not for SSS and SDS ($p<0.4$).

Differences between cameras for the NC images showed significant differences for SDS ($p=0.52$) but not for SSS and SRS ($p<0.0001$). A comparison of the classification of patients based on SSS (disease severity) for the ACSC datasets is shown in Table 4.4.

Table 4.4. Comparison of SSS categorized by severity.

SSS-ACSC	CZT				
	Low-normal	High-normal	Mild	Moderate	Severe
INF					
Low-normal	23	7	2	0	0
High-normal	10	3	9	0	0
Mild	3	8	15	2	0
Moderate	0	0	2	1	4
Severe	0	0	0	3	16

Cohen's kappa test showed a concordance of $\kappa=0.40$ and McNemar's test showed no significant marginal inhomogeneities in the ACSC datasets between the cameras ($p>0.77$).

4.4 Discussion

One concern with the application of DEW scatter estimation is that the scattered photons in the lower energy window have a different spatial distribution than those in the photopeak due to an increase in the average scattering angle. The triple-energy-window (TEW) approach [73] minimizes the error in this assumption by using narrow energy windows close to the photopeak. We chose to use DEW in this study as this is the manufacturer implemented approach on our conventional camera and we wished to minimize procedural differences and minimize the noise in the scatter estimate associated with a narrow TEW window. Using a narrow window immediately below the photopeak would also increase the relative number

of the low-energy unscattered photons compared to low-energy scattered photons (Figure 3.1). Scatter correction, applied as a subtraction to the projection data prior to reconstruction, was observed to increase noise in the images (Table 4.3, Figure 4.3). This approach also distorts the Poisson nature of the noise in the projection data and so degrades the performance of the MLEM iterative reconstruction algorithm. Previous work has shown improved reconstruction accuracy by adding the scatter estimate to the forward-projector of the iterative reconstruction [63], however this approach was not available with the vendor provided software used in this study. Incorporation of scatter into the reconstruction would be expected to similarly improve the images from the dedicated camera, but further study would be needed to validate this assumption.

The difference in the SDS for ACSC (Table 4.2, column 4) was significantly less than that for NC. This reduction in correlation is likely due to the increase in noise in the images due to attenuation and scatter correction. The reduction in correlation is most apparent with SDS because the range of SDS values is much less than for SSS or SRS and there are a large number of SDS values close to zero (no ischemia) [152]. Our results showed that the DEW SC method applied to clinical studies on the CZT camera worked on par with the DEW correction on the Infinia SPECT camera. The results in Figure 4.3 and Table 4.4 showed similar performance and McNemar tests showed no bias toward one camera or the other. While the overall concordance calculated in Table 4.4 was low ($\kappa = 0.40$), the majority of discordant cases differed only by a single disease category. By collapsing to a binary classification of normal (low-normal and high-normal) and abnormal (mild, moderate, and severe),

the concordance increased to $\kappa = 0.60$. Using data in Table 4.4, Kendall's tau was calculated to be 0.723 which shows strong correlation between rankings by the two cameras ($p < 0.001$).

Attenuation correction improved the correspondence between the Infinia and the CZT cameras. This was due to the difference in the appearance and prevalence of attenuation effects with CZT [14]. An attenuation artifact can cause a matched increase in the SSS and SRS. Therefore, when an attenuation artifact is present with one camera and reduced or absent with the other camera, it introduces discrepancies in the measured SSS and SRS scores. As the CZT shows reduced attenuation effects compared to the Infinia [14], this introduces a systematic reduction in SSS/SRS and so the mean difference in the SSS/SRS is negative (Table 4.3). Because attenuation artifacts are present in both rest and stress, the SDS is not affected and the difference in SDS is small. The difference in SSS/SRS was significantly less with AC and the difference in SDS was not significantly different. Attenuation correction increases noise in the images and hence the uncertainty in the SSS/SRS differences, but removal of attenuation artifacts counters this by reducing differences. The net result was seen to be a reduction in variability for SSS and no change for SRS and SDS (Table 4.3). The use of attenuation correction without scatter correction with conventional cameras is known to potentially introduce artifacts[26]. Comparing AC on the CZT to ACSC on the Infinia camera, we observed a significant increase in the SSS/SRS/SDS differences between the cameras (Table 4.3). This suggests that scatter correction is having a significant effect on the scores with the conventional camera and that AC on the CZT is not

equivalent to ACSC on the Infinia. Implementation of SC for the CZT system restored concordance with the Infinia system, and the mean differences between the cameras were not significantly different for AC on both cameras compared to ACSC on both cameras. Use of subtraction based SC did, however, increase noise; the SD of the differences in scores for ACSC were significantly larger than for AC for SSS/SRS/SDS. The presence of the low-energy tail suggests that the noise introduced from DEW SC will be greater for the CZT system than for the NaI-based cameras. However, if we consider just those studies that are normal on the Infinia ($SSS < 4$), we find that the standard deviation of scores from images with scatter and attenuation correction is 1.06, versus 1.08 for the CZT images. A Wilcoxon's signed rank test between these two data sets shows no statistical significance ($p=0.2$) therefore suggesting that any noise increase in the ACSC CZT images over that of the Infinia ACSC images is small.

4.5 Conclusions

This study showed that SC using the DEW approach was effective for tetrofosmin images acquired on the Discovery NM530c camera and generated similar images to DEW scatter corrected images on the Infinia Hawkeye. Correcting for attenuation without SC correlated well with the attenuation corrected Infinia images but introduced a bias in the summed scores.

Chapter 5 Analytically-Based Photon Scatter Modeling For A Dedicated Cardiac SPECT Camera

5.1 Introduction

In the previous two chapters, a modified version of the dual energy window (DEW) method was used to estimate photon scatter. A concern with the DEW method, and other energy-based methods, is that the photopeak window contains largely photons with a small deflection angle while lower energy windows will mostly measure photons with large deflection angles and higher order scatter. Thus the scatter measured in the lower energy window has a different spatial distribution than that measured in the photopeak. In addition, noise in the scatter estimate results in an increase in the image noise when it is used to correct the projection data used in image reconstruction.

An alternative approach is to model the scatter. Model-based methods accurately calculate the detected scatter based on an estimate of the source distribution, a map of the scattering medium, and knowledge of the physics of photon interactions with matter. The scatter kernels can be essentially noise-free and so the scatter estimate does not include the additional noise inherent in a separate scatter measurement. For conventional cameras, several model-based methods have been developed including effective scatter source estimation [91], slab-derived scatter estimation [153], convolution-based forced detection [87], Monte Carlo (MC) methods [154], and calculation of the scatter distribution directly from the Klein-Nishina equations [107, 109]. The model-based methods are computationally demanding, but have all

been shown to provide accurate scatter estimates in phantom and clinical studies using traditional cameras with parallel-hole collimators [63]. However, model-based approaches to scatter estimation for pinhole-collimated dedicated cardiac cameras have not been developed.

