Evaluation of a Dedicated SPECT-CT Mammotomography System
for Quantitative Hybrid Breast Imaging

by

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Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Biomedical Engineering in the Graduate School of Duke University

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ABSTRACT

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Abstract

The overall goal of this dissertation is to optimize and evaluate the performance of the single photon emission computed tomography (SPECT) subsystem of a dedicated three-dimensional (3D) dual-modality breast imaging system for enhanced semi-automated, quantitative clinical imaging. This novel hybrid imaging system combines functional or molecular information obtained with a SPECT subsystem with high-resolution anatomical imaging obtained with a low dose x-ray Computed Tomography (CT) subsystem. In this new breast imaging paradigm, coined "mammotomography," the subject is imaged lying prone while the individual subsystems sweep 3-dimensionally about her uncompressed, pendant breast, providing patient comfort compared to traditional compression-based imaging modalities along with high fidelity and information rich images for the clinician.

System evaluation includes a direct comparison between dedicated 3D SPECT and dedicated 2D scintimammography imaging using the same high performance, semiconductor gamma camera. Due to the greater positioning flexibility of the SPECT system gantry, under a wide range of measurement conditions, statistically significantly (p<0.05) more lesions and smaller lesion sizes were detected with dedicated breast SPECT than with compressed breast scintimammography. The importance of good energy resolution for uncompressed SPECT breast imaging was also investigated. Results clearly illustrate both visual and quantitative differences between the various energy windows, with energy windows slightly wider than the system resolution having the best image contrast and quality.
An observer-based contrast-detail study was performed in an effort to evaluate the limits of object detectability under various imaging conditions. The smallest object detail was observed using a 45-degree tilted trajectory acquisition. The complex 3D projected sine wave acquisition, however, had the most consistent combined intra and inter-observer results, making it potentially the best imaging approach for consistent clinical imaging.

Automatic ROR contouring is implemented using a dual-layer light curtain design, ensuring that an arbitrarily shaped breast is within ~1 cm of the camera face, but no closer than 0.5 cm at every projection angle of a scan. Autocontouring enables simplified routine scanning using complex 3D trajectories, and yields improved image quality. Absolute quantification capabilities are also integrated into the SPECT system, allowing the calculation of \textit{in vivo} total lesion activity. Initial feasibility studies in controlled low noise experiments show promising results with total activity agreement within 10% of the dose calibrator values.

The SPECT system is integrated with a CT scanner for added diagnostic power. Initial human subject studies demonstrate the clinical potential of the hybrid SPECT-CT breast imaging system. The reconstructed SPECT-CT images illustrate the power of fusing functional SPECT information to localize lesions not easily seen in the anatomical CT images. Enhanced quantitative 3D SPECT-CT breast imaging, now with the ability to dynamically contour any sized breast, has high potential to improve detection, diagnosis, and characterization of breast cancer in upcoming larger-scale clinical testing.
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<td>Multi-Modality Imaging Laboratory</td>
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<td>Modulation Transfer Function</td>
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Chapter 1

Introduction

The overall goal of this dissertation is to optimize and evaluate the performance of the single photon emission computed tomography (SPECT) subsystem of a dedicated three-dimensional (3D) dual-modality breast imaging system for enhanced semi-automated, quantitative clinical imaging. This novel hybrid imaging system combines functional or molecular information obtained with a SPECT subsystem with high-resolution anatomical imaging obtained with a unique quasi-monochromatic, low dose x-ray Computed Tomography (CT) subsystem. In this new dedicated breast imaging paradigm, which has been coined "mammotomography," the subject is imaged lying prone while the individual subsystems sweep 3-dimensionally about her uncompressed, pendant breast, providing additional comfort compared to traditional compression-based imaging modalities.

This doctoral thesis largely focuses on characterizing and enhancing performance of the SPECT subsystem to provide concrete motivation for further clinical testing of this unique hybrid mammotomography system. The characterization includes a direct comparison between dedicated 3D SPECT and dedicated 2D scintimammography imaging using the same gamma camera. The importance of energy resolution in breast imaging was also investigated, along with an observer-based study to evaluate the limits of object detectability under various imaging conditions. Enhancements to the SPECT subsystem include: 1) the ability to automatically contour non-uniform breast sizes, 2) the development
of absolute quantification methods, and 3) the ability to better discern and localize regions of interest with the combined CT subsystem. The calculation and setup for manually-defined 3D SPECT camera paths (trajectories) is time consuming and not quickly adaptable to different breast shapes and sizes, and it is therefore impractical for idealized, routine clinical imaging. The vast array of breast shapes in healthy and diseased women necessitates the design and implementation of real-time, automated, and robust 3D contouring for quick, highly adaptable patient setup and close-proximity, high resolution molecular imaging. The investigation of absolute quantification methods, allowing the calculation of total lesion activity, will also potentially boost the diagnostic power of the hybrid system.

Ultimately, the objective of this research is to aid the hybrid system’s transition from phantom-based imaging in a laboratory to routine imaging in a clinical setting, benefitting women for diagnosis, management, and treatment monitoring of breast cancer. The main hypothesis of this dissertation is that enhanced 3D SPECT-CT breast imaging, with the ability to dynamically contour any sized breast, will potentially improve detection, diagnosis, and characterization of breast cancer; aid in staging and monitoring cancer therapy; and provide a patient-flexible imaging modality ready for full-scale clinical testing.

1.1 Clinical Significance and Background

Breast cancer is the most commonly diagnosed non-skin cancer among women, with a 209,060 new cases of invasive cancer and 40,230 resulting deaths projected for 2010 [1]. Breast cancer is the second cause of death due to cancer in women in the United States, after lung cancer. The probability of developing invasive breast cancer at some time in a woman's life is just under 1 in 8 (12%) [2]. While the number of detected incidences has increased
over the last twenty years, survival rates have also steadily increased, due to advances in breast cancer detection and improved adjuvant treatment options [3, 4]. The 5-year relative survival for localized breast cancer (stages 0-I) has increased to nearly 100% today. This number drops to 86% if the cancer has spread regionally to the lymph nodes (stage IIA), and down to 20% for women with distant metastases (stage IV) [2]. Thus, early detection of a primary breast cancer is vital because treatment of small tumors allows for smaller surgeries (increased breast conservation) and decreased chance of recurrences.

1.1.1 Breast Cancer

The female breast is primarily made up of many component parts, including lobules (milk-producing glands), ducts (tubes that carry milk from the lobules to the nipple), connective (fibrous) tissue that surrounds the lobules and ducts, fat, and skin (Figure 1.1) [2]. Breast cancer can be considered a group of diseases defined by uncontrollable growth and replication of cells that originate within the breast, and that often later invade the surrounding tissues or spread (metastasize) to distant areas of the body. Breast cancer results from damage to DNA within the cell, which causes the abnormal cellular behavior. Most breast cancers begin in the cells that line the ducts (ductal cancers) [2], while others begin in the cells that line the lobules (lobular cancers) [5], and a small number start in other surrounding tissues.

Cancers that have not spread beyond their localized area are called *in situ*, for example ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS). These early-stage, pre-invasive cancers are not palpable, as the cells have not yet formed into a tumor mass. About 1 in 5 new breast cancer cases identified are DCIS [2]. Once the malignant cells
Cooper’s Ligaments
Provides support and a frame work for the glandular and fatty tissue

Intraglandular Fat (Adipose Tissue)
Fatty tissue intermingled with the glandular tissue

Lobules (Glandular Tissue)
Where milk is produced

Subcutaneous Fat
Fatty tissue just under skin

Milk Duct
Transport milk from glandular tissue to the nipple

Nipple

Areola

Normal Cranio-caudal Mammogram

Subcutaneous fat

Nipple

Glandular body

Mammary ducts and aerola ducts

Cooper’s ligaments

Figure 1.1 (TOP) Breast anatomy of a lactating breast. ©Medela AG, Switzerland, 2006. (BOTTOM) Breast anatomy of a normal cranio-caudal screen-film mammogram. ©Yale-New Haven Medical Center, 2004
spread beyond their localized area into the surrounding tissue, they are considered invasive cancers. The most commonly diagnosed breast cancer is invasive (or infiltrating) ductal carcinoma (IDC), accounting for approximately 80% of invasive breast cancers. IDC begins in the ducts, breaks through the ductal walls, and grows into the fatty tissue of the breast. Scar-like tissue forms, making the cancer easier to palpate and detect on an x-ray mammogram. Invasive lobular carcinoma, originating in the lobules, is less palpable and harder to detect on mammograms. It accounts for about 10% of invasive breast cancers. The remaining invasive breast cancers include medullary (3-5% prevalence), inflammatory (1-3%), tubular (2%), papillary (1-2%), and various other rare carcinomas.