The goal of this study was to evaluate the accuracy of an analytically-based scatter estimation method [109] modified for a dedicated cardiac SPECT camera with pinhole collimators and CZT detectors. The approach is based on the analytic photon distribution (APD) method which has been validated for traditional NaI parallel-hole cameras against Monte Carlo, phantom and clinical datasets [110, 111, 155] and has been shown to produce images that are quantitatively accurate to within 5% [60]. To validate the APD method for the pinhole CZT camera, we have compared calculated scatter distributions with physical phantom measurements, assessed the effect of APD-SC on measuring activity concentrations and explored feasibility of application to clinical ^{99m}Tc -tetrofosmin myocardial perfusion images.

5.2 Methods

5.2.1 Analytical Photon Distribution Scatter Estimation Method

The APD method is used to calculate the scatter distribution function (SDF) for individual source voxels as was done previously for cameras with parallel-hole collimation[109]. Its calculation uses no free-fitting parameters, therefore, the scatter calculations are solely determined by the characteristics of the camera, an attenuation map of the scattering medium and an estimate of the source distribution. The SDF can be initially described as the continuous distribution of

probabilities that photons emitted by a particular source voxel will undergo Compton or Rayleigh scattering in the surrounding scattering medium and then be detected in a particular detector element. However, the SPECT projection data, the reconstructed estimate of the source distribution, the CT attenuation map and therefore the electron-density map are all discrete data sets. Therefore it is more meaningful to bin this continuous probability distribution and calculate the total probability that a photon originating from a voxel centered at point $\vec{s}_j$ is detected in detector element at point $\vec{n}_i$. The SDF of discretized first order Compton scatter $\text{SDF}^{(1)}$, is obtained by integrating the continuous $\text{SDF}^{(1)}$ function over the area A_i of a pixel centered at $\vec{n}_i$ on the detector surface and also integrating over the volume V_k , of the scattering voxel centered at $\vec{t}_k$ relative to the origin:

$$\begin{aligned} \text{SDF}^{(1)}(\vec{s}_j, \vec{t}_k, \vec{n}_i) = & \int_{A_i} d^2n \int_{V_k} d^3t \rho_e(\vec{t}_k) \frac{d\sigma(\theta, \alpha)}{d\Omega} P_E(\theta) F(\xi) \frac{\cos \xi}{4\pi r_{s_j \rightarrow t_k}^2 r_{t_k \rightarrow n_i}^2} \exp\left(-\int_{\vec{s}_j}^{\vec{t}_k} \mu(x) dx \right. \\ & \left. - \int_{\vec{t}_k}^{\vec{n}_i} \mu(x, E(\theta)) dx \right) \end{aligned} \quad (8)$$

where $\rho_e(\vec{t}_k)$ is the electron density at position $\vec{t}_k$, $\frac{d\sigma(\theta, \alpha)}{d\Omega}$ is the Klein-Nishina scattering cross-section (assuming free electrons in the scattering medium – no binding effects), $P_E(\theta)$ is the probability that a photon which has Compton-scattered through an angle θ will be measured as having an energy within the chosen energy window of the detector, $F(\xi)$ is the collimator acceptance function - the probability that a photon reaching the pinhole collimator at an angle ξ with respect to the pinhole normal will pass through the pinhole aperture and reach the

detector surface, $\frac{\cos \xi}{4\pi r_{t_k \rightarrow n_i}^2} d^2 n$ is the solid angle of a sphere centered at the scattering voxel $\vec{t}_k$ and subtended by the detector pixel element n_i , $r_{s_j \rightarrow t_k}$ is the distance between points $\vec{s}_j$ and $\vec{t}_k$ and finally, $\mu(x, \theta)$ is the linear attenuation coefficient as a function of position x and photon energy $E(\theta)$: the energy of a photon that has undergone a first-order Compton interaction with scattering angle θ . A schematic diagram of the paths of unscattered and scattered photons are shown in Figure 5.1.

Figure 5.1 Schematic diagram of two different photon paths. The solid line shows the path of a primary or unscattered photon which travels directly from the source voxel positioned at $\vec{s}_j$ to the detector element at $\vec{n}_i$. The first order scattered photon is shown by the dashed line, originating at source position $\vec{s}_j$ and scattering once at $\vec{t}_k$ and is then detected at $\vec{n}_i$. Angle θ is the scattering angle and ξ is the angle between the path of the scattered photon and the normal to the detector.

In order to calculate $F(\xi)$, ray tracing through the aperture was used based on specifications provided by the manufacturer under a research agreement. Each object voxel was subdivided into a $5 \times 5 \times 5$ array and each projection pixel into an 11×11 array generating 125×121 rays that were used to estimate each system matrix element. The contribution of each ray that passed through the aperture was

weighted by $\cos(\theta) \times sp / d^2$ where θ is the angle between the detector normal and the ray, sp is the sub-pixel area and d is the distance between source and detector elements [139]. Edge penetration of the collimator was modeled with an effective pinhole diameter [139]. The ray was not considered to have passed through the aperture if the angle between the ray and the normal of the pinhole aperture plane was greater than the opening angle of the pinhole. The calculations for $F(\xi)$ are done theoretically, assuming independence from photon energy. Aspects like the septal penetration will depend on photon energy. An alternative approach would be to measure the $F(\xi)$ function directly by experiment. Errors between theoretical and measured acceptance functions are expected to be small and are mitigated by the blurring from the intrinsic spatial resolution of the detector.

The image volume size modeled was $70 \times 70 \times 50$ with a voxel size of 4 mm^3 . The primary (unscattered) distribution function kernel (PDF) is calculated from $F(\xi)$ as:

$$\text{PDF}(\vec{s}_j, \vec{n}_i) = \int_{A_i} d^2n P_E(0) F(\xi) \frac{\cos \xi}{4\pi r_{s_j \rightarrow n_i}^2} \exp\left(-\int_{\vec{s}_j}^{\vec{n}_i} \mu(x, E(0)) dx\right) \quad (9)$$

$P_E(\theta)$ is calculated as the probability that a photon Compton scattered through angle θ will be measured as having an energy within the energy window of the detector:

$$P_E(\theta) = \frac{1}{2} \left[\text{Erf}\left(\frac{154 - E(\theta)}{\sqrt{2} fwhm(E(\theta))}\right) - \text{Erf}\left(\frac{126 - E(\theta)}{\sqrt{2} fwhm(E(\theta))}\right) \right] \quad (10)$$

where 154 and 126 are the upper and lower limits of the energy window used ($140 \pm 14 \text{ keV}$). The energy resolution full width at half-maximum at the scattered

photon energy $fwhm(E(\theta))$ was estimated by fitting a second order polynomial function to FWHM values calculated from measured point source energy spectra for ^{99m}Tc , ^{57}Co and ^{201}Tl . The intrinsic efficiency of the detector crystal has been assumed to be constant in these calculations. There will be a small variation in the intrinsic efficiency with photon energy. These variations would skew the shape of the energy distribution away from the Gaussian that is assumed in equation (10). The error introduced by this effect is not expected to be large for the energy window used in these experiments, but may need to be considered for other windows.

It should be noted that maps of $\rho_e(\vec{t}_k)$ are not usually available in most SPECT studies. These values are estimated from attenuation maps, which are generated after acquiring a CT image and coregistering with the acquired SPECT data. Linear interpolation is used to obtain electron densities for each voxel using the relationship between μ and ρ_e for water, lung, bone and tissue at the photopeak energy of the isotope, $\mu(E = 140.5 \text{ keV})$.