As mentioned, breast cancer mortality rates have been declining [1], likely due to increased awareness, earlier detection, and improved treatment methods. Early detection of smaller lesions dramatically increases survival rates and the number of treatment options, and it allows for potential breast conservation. Thus, many scientists, engineers, companies, and research groups like our own are trying to develop improved systems and methods for reliably detecting breast cancer at the earliest stage possible.

1.2 Breast Imaging Modalities

1.2.1 X-Ray Mammography

X-ray mammography is currently the main screening modality for the general population and considered the “gold standard” of early breast cancer detection (Figure 1.2). Mammography is relatively inexpensive, low risk, and widely available, and it has proven its clinical value over many years of use. A systematic review of screening studies by the U.S. Preventative Services Task Force showed an overall sensitivity for mammography of
Figure 1.2: Photograph of a woman being positioned for a medio-lateral oblique acquisition with a modern x-ray mammography imaging system. Photo obtained from the National Cancer Institute (Rhoda Baer, Photographer).

between 77% and 95% and an overall specificity between 94% and 97% [6]. Another systematic review indicated that mammography has been effective in reducing the mortality rate by between 20 and 35% for women aged 50-69 years and slightly less for women aged 40-49 [7], who tend to have more dense breast tissue.

X-ray mammography, however, has many known limitations including a low positive predictive value and frequent false negatives, especially for women with dense breast tissue, post-surgical recurrence, and fibro-cystic breast disease [8-10]. Breast density and age are
important predictors of mammography-screening accuracy. From randomized U.S. trials, adjusted sensitivity for mammography ranged from 63% in women with dense breasts to 87% in women with nearly completely fatty breasts [11]. Several studies have demonstrated that women with higher breast density on mammography are at increased risk of developing breast cancer [12, 13]. Extremely dense breasts occur in ~7-12% of screened women [14, 15], including young patients and those on hormone replacement therapy. The widespread use of digital detector x-ray mammography has led to improved accuracy for dense breasted women and women under the age of 50 [15]. Nonetheless, mammography still suffers from structural overlap and low contrast between lesions and the fibroglandular background, which have similar attenuation coefficients.

1.2.2 Emerging Breast Imaging Modalities

The well-known limitations of mammography have led to the investigation of many complementary or alternative imaging techniques, with the goals of aiding breast diagnosis and staging, reducing unnecessary biopsies, earlier lesion detection, and detecting occult lesions which might otherwise progress undiagnosed. One of the first and currently most accepted of these methods is dynamic contrast enhanced-magnetic resonance imaging (DCE-MRI) [16-20]. Unlike mammography, DCE-MRI is a 3D volumetric imaging technique that does not use ionizing radiation and is insensitive to breast density [21]. DCE-MRI uses specialized RF coils to monitor the temporal flow characteristics of an MRI contrast agent (usually gadolinium-based) through tissue by rapidly acquiring MRI images during the injection of the agent. The character of the flow through a suspicious volume, which is different from flow through normal surrounding tissue, is used to diagnose breast
cancers. The American Cancer Society currently recommends that women with high risk of developing breast cancer (e.g., carriers of the \textit{BRCA1} or \textit{BRCA2} gene) should undergo regular breast cancer screening follow-ups with DCE-MRI [22]. The reported sensitivity of DCE-MRI for breast cancer ranges from 77% to 100%; specificity reported in the literature ranges from 42% to 96% [23-28]. The lower specificity, high cost per scan and limited availability of DCE-MRI have slowed its widespread adoption to the general population.