The total unscattered photon distribution (UPD) and first order Compton-scattered (APD⁽¹⁾) photons at each element of each detector panel are obtained by summing the product of the source activity intensity and the appropriate PDF or SDF over all voxels containing activity:

$$\text{UPD}(\vec{n}_i) = \sum_{j=1}^J I_j \text{PDF}(\vec{s}_j, \vec{n}_i) \quad (11)$$

$$\text{APD}^{(1)}(\vec{n}_i) = \sum_{j=1}^J I_j \sum_{k=1}^K \text{SDF}^{(1)}(\vec{s}_j, \vec{t}_k, \vec{n}_i) \quad (12)$$

where I_j is the source strength (number of photons emitted from the source

during the time of acquisition of the projection) in voxel j located at $\vec{s}_j$, J is the total number of source voxels and K is the total number of scatter voxels. Further details on the APD technique can be found in [109]. The true source strength I_j is unknown prior to reconstruction, but can be estimated initially using a reconstruction of the projection data. This calculation does not include compensation for scatter, but can include attenuation correction and collimator modeling. This source estimate can be updated as the iterative reconstruction progresses as necessary.

For isotopes with energies similar to ^{99m}Tc , the scattered photons detected in the photopeak energy window ($140 \text{ keV} \pm 10\%$) are dominantly first-order Compton scattered photons. Monte Carlo studies show that Compton-scattered photons constitute 97% of the total scatter contribution at the photopeak energy of ^{99m}Tc (140.5 keV) while the detected Compton-scattered photons are primarily those which have scattered once (87%) or twice (12%) with higher orders only contributing 1% [156]. Determination of the SDF for each different order of scatter requires a separate calculation and consequently significantly increases the computation time. Therefore, in this study the calculated first order SDF is scaled by 1.18 ($1/(0.87 \times 0.97)$) in order to include second and higher order Compton scatter as well as Rayleigh events which all constitute a very small fraction of scatter in the photopeak window of ^{99m}Tc . This approach makes the approximation that the spatial distribution of higher-order scatter events is similar to that of first-order scatter.

To calculate an APD estimate of scatter, acquired projections are reconstructed with AC but without SC and used as an estimate of the source distribution (I_j).

Attenuation maps are generated from a CT scan that is manually coregistered with the emission data and are used to generate $\rho_e(\vec{t}_k)$ distributions. Finally, the total projection data are calculated as $TPD = UPD + 1.18 \times APD^{(1)}$ using equations (11) and (12). However, since I_j was estimated from a reconstruction without SC, it contains scatter and so overestimates the activity. Consequently, the corresponding TPD calculation will overestimate the signal in the measured projection data. One solution to this problem would be to perform an iterative reconstruction in which the APD scatter estimate was included in the forward projector. This requires recalculation of the APD distribution at each iteration, which is computationally demanding. Instead, we approximate the effects of scatter as a simple scaling of the source distribution and re-scale the TPD projections to compensate. This approximation ignores the differences in spatial distribution of the scatter signal compared to the unscattered signal but provides a very rough ‘1st-order’ compensation. Scaling estimates are made for each projection by minimizing the square error between the scaled projections returned by the APD calculation and the acquired projections.

5.2.2 Computational considerations

5.2.2.1 Interpolation between SDF for different point sources

The SDF for individual source voxels that are separated by small spatial distances show little variation. Therefore, an interpolation method was implemented, similar to the APDI approach [110], to decrease computation time by limiting the number of source voxels used to compute the APD. First, the full SDF calculation is done for

only a subset of the activity distribution voxels. Second, the scatter contributions from the remaining voxels are calculated using tri-linear interpolation. Also, in the original APDI work the sampled SDFs were shifted such that the peak of each SDF aligned with the spatial position of the source (corresponding to a scatter angle of zero degrees). In this study, the sampled SPFs were not shifted in order to accelerate the interpolation process. The original APDI work on cameras with parallel-hole collimation [110] sub-sampled the source distribution by 1/64 of the total number of voxels. We evaluated a range of sub-sampling from 1 in 2 to 1 in 16 voxels and found (data not shown) that using 1 of every 11 voxels provided a good compromise between acceleration and preserving the accuracy of the scatter profile resulting in an RMSE of 0.01 compared to the full calculation.

5.2.2.2 Restricting the number of scattering voxels considered for each point

Since Compton scatter is forward oriented, the probability of scatter is the highest for small deflection angles and drops rapidly as the angle increases, while increasing again as the scattering angle approaches 180° . Larger scattering angles also decrease $P_E(\theta)$, the likelihood of detecting the scattered photon in the energy window. In addition, detection sensitivity decreases with increasing distance from the pinhole collimator therefore the scatter contribution from scattering voxels located far from the pinhole can be safely ignored. Analysis of the spatial distribution of scatter measured by each detector for individual source voxels placed inside a uniform water medium showed that 99.9% of the scatter contribution is generated from scatter voxels within a spherical region 7.2 cm in

diameter, centered at the midpoint between the source voxel and the center of the pinhole. Therefore, in the interest of accelerating the calculations, only scatter voxels within this spherical region, estimated separately for each source voxel, were used, which provided an acceleration of 2×.

5.2.3 Point source experiments

The accuracy of the APD calculations was first evaluated using measured projections from a point source inside a homogeneous scattering medium of water. A point-source was created by placing a droplet of ^{99m}Tc -tetrofosmin inside a capillary tube which has an internal diameter of 1.1 mm and a length of 75 mm. The activity of the droplet was 90 μCi and the length of droplet inside the tube was approximately 1 mm.

To measure the true activity (I_j) of the droplet while minimizing the effects of scatter and attenuation, the source was placed on a Styrofoam holder and scanned for 10 min at the centre of the FOV of the scanner without the presence of any scattering material. The projections were reconstructed without AC as the effect of scatter and attenuation through air was assumed to be negligible. The true activity of the point source as measured by the scanner was determined by summing image values in a 10-voxel radius surrounding the peak activity in the reconstructed image. This radius was chosen ensure no activity was lost due to the resolution of the camera.

The capillary tube containing the droplet of activity was then affixed to the inside of a water bottle cap, the plastic bottle (500ml) was filled with water and the cap

was fastened. This placed the point source approximately in the centre of the filled water bottle. The point source was scanned for 15 hours in order to obtain good count statistics. The energy window used was $140.5 \text{ keV} \pm 10\%$.

AC was applied using a CT scan that was acquired on an Infinia Hawkeye 4 SPECT/CT system (GE Healthcare) (120 kVp, 1.0 mA, 2.0 rpm). To assist with registration of the point-source emission data to the CT images, fiducial markers made using an iodinated contrast agent mixed with $^{99\text{m}}\text{Tc}$ -tetrofosmin were affixed to the outside of the bottle and a 10 min SPECT scan was acquired on the CZT camera while preserving the original positioning of the phantom. The CT images were manually co-registered to the SPECT images using vendor-supplied quality assurance tools, and used to generate attenuation maps for the APD calculation and AC reconstruction of the scan. A threshold set to 50% of the maximum value was used to locate the point source in the reconstructed image. The true activity of the point source (from the in-air acquisition) was then corrected for physical decay and scaled by the scan length (15 hours) and the value was assigned to the identified voxels.