Breast ultrasound is also a promising adjunct to screening mammography [29-31], particularly in discriminating between benign and malignant cysts [32, 33]. Ultrasound provides real-time images through the use of non-ionizing ultrasonic waves. Results of a recent study indicated increased sensitivity when using ultrasound and mammography in combination versus using mammography alone (77.5% vs. 50%), but with a drop in specificity (89% vs. 95%) [34]. Previous results have also reported improved sensitivity using breast ultrasound [35]. However, breast ultrasound also has a reported low positive predictive value (8.9%) [34], decreasing its likelihood of gaining widespread acceptability as a primary screening tool in the U.S.. The technique is also operator-dependent, although improvements are being made in developing whole-breast, automated ultrasonic imaging devices [36, 37].

Digital breast tomosynthesis (DBT) is an emerging dedicated breast imaging modality that creates a limited-tomographic pseudo-3D image of the breast, by acquiring multiple x-ray images in a short arc above the breast [38-40]. The breast is positioned the same way it is in a conventional mammogram with breast compression, but generally with slightly less compression applied in order to improve patient comfort. When used in a trial with mammography, DBT has been shown to reduce recall rates versus using
mammography alone [41-43]. U.S. clinical studies are underway to vet DBT as a breast screening modality. Early results are encouraging, yet it remains to be seen what the future clinical role of DBT in breast cancer detection and diagnosis may be [44, 45].

Dedicated breast CT, also termed “Computed mammoTomography,” for both screening and diagnosis is being investigated at several research laboratories [46-48] with promising initial results [47-55]. While mammography is a 2D compressed breast imaging modality, CT generates a 3D image of an uncompressed breast from a series of two-dimensional projection images, providing a 3D volume of detailed anatomical information. 3D volumetric data remove overlapping structures, more clearly distinguishing them, and thus should more easily illustrate anomalies in soft tissue, such as disease. Attenuation coefficients can also be extracted from the CT images, for potential in vivo characterization [56]. The emergence of compact, high-resolution digital flat panel detectors has allowed for improved spatial resolution and lower patient dose compared to traditional fan-beam CT approaches used in whole-body CT scanners. Initial studies and simulations have shown that CT outperforms x-ray mammography in observer-based studies, even at an overall radiation dose, equivalent to mammography, to the patient [57, 58].

Nuclear medicine molecular imaging methods have also been adapted for detection and diagnosis of breast cancer. These techniques are powerful complements to structural imaging modalities (e.g. CT and mammography) because of their ability to provide functional information that can help distinguish malignant from benign tissue. Small concentrations of injected tumor-avid radiolabeled compounds are imaged, providing functional information about the metabolic uptake of the lesion. Scintimammography was one of the first nuclear medicine-based dedicated breast imaging alternatives to
mammography. Scintimammography utilizes one or more gamma cameras to acquire 2D planar images of injected radioisotopes that are usually $^{99m}$Tc radiolabeled. Early scintimammography studies, using conventional whole-body gamma cameras and no breast compression for prone lying women, yielded a sensitivity and specificity of approximately 85% [59, 60], but sensitivity dropped significantly for tumors smaller than 1 cm in diameter [61]. To overcome this, several groups have investigated higher resolution, small field-of-view cameras for planar scintimammography, since re-termed molecular breast imaging (MBI) or breast-specific gamma imaging (BSGI) [62-65]. Combining mammography and scintimammography has resulted in a significant increase in accuracy of diagnosis of primary breast cancers [66]. Studies have also indicated that the accuracy of scintimammography is unaffected by breast density, and that women with dense breasts may benefit most from this complementary imaging technique [67, 68]. Given the increased image information content and improved image characteristics, the diagnostic accuracy of nuclear medicine images may be further improved when using 3D tomographic techniques [69].

Dedicated breast SPECT has been investigated for both clinical cameras [70-73] and dedicated systems [74-76], yielding improvements in lesion contrast and signal to noise ratios (SNR) by up to a factor of three [70, 77]. Breast imaging with clinical SPECT cameras is limited by the bulkiness of the large, whole body cameras, which results in a larger radius of rotation and hence blurred resolution. Because spatial resolution degrades with increasing distance in SPECT, the larger camera radius of rotation (ROR) results in a fall-off in contrast, resolution and image quality, though use of a pinhole collimator does make the approach feasible [71, 74, 78-81]. To overcome this, several groups have also investigated using compact cameras for SPECT [82-85]. From simulated ideal-observer analyses,
dedicated breast SPECT was the most effective in comparisons between planar, conventional SPECT, and dedicated SPECT [69].