To account for background activity, a 60 min blank scan was acquired. The blank scan projections were then scaled to the duration of the point-source scan and added to the APD scatter calculation. The background count-rate was found to be approximately 19 counts per second, averaged over the 19 detectors.

The experiment was repeated using a heterogeneous phantom, in which the activity of the point source was $70 \mu\text{Ci}$. This created a more complex scattering environment, in which the scattering probability changes considerably over the

spatial domain of the phantom. An anthropomorphic torso phantom (Data Spectrum Corporation, Hillsborough NC) was filled with water and the capillary tube was taped to boundary of the left lung compartment. The scan duration for this experiment was 28 hours. In these experiments, since true estimates of point source activity were used to generate APD scatter calculations, no re-scaling was required.

5.2.4 Cardiac-Torso Phantom Experiments

To evaluate the quantitative accuracy of the APD scatter correction technique for a distributed source, data previously acquired from 15 ^{99m}Tc -SPECT phantom experiments (with seven unique fill conditions) using an anthropomorphic torso phantom with a cardiac insert (Data Spectrum Corporation) were used [157] . Briefly, the true activity in the myocardial compartment of the phantom was measured using a dose calibrator. Activity ratios in the heart, liver and lung compartments were selected to resemble a typical ^{99m}Tc -sestamibi scan in our clinic. Experiments were repeated with (hot) and without activity (cold) in the soft tissue compartment of the phantom, as well as increased proximal activity (enhanced liver) which was produced by filling a saline-bag with the same activity concentration as the liver and taping it adjacent to the posterior wall of the heart compartment. For each SPECT study, a CT scan (120 kVp, 1.0 mA and 2.0 rpm) was acquired for AC using an Infinia Hawkeye 4 SPECT/CT system (GE Healthcare).

The attenuation and electron-density maps for the APD calculations were generated from the CT images. The CT images were manually co-registered with emission data acquired by the NM530c using vendor-supplied quality assurance

tools. Initial emission images with AC but no SC were reconstructed off-line, using an in-house MLEM algorithm, into $70 \times 70 \times 50$ image volumes with a voxel size of $(4 \text{ mm})^3$. The MLEM algorithm ran for 100 iterations and no priors or post-filtering were applied to preserved quantitative accuracy. Using these images as an estimate of the source distribution, APD scatter projections were generated and then subtracted from the originally acquired photopeak projections (APD-SC). The performance of the APD-SC was compared to a DEW scatter correction method. The DEW-SC images were created using DEW scatter projections ($120 \text{ keV} \pm 5\%$) that were extracted from the acquired listmode SPECT data. The DEW-SC method used has been previously presented [134, 157]. Briefly, the projections from the lower-energy scatter window are subtracted from the photopeak window and the result was then rescaled to compensate for the presence of unscattered photons in the scatter window.

The quantitative accuracy of the methods was assessed by measuring the myocardial activity in the reconstructed images. A heart mask was generated for each scan individually using the forward projected and reconstructed CT-based binary template of the myocardial compartment. The summation of activity values for pixels inside this mask were compared with the true activity as measured by the dose calibrator, after adjusting for the scan length and correcting for decay. The experimental setup for these experiments have been previously published [157] however in this evaluation, the performance of the APD-SC method is compared to the modified DEW method studied previously. The significance of differences between mean error values was determined using T-tests for the means and F-tests

for the uncertainties. In all tests, a p -value of 0.05 was used to determine significant differences between conditions.

5.2.5 Clinical Feasibility Study

We investigated the feasibility of applying our technique to patient data using 5 anonymized patient studies. Myocardial perfusion studies with CT-AC which displayed high extra-cardiac activity adjacent to the myocardium were selected from a previous study on scatter correction [134]. The studies were acquired on the NM530c camera using standard cardiac 1-day rest/stress acquisition protocols with ^{99m}Tc -tetrofosmin (rest: 350 MBq, 5 min acquisition; stress: 1100 MBq, 3 min acquisition). Similar to the phantom studies, CT images were acquired on an Infinia Hawkeye system and then manually coregistered to the emission data to allow generation of attenuation maps and AC. Acquired emission and attenuation data were processed in a manner similar to the phantom experiments and APD scatter estimates were generated.

To compare the accuracy of the APD calculated projections between the phantom and clinical images, a root mean squared error (RMSE) figure of merit was considered. The RMSE was defined as

$$\text{RMSE}^{MYO} = \sqrt{\sum_{p=1}^P \frac{1}{S_p^{MYO}} \sum_{i=1}^{I^{MYO}} \frac{(M_i - TPD_i)^2}{I^{MYO}}} \quad (13)$$

where M is the measured projection as acquired by the scanner, TPD is the total projection as calculated by adding the forward projection, APD estimate and background estimate, S_p^{MYO} is the summation of activity inside the myocardial region

for projection p and P is the total number of projections. The subscript i spans the total number of pixels in the myocardium for each projection (I^{MYO}). The myocardial region was delineated manually on each measured projection and applied to both measured and APD projections.

5.3 Results

5.3.1 Point source experiments

Line profiles through the APD-calculated projections show good agreement with the measured projections (Figure 5.2) for both homogeneous and inhomogeneous scattering media.

The noise levels in the APD scatter estimates from the phantom experiments are greatly reduced compared to the DEW approach (Figure 5.3). The DEW estimate is calculated by compensating for the low energy tail effect [134], i.e. the unscattered counts measured in the lower energy window, resulting in an increase in noise levels. Since the APD estimate calculates scatter based on the Klein-Nishina equation, the estimate is virtually noiseless.

Figure 5.2. APD calculations show agreement for point source experiments. Column A shows results for scatter calculations in a uniform scattering medium of water. Column B shows the performance of the calculations for a point source placed inside an anthropomorphic torso phantom.

Figure 5.3. Left: DEW scatter estimate compared to APD-calculated scatter estimates for a phantom acquisition. The dashed lines show line profile placement used for the comparison (right), demonstrating the elevated noise levels in the DEW estimate.

5.3.2 Cardiac-Torso Phantom Experiments

Mean errors in activity measurements for all phantom studies are shown in Table 5.1. Scatter correction using the APD approach was successful in reducing the mean error by two-fold in the datasets with larger scatter ('Hot' and 'Enhanced Liver') and reducing the uncertainty in the error by two-fold in the 'Hot' and 'Cold' datasets. Lack of statistical significance may be due to the limited number of experiments (only 5 repetitions for each configuration). In the case of elevated scatter ('Enhanced liver'), scatter correction with the APD approach significantly reduced the mean error in activity measurement compared to DEW, however the uncertainty in the mean errors did not change significantly. In the 'Hot' dataset, APD-SC reduced the mean error by 4.5% compared to DEW which wasn't statistically significant ($p = 0.08$), but was suggestive of a change.

Table 5.1. Percentage error between activity measured in reconstructed images and true activity inserted into cardiac compartment of the anthropomorphic torso phantom. "Hot" and "Cold" refer to acquisitions with and without activity in the soft-tissue compartment of the phantom, respectively. "Enhanced-liver" refers to the case of extreme extra-cardiac activity levels introduced by taping a saline bag containing the same activity concentration as the liver compartment, to the inferior-posterior wall of the myocardial compartment.

	Hot ($n = 5$)	Cold ($n = 5$)	Enhanced liver ($n = 5$)
DEW-SC	8.5 ± 4.4	5.4 ± 3.2	31.0 ± 12.5
APD-SC	4.0 ± 2.3	4.0 ± 1.5	$15.5^* \pm 8.9$

Note: DEW-SC, dual energy window scatter correction; APD-SC, analytic photon distribution scatter correction; SD, standard deviation.

**indicates statistical significance compared to APD-SC ($p = 0.007$).*

†indicates statistical significance compared to 'Enhanced liver' ($p < 0.02$)

Comparisons of the RMSE for the phantom and clinical datasets (Table 5.2) showed that the elevated levels of scatter did not significantly contribute to a change in RMSE ($p > 0.2$). APD calculations show that the scatter fraction in the 'Enhanced liver' dataset is significantly higher than the 'Cold' dataset ($p = 0.01$) but

not different than 'Hot' or the clinical dataset ($p = 0.08$ and $p = 0.27$, respectively). The scatter fractions are consistent with the expected scatter fraction of $\sim 34\%$ [158].

Figure 5.4. Projections for a clinical ^{99m}Tc -tetrofosmin cardiac SPECT acquisition: the comparison between acquired projections (A) and the total TPD modeled projections (B) shows good agreement. Panel (C) shows the UPD primary estimate and panel (D) shows the APD scatter estimate.

Table 5.2. Comparisons of root mean squared errors (RMSE) and scatter fractions (SF) between phantom experiments and clinical APD calculations. “Hot” and “Cold” refer to acquisitions with and without activity in the soft-tissue compartment of the phantom, respectively. “Enhanced-liver” refers to the case of extreme extra-cardiac activity levels. T-test comparisons show that elevated levels of scatter did not significantly contribute to a change in RMSE.

		Phantom APD-SC		Clinical APD-SC	
		RMSE	SF (%)	RMSE	SF (%)
		Hot ($n = 5$)		$(n = 5)$	
Mean	0.17		26.4 [†]	0.17	29.6
SD	0.02		0.7 [§]	0.02	3.3
		Cold ($n = 5$)			
Mean	0.19		24.1		
SD	0.07		2.3		
		Enhanced liver ($n = 5$)			
Mean	0.18		28.5 [†]		
SD	0.05		2.5		

Note: APD-SC, analytic photon distribution scatter correction; SD, standard deviation;

[†] indicates statistical significance compared to ‘Cold’ ($p < 0.04$)

[§] indicates statistical significance compared to ‘Enhanced liver’ ($p < 0.02$)

The line profiles through APD scatter estimates for a clinical ^{99m}Tc -tetrofosmin cardiac SPECT acquisition show good agreement with the measured projections (Figure 5.5). Since the APD technique is unable to model activity that is not visible in the FOV of the scanner, the modeled profiles underestimate activity at the edges (Figure 5.5 (c) and (d)). However, these figures show that when the myocardium is positioned centrally, the mismatch visible at the edges does not greatly affect the goodness of fit at the centre.

Figure 5.6 shows the effect of ‘bad’ detector pixels on the goodness of fit for a point-source scanned with a long acquisition time. These pixels have been identified during camera quality assurance measurements as unreliable (e.g. too noisy) and are turned off during imaging. The camera calculates the value for those pixels using 2D interpolation from neighboring active pixels. As seen in the figure, the

interpolation can lead to reduced counts in areas with rapidly changing count levels. However, this effect is not seen in clinical images: Figure 5.5 (a) shows the same line profile where the image tends to have much lower spatial-frequency content. The list of non-responsive pixels is available for each image acquisition on the CZT camera. Using this information, the effect of the 'bad' pixels can be applied to the modeled APD, if desired, to more closely match the camera's response.

5.3.3 Calculation time

The analysis of calculation times showed that by restricting the scattering region to a 7.2 cm sphere and using the APDI method (limiting calculation to 1 of 11 source voxels), the calculation time reduces by a factor of ~ 22 compared to a full calculation. As an example, the processing for a typical phantom acquisition with 130000 nonzero source voxels is reduced to ~ 12000 voxels and takes 7 hours and 45 min on a PC using parallel processing (Intel Xeon X5650 @ 2.67 GHz, with 24 concurrent execution threads).

Figure 5.5. Profile comparisons showing the fit between APD scatter estimates and measured projections for a clinical ^{99m}Tc -tetrofosmin cardiac SPECT acquisition. The acquired projections are depicted on the top row and show the placement of the line profiles. Non-adequate sampling at edges of the reconstructed FOV is demonstrated by mis-match in the top edge (c) and bottom edge (d) of modeled profiles.

Figure 5.6 The effect of non-responsive detector pixels on measured projections, shown for a point source measurement in air (same phantom as Figure 5.2(A) but different detector panel). As reported by the camera, pixels 16 and 17 have been turned off and their measured counts are calculated by interpolating from neighboring pixels (Measured). This results in an underestimation in areas of rapidly changing count levels as seen in this point source measurement, however it is not a factor in clinical images: the profile shown in Figure 5.5(A) passes through the same pixels as in Figure 5.6. A closer match between modeled and measured profiles is achieved when interpolation of non-responsive pixels is included in the modeling.

5.4 Discussion

For CZT detector systems, the use of energy-based approaches is hampered by the presence of a low-energy tail in the detector energy response. This is influenced by factors such as incomplete charge collection on detector boundaries, the finite size of the signal contact and depth of interaction dependences [10]. Consequently, the DEW-SC approach leads to a higher increase in noise than with conventional SPECT cameras due to the subtraction of true counts detected in the low-energy tail. The DEW-SC approach used in this study [134] was modified from the original

concept [66] to account for true counts detected in the lower energy window during the acquisition, however the high noise level is evident when comparing to the APD calculation, which uses noise-free scatter kernels (Figure 5.3). Subtracting the scatter estimate from the acquired projections prior to reconstruction introduces a further problem with noise. Even with an accurate mean scatter estimate, noise in either the estimate or the original acquired data can lead to negative projection values following the subtraction. In addition, the subtraction distorts the Poisson nature of noise in acquired SPECT emission data and therefore degrades the performance of the iterative reconstruction algorithm. Other authors have shown improved reconstruction performance by adding the scatter estimate to the forward-projector of the iterative reconstruction [63]. Unfortunately, the ability to incorporate scatter additively into the forward projector was not available with the current version of the reconstruction code used in this study. A limitation of the APD technique is that, like other model-based SC methods, it is not able to include activity originating from outside of the visible FOV of the scanner into the scatter calculation. Nonetheless, given that with cardiac imaging the heart is positioned at the centre of the FOV, the impact of sources outside of the FOV is expected to be small [159]. This effect is visible in profiles shown in Figure 5.5 (c) and (d) where the modeled profiles do not match as well at the edge of the FOV, while the fit over the myocardium remains very accurate. Quantitatively, our phantom results show that the accuracy of activity measurement in the heart is preserved in the presence of hot structures extending outside of the FOV of the reconstruction. The accuracy is at least equal to that of DEW which measures scatter and so inherently includes

scatter from out-of-FOV sources.