Positron emission imaging has also been applied to detection and characterization of breast cancer. The first of these systems, known as a positron emission mammography (PEM) scanner, was proposed in 1994 [86]. A pre-clinical trial of this camera in 16 subjects with suspicious breast lesions yielded a sensitivity of 80%, a specificity of 100% and a diagnostic accuracy of 86% [87]. A number of other investigators are also developing dedicated breast-PET imaging systems [88-93]. The first commercially available PEM scanner utilizes two sets of scanning planar detectors and women are imaged with breast compression which is also important in immobilizing the breast (Naviscan PET Systems, San Diego, CA) [94]. A multi-center trial of this device in 77 women reported a lesion detection sensitivity of 90% and a specificity of 86% [95].

Other imaging techniques, such as microwave and optical imaging have also been applied to breast cancer detection [96-99]. Non-ionizing, near-infrared diffusive optical imaging, for example, is currently being investigated as a non-invasive method for the detection of breast cancer. In this technique, photon absorption is separated from scattering using time- or frequency-domain measurements and models [100, 101]. This technique is based on the differences in photon absorption and scattering cross section in tumor and normal tissue [102]. The clinical impact and role of these various other imaging techniques in breast cancer imaging remains to be seen.
1.3 Background Physics

1.3.1 $^{99m}$Tc Radionuclide Production

$^{99m}$Tc is an unstable radionuclide that emits gamma rays ($\gamma$-rays) with a transition energy at 140.6 keV. $^{99m}$Tc is widely used in nuclear medicine imaging applications due to its convenient 6.02 hour half-life. $^{99m}$Tc is a daughter radionuclide of $^{99}$Mo, an unstable isotope of Molybdenum. A $^{99}$Mo-$^{99m}$Tc generator contains the parent activity as molybdate $^{99}$MoO$_4^{2-}$, which is relatively tightly ionically bound to an alumina (Al$_2$O$_3$) column with +2 net charge. As $^{99}$Mo decays, the resulting $^{99m}$TcO$_4^{-}$ (pertechnetate) is more weakly ionically bonded to the alumina column and can be eluted or “milked” from the column using an aqueous saline (Na$^+$) solution [103]. Commercially available sterilized generators are generally used for a week and then discarded because of the natural decay of the $^{99}$Mo parent. $^{99m}$Tc can be used to label many agents, such as the only U.S. Food and Drug Administration (U.S. FDA) approved breast imaging agent (Miraluma®), which chemically is $^{99m}$Tc-sestamibi ($^{99m}$Tc-hexakis-2-methoxyisobutyl isonitrile or $^{99m}$Tc-MIBI) and was originally solely marketed as a cardiac imaging agent (Cardiolite®). Uptake of $^{99m}$Tc-MIBI is facilitated by passive diffusion through the tumor cell membrane with subsequent concentration inside the mitochondria resulting from a negative mitochondrial membrane potential [104]. $^{99m}$Tc-sestamibi concentrates in breast tumors with a reported average 6:1 contrast ratio compared to surrounding tissue [105]. $^{99m}$Tc was the radionuclide of choice for all of the experimental SPECT phantom studies in this thesis. Intravenously injected $^{99m}$Tc-sestamibi was used for pilot patient volunteer studies (see §5.2, §6.5), with the exception of one volunteer subject.
who was imaged using $^{99m}$Tc-methylenediphosphonate (MDP) [106], which had been administered earlier in the day for a SPECT bone scan (see §6.5).

1.3.2 Production of X-rays

X-rays and $\gamma$-rays are electromagnetic waves, with an energy $E$ proportional to their frequency $\nu$, as described in this fundamental expression [103, 107]:

\[ E = h\nu = \frac{hc}{\lambda} \]  

(1.1)

where $h$ is Planck’s constant ($6.63 \times 10^{-34}$ J•sec), $c$ is the speed of light ($3 \times 10^8$ m/s), and $\lambda$ is the wavelength of the photon. Clinically used x-rays and gamma ray photons have a wavelength ranging from a few picometers to a few nanometers.