The scatter profiles modeled using the APD method in this chapter only include the contribution from 1st order Compton scattering. This overlooks incoherent scattering function (ISF) form factors because using Klein-Nishina scattering cross-sections assumes that the scattering media consist of free electrons (section 1.4.1). Also, the contribution from Rayleigh scatter and 2nd order and higher Compton scatter are not included. Replacing the scattering cross-sections with ISF cross sections and including Rayleigh scatter would provide a small increase in accuracy and reduce the 1.18 scaling factor needed to correct for their absence – thereby reducing noise amplification, with minimal increase in overall computation time. Adding higher order scatter would substantially increase calculation time as it involves another 3D integration and present experiments suggest that the error from not including it is small, therefore, including a higher order scatter calculation is probably not justified.

In principle, the APD method can be extended to dual isotope imaging in an aim to reduce the cross-talk (from both scattered and unscattered photons) detected in the lower-energy window but originating from the isotope with the higher energy. In energy windows below the photopeak, Rayleigh events along with second and higher order Compton scatter constitute a larger fraction of scatter which may necessitate a more complete calculation rather than a simple rescaling of the first-order Compton scatter distribution. Another difficulty is to differentiate true counts from scattered photons below the photopeak in the presence of the low-energy tail as measured by CZT detectors.

The current long computation time of the APD technique prohibits its integration into the clinic. Originally, camera-specific components of the calculation were saved as pre-calculated look-up tables to accelerate the scatter estimation [109]. In those investigations, symmetries in the response of the detector to translation of the source location were exploited to reduce the size of the required look-up tables. However this is not possible with the NM530c since the SDF is not invariant to translation in the plane parallel to the surface of the detector as is the case with parallel-hole collimators. Direct pre-calculation of the scatter system matrix required $70^2 \times 50 \times 32^2 \times 19 = 5 \times 10^9$ elements which remains somewhat large for most current computers. Therefore, in our study, calculation of the SDF for each voxel was performed “on the fly” which greatly increases the calculation time. The purpose of this study was to validate the accuracy of the APD method on a dedicated camera with pinhole-collimation for the first time, and serve as a bench-mark for further studies. In the future, further optimization of the code and integration of GPU programming can be used to accelerate the calculations and help make this a practical option for clinical implementation.

5.5 Conclusions

Projections generated using the APD model-based scatter estimation method agree well with acquired data on a dedicated cardiac SPECT scanner with pinhole collimators for both phantom and clinical studies. APD-SC images have lower noise than DEW-SC images and provided a more accurate measure of cardiac activity in high-scatter scenarios.

Chapter 6 Conclusions

6.1 Summary of Work

This thesis developed and verified two scatter estimation algorithms in order to facilitate quantitatively accurate measurements of ^{99m}Tc -activity with the GE Discovery NM530c SPECT camera. The first method was a modification of the DEW-SC method [160] to take into account the detection of unscattered photons below the photopeak (the low-energy-tail effect in the detected energy spectrum). This study showed that scatter correction improved quantitative activity and a mean error of $5 \pm 4\%$ was achieved by implementing AC, DEW-SC and PVC. Applied to clinical data, the images from the NM530c camera which were processed with the developed SC were shown to agree with images reconstructed using a manufacturer implemented standard DEW-SC from data acquired on a conventional SPECT camera in the same patients. However, we noted that the DEW-SC approach with the cardiac CZT camera led to a greater increase in noise than was seen with DEW-SC on conventional NaI cameras. While the noise increase was acceptable for clinical single-isotope ^{99m}Tc -imaging, for lower-count studies or for imaging isotopes with higher scatter fractions such as ^{201}Tl , the corrected images might contain too much noise for clinical evaluation. The second SC method was a modification of the analytic photon distribution method [109] to model scattered photons acquired with the CZT-based multi-pinhole NM530c camera. This method was successful at reducing noise compared to DEW-SC and provided more accurate quantification of myocardial activity in a high-scatter scenario.

6.2 Future Directions

6.2.1 Clinical impact of quantitative cardiac SPECT

In this thesis, I have developed and verified the accuracy of scatter correction methods for a pinhole cardiac SPECT camera with CZT detectors with the ultimate goal of providing quantitative SPECT images of the heart. Currently, few clinical applications of quantitative cardiac SPECT exist because SPECT imaging has generally been developed without routine application of attenuation or scatter correction. Since the application of these corrections in PET imaging has been in place since its inception, reconstructed PET images are consistently quantitative. Thus it is through the application of quantitative PET imaging that we see where the potential applications of quantitative SPECT lie. One exciting application is in the measurement of regional myocardial blood flow (MBF) in units of mL/min/g of heart tissue which is routinely done using PET imaging studies [161, 162]. Measurement of MBF can show exactly how much blood flow is present rather than just a relative measure of whether some parts of the heart have more or less flow than others. Also, absolute measurements of MBF more accurately diagnose extensive multivessel coronary artery disease, which can go undiagnosed or under-diagnosed with relative myocardial perfusion imaging [150, 163]. Additionally, by expressing diagnostic metrics in absolute units, normal databases can be assembled which are normalized across patients habitus and camera types. This can facilitate standardization of protocols between different diagnostic centres [164, 165].

Finally, other tracers (now available or being developed) like ^{123}I -mIBG for

evaluation of heart failure provide their information via quantitative measures like heart-to-mediastinal ratio or wash-out rate [166]. Although this study used just standard gamma cameras, there is interest in using the new cardiac CZT-based cameras for these measurements, as evidenced by recent publications [167, 168]. Absolute quantitation of these images may reduce the uncertainty in these measures by removing the need for a reference region and reducing the presence of attenuation and scatter-based artifacts.

6.2.2 APD scatter modeling

Complete modeling of photon scatter using analytically-based methods is a complex and time-consuming endeavor. The implementation of APD scatter modeling in this thesis was simplified by only considering the first order Compton scatter in the calculation. More accurate scatter modeling can be achieved by adding second and higher order scatter as well as Rayleigh scattering, as was done in [109, 110], but at the expense of computation time. At present, the long computation time (~8 hours) prohibits use in routine clinical workflow, but this might be improved by code optimizations and utilizing GPU programming units. Additionally, certain simplifications can be explored to reduce the computation load. The scatter response function calculation may be reduced to a subset of detector pixels, with the scatter response for the remainder of detector pixels determined by interpolation – in a manner similar to section 5.2.2.1 used for sub-sampling of source voxels. Additionally, to accelerate calculation of attenuation, a central path approximation may be considered for each detector, or detector-quadrant, for instance. These

simplifications come at the cost of accuracy, but could substantially accelerate the calculations to a point where routine implementation becomes feasible. The current APD method would serve as a baseline against which the accuracy of the accelerated methods could be evaluated. Furthermore, the performance of the APD-SC method should be evaluated against other model-based SC methods validated for CZT-based cameras [75, 89].

Application of the APD modeling of scatter can also be used to model the cross-talk in dual-isotope SPECT studies. A recent study incorporated the use of a model-based SC method for cross-talk correction with the GE-NM530c [75]. The current implementation of the APD-technique was successful for single tracer scatter-modeling within the photopeak. To extend the technique to lower energy windows for the purpose of cross-talk correction would require evaluation of the accuracy in using just the 1st-order Compton scatter and also a means of accurately estimating the low-energy tail contribution of unscattered photons.

In addition to correcting for cross-talk, modeling the photon distribution in lower energy windows might have other benefits. Extending the APD method to model the photons detected in a lower energy window immediately below the photopeak, might allow us to make use of the un-scattered photons detected in the low-energy-tail. In theory, the counts extracted from the low-energy-tail could be added to the photopeak, improving count statistics, potentially allowing a reduction in the injected dose [169]. This would necessitate a validated model of the low-energy-tail response, similar to that developed in [75].

6.2.3 Scatter inclusive reconstruction and patient motion

A limitation of both SC methods in this thesis was that the estimated scatter was subtracted from the measured data, in projection space. Ideally, the scatter information is added to the system matrix, and a scatter-inclusive iterative reconstruction used. This process preserves the Poisson distribution of counts in the projection data and reduces noise in the scatter corrected result, however, the computational burden of modifying the system-matrix to include a patient-specific scatter calculation is added to the reconstruction.

Another limitation of these studies is that in the course of imaging, the phantom was static and did not exhibit breathing motion or contractile motion of the heart that is present in patients. Physiological motion of the heart is a major source of error in cardiac imaging and can affect diagnostic accuracy [170]. It is recognized that the situation when imaging the living human is very different than phantoms and hence, the excellent results obtainable in phantom experiments may not be as easy to replicate in humans. In order to further improve accuracy of activity measurements in clinical scenarios, target motion should also be accounted for.

6.3 Final Thoughts

The new dedicated cameras discussed in this thesis offer promising features but are very different from traditional systems. They show great promise to reduce patient doses and accelerate image acquisition and also have the promise of providing new information, like MBF measurements through dynamic imaging. However, there is still a great deal to learn regarding the implications of the new

camera designs and detector materials. This thesis provides one step along this road by presenting techniques to accurately correct for patient scatter in cardiac SPECT images, and thereby generate quantitatively accurate images. More work is needed to continue to grow our understanding of the new technologies now being used for cardiac SPECT imaging and thereby to realize the exciting potentials inherent in these new cameras.

Appendices

Appendix A - The 17 segment model

Segment models are used to divide polar maps of the LV into smaller regions to allow for regional quantification and localized assessment of disease. In the 17 segment model, the polar map is divided into 17 smaller regions with the outer ring representing the base of the heart and the innermost region representing the apex. This model has been recommended by ASNC (American Society of Nuclear Cardiology) as the standardized structure for myocardial perfusion imaging reports, as it allows for intra- and cross-modality comparison of myocardial perfusion data and provides the best agreement with the available anatomical data [171, 172]. This is also the clinical standard used at the UOHI. The names of the regions corresponding to the numbers displayed on the polar map are listed below.

Figure A-1. The 17 Segment Model.

1. Basal Anterior	10. Mid Inferior
2. Basal Anteroseptal	11. Mid Inferolateral
3. Basal Inferoseptal	12. Mid Anterolateral
4. Basal Inferior	13. Apical Anterior
5. Basal Inferolateral	14. Apical Septal
6. Basal Anterolateral	15. Apical Inferior
7. Mid Anterior	16. Apical Lateral
8. Mid Anteroseptal	17. Apex
9. Mid Inferoseptal	

Appendix B - Ottawa Health Research Ethics Board (OHREB) Application

This appendix contains correspondence with the Ottawa Health Research Ethics Board that was necessary to gain access to the clinical scan data used in this thesis. It consists of three sub-appendices:

B.1 - OHREB ethics protocol

B.2 - Ph.D. supervisory committee approval

B. 3 - OHREB approval letter

B.1 OHREB ethics protocol

Protocol: The impact of scatter correction on a new CZT-based dedicated cardiac SPECT camera for ^{99m}Tc -tetrofosmin.

Background

Heart disease is one of the three leading causes of death in Canada and coronary artery disease represents the most common form of heart disease. The coronary arteries supply blood to the heart muscle (myocardium); therefore myocardial perfusion imaging, MPI, is an effective tool in the diagnosis of coronary artery disease.

MPI involves injection of a radiopharmaceutical, followed by imaging of the cardiac distribution of radiopharmaceutical accumulation, using a SPECT scanner. As the photons leave the myocardium, they undergo interactions in the surrounding body tissue, which causes loss of contrast in the final image. This effect is commonly referred to as photon scatter, and is a source of image degradation in MPI.

Many methods have been proposed to compensate for scatter. One large class of

these methods is subtraction-based, in which an estimate of the scatter contribution in the projection data is subtracted from the measured projection data. In our clinic, vendor supplied software on one of our traditional SPECT cameras relies on such a method to compensate for scatter. However, our new CZT-based dedicated SPECT camera does not have such capabilities. The goal of this protocol is to evaluate a subtraction-based scatter correction (SC) method developed in-house for our new dedicated camera by comparing it to scatter-corrected images from our traditional camera – for patients who have had scans acquired on both cameras.

Research Questions

Does the in-house-developed scatter correction method correct for scatter on the dedicated cardiac CZT camera as well as the commercial correction method applied on a traditional camera? Is there greater concordance between images acquired on the two systems when scatter correction is applied?

The study hypothesis is that scatter correction on the CZT camera will improve concordance with imaging on a traditional camera with respect to defect severity and diagnosis.

Participants

Patients who were scanned using routine clinical protocols between 4/2009 and 4/2013 who have images acquired on the same day with both a traditional gamma camera and the NM530c (CZT-based) dedicated gamma camera. Patient data is collected as part of our approved nuclear cardiology registry (HI-protocol #2004959-01H). Patient consent is obtained for inclusion in the registry database, the details of which are shown in the “Nuclear Cardiology Registry Consent Form”

(uploaded in Additional documents). We wish to access this data in order to perform a retrospective analysis.

Proposed Method

Images will be retrospectively examined from patients that underwent rest/stress cardiac perfusion scans with ^{99m}Tc -tetrofosmin on both a traditional SPECT/CT camera (INF; Infinia-Hawkeye4, GE Healthcare) and the new CZT-based dedicated cardiac SPECT camera (CZT; Discovery NM530c, GE Healthcare) using a standard protocol, on the same day and who have consented to be part of the Nuclear Cardiology Registry.

Image acquisition

Patients referred to the clinic for cardiac testing were injected with ^{99m}Tc -tetrofosmin and a rest/stress cardiac perfusion study was performed using the INF camera as per our routine clinical protocols. A CT scan was obtained (1mA, 120kVp, 2 rpm) for attenuation correction (AC). CZT images were taken immediately after INF imaging. No additional image acquisitions are required for our study.

Image reconstruction for the traditional SPECT/CT camera (Infinia Hawkeye4)

Vendor supplied software will be used for scatter correction and image reconstruction. Separate data sets will be created that include reconstruction with no-corrections (NC), with AC (AC), and with AC and SC (ACSC). This is done to study the effect of each correction individually.

Image reconstruction for the CZT-based SPECT camera (Discovery NM530c)

CZT list files will be re-binned into a photo-peak energy window ($140.5\text{keV} \pm 10\%$) and a lower energy window ($120\text{keV} \pm 5\%$) and will be exported offline and

processed using custom in-house software for scatter correction following the dual energy window (DEW) method [1]. Scatter corrected projections will be uploaded back into the camera for image reconstruction. Similar to INF imaging, NC, AC and ACSC datasets will be generated. The INF CT images will be imported into the CZT for AC.

Classification of severity

Reconstructed images will be transferred to our Hermes workstation to be processed using the 4DM software (Invia) package for cardiac analysis. Images will be reformatted into polar maps that are normalized to the maximum uptake in the heart. A standard 17-segment model will be used. Summed stress (SSS), rest (SRS), and difference (SDS = SSS - SRS) scores will be generated as indicated below:

$$SSS / SRS = \sum_{i=1}^{17} \begin{cases} 0, & P_i \geq 75 \\ (75 - P_i)/10, & 35 < P_i < 75 \\ 4, & P_i \leq 35 \end{cases}$$

where P_i is the normalized uptake in a single segment of the polar map. The SSS, SRS and SDS observables will be used to classify the severity of the disease for each patient as seen across the processed datasets.

Demographics and Scan data

We are requesting access to information recorded as part of the Nuclear Cardiology Registry. For reference, we have attached the corresponding Data Request Form. MRN, Patient name and study dates are requested to confirm identification of matched image sets.

A summary of patient demographics will be recorded for the purpose of describing the patient population used in the study. Demographics will be recorded

in aggregate form and will include: age, gender, body mass index (BMI), pre-test likelihood, cardiac history and risk factors (previous CABG, previous PTCA/PCI, family history of cardiac disease, current smoker, ex-smoker, hypertension and hyperlipidemia).

We also request information on the scan (as detailed on the attached Data Request Form): test information, imaging information, stress protocol and final interpretation. Only aggregate form of scan data and demographic statistics will be reported/published from this work; individual data will not be reported.

Data Security

Upon electronic retrieval of the MPI studies from the database, an alpha-numeric code will be assigned to replace all patient identifying information and study datasets will be anonymized. A file linking the alpha-numeric codes to patient name/MRN will be maintained securely (password protected) on the institution network. This file will be the only possible method to track the data back to the patient MRN. The data analysis computer is password protected and kept in a locked office.

Secondary use of data

The requested access to the nuclear cardiology registry is for secondary use of data: 'observational studies' in the "Nuclear Cardiology Registry Consent Form" (uploaded in Additional documents). The following specific conditions are met by this study: the research involves no more than minimal risk to the participants and the research does not involve a therapeutic intervention, or other clinical or diagnostic interventions.

Dissemination

Results from this study will be published in a peer-reviewed nuclear medicine/medical imaging journal.

Contact Information:

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[1] R. J. Jaszcak, K. L. Greer, C. E. Floyd, Jr., C. C. Harris and R. E. Coleman, "Improved SPECT quantification using compensation for scattered photons," J Nucl Med, **25** (8), 893-900 (1984).

B.2 Ph.D. supervisory committee approval

8 May 2013
Research Ethics Review Board
The Ottawa Hospital
Ottawa, Ontario

RE: PhD Supervisory Committee Approval for

The impact of scatter correction on a new CZT-based dedicated cardiac SPECT camera for 99mTc-tetrofosmin.

Dear Sir/Madam,

I am writing on behalf of the PhD Supervisory Committee for Mr. Amir Pourmoghaddas. We are aware and approve of the protocol entitled “The impact of scatter correction on a new CZT-based dedicated cardiac SPECT camera for 99mTc-tetrofosmin”. This research will form part of Mr. Pourmoghaddas’ PhD research project and be included as part of his PhD thesis.

R. Glenn Wells
Associate Professor, Dept. of Medicine (Cardiology), University of Ottawa
Adjunct Professor, Dept. of Physics, Carleton University

University of Ottawa Heart Institute 40 Ruskin St., Ottawa, ON

Cc: Lora Ramunno, University of Ottawa,
Paul Johns, Carleton University

B.3 OHREB approval letter

**Ottawa Health Science Network Research Ethics Board/ Réseau des sciences de la santé
d'Ottawa Conseil d'éthique de la recherche**

Civic Box 411 725 Parkdale Avenue, Ottawa, Ontario K1Y 4E9 613-798-5555 ext. 14902 Fax : 613-761-4311
<http://www.ohri.ca/ohsn-reb>

July 08, 2013

Dr. Glenn Wells
Division of Cardiac Imaging,
University of Ottawa Heart Institute
40 Ruskin Street H 2103
Ottawa, ON K1Y 4W7

Dear Dr. Wells:

Re: Protocol # 20130384-01H The impact of scatter correction on a new CZT-based dedicated cardiac SPECT camera for 99mTc-tetrofosmin

Protocol approval valid until - July 07, 2014

I am pleased to inform you that your Application for Chart Review underwent expedited review by the Ottawa Health Science Network Research Ethics Board (OHSN-REB), and is approved. No changes, amendments or addenda may be made to the protocol without the OHSN-REB's review and approval.

Protocol dated July 8, 2013 has been approved.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHSN-REB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Health Science Network Research Ethics Board (OHSN-REB) was created by the merger of both the Ottawa Hospital Research Ethics Board (OHREB) and the Human Research Ethics Board (HREB) for meetings held at the University of Ottawa Heart Institute.

OHSN-REB complies with the membership requirements and operates in compliance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; the International Conference on Harmonization - Good Clinical Practice: Consolidated Guideline; the provisions of the Personal Health Information Protection Act 2004; and the Food and Drug Act of Health Canada and its applicable Regulations.

The OHSN-REB has reviewed and approved the clinical trial protocol and informed consent form for the trial which is to be conducted by the qualified investigator named above at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

Raphael Saginur, M.D.
Chairperson
Ottawa Health Science Network Research Ethics Board

For

Jim Robblee, M.D.
Vice-Chairperson
Ottawa Health Science Network Research Ethics Board

RS/dw (Revised July 15, 2013 - kh)

Appendix C Permission to use copyrighted material in a thesis

Title of thesis: Quantitative Imaging With a Pinhole Cardiac SPECT CZT Camera

Degree: Ph.D. Physics

Graduating year: 2016

Permission is hereby granted to: Amir Pourmoghaddas

To reproduce the following in the thesis:

- Figure 1.8. Relative importance of the three main modes of photon interaction in water, for the energy range common to SPECT imaging [20](*adapted with permission (Appendix C)).*

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Name in print: R. Glenn Wells

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