The x-rays used for medical imaging in our lab are produced when high-energy electrons interact with a metal target and convert their energy into electromagnetic radiation within a vacuum x-ray tube insert. The x-ray tube insert consists mainly of a tungsten filament (cathode) and a rotating tungsten-rhenium target (anode), constructed on a molybdenum core and backed with graphite to conduct heat from the target (Figure 1.3). An external power supply (model CPX160, Electromed Inc., Montreal, PQ) supplies a high voltage across the positively charged anode and negatively charged cathode junction. With the high current flowing through the filament, electrons are “boiled off” in a process known as thermionic emission. The high-energy electrons accelerate across the junction, forming a focused electron beam that bombards the tungsten anode at the focal spot of the tube. Approximately 99% of time, the electrons convert their energy into heat, while the remaining electrons convert their energy into electromagnetic radiation, or x-rays [107].
Figure 1.3: Superimposed photograph and schematic of the major X-ray tube components overlaid approximately on the actual tube. Electrons, generated from the focusing-cup filament (cathode), collide with the rotating target (anode) to produce photons.
Two types of x-rays are generally relevant for the breast CT system in this research: 1) Bremsstrahlung and 2) characteristic x-rays. Bremsstrahlung, German for “braking radiation,” occurs when a negatively charged electron approaches the positively charged nucleus of an atom in the target material and suffers a radiation loss due to deceleration. The electron produces a bremsstrahlung x-ray with energy proportional to the electron’s loss in kinetic energy. This energy loss is dependent on the incident kinetic energy and the atomic number of the target, Z. Bremsstrahlung accounts for x-rays with energies that cover the entire range of the energy spectrum. The tungsten target material commonly used in CT tubes is chosen for its high x-ray producing efficiency (Z=74) and its high density and heat capacity (ρ=19.25g/cm³, C_p=24.8/°K-mol).

The second type of x-rays, characteristic x-rays, are produced when a high-energy electron collides with one of the inner-shell electrons of the target atom and frees the inner-shell electron [107]. The vacant shell hole is quickly filled by an upper-shell electron seeking a lower energy state. This transition produces x-ray photons with energy equal to the difference in binding energies between the two shells. These photons are called “characteristic x-rays” because their energies are unique to each atom, and therefore unique to the anode material from which they radiate. For example for tungsten, when a K-shell electron is liberated and filled with an L-shell electron, a 59 keV monochromatic x-ray is generated.

1.3.3 Photon Interactions with Matter

Three photon interactions with matter are important in the energy ranges of x-ray and nuclear medicine radiation measurements: Compton scattering, photoelectric
absorption, and coherent scattering.

1.3.3.1 Compton Scattering

Compton scattering takes place when a photon collides with a loosely bound outer-shell orbital electron of an atom in the material. The photon is deflected at a scattering angle $\theta$ and transfers some of its energy to the recoil electron. The energy of the scattered photon can be calculated from the energy of the incident photon and the angle of the scattered photon:

$$E_{sc} = \frac{E_o}{1 + \left(\frac{E_o}{m_c^2}\right)(1 - \cos \theta)}$$

(1.2)

where $E_{sc}$ is the energy of the scattered photon, $E_o$ is the incident photon energy, and $\theta$ is the angle of the scattered photon (with respect to the incident trajectory) [108]. The energy of the recoil electron is simply the difference between $E_o - E_{sc}$.

The probability of Compton scattering per atom of the absorber is proportional to the atomic number of the material, Z. The angular distribution of the scattered photons is predicted by the Klein-Nishina formula (for the differential scattering cross section $\frac{d\sigma}{d\Omega}$) [109]:

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

(1.3)

where $\alpha = \frac{hv}{m_e c^2}$ and $r_o$ is the classical electron radius. A polar plot of the angular distributions of Compton scattered photons at relevant energies and absorbers for SPECT-CT in this thesis is shown in Figure 1.4. As the energy of the incident photons increase, the
Figure 1.4: Klein-Nishina polar plot of the relative number of scattered low energy (36keV and 140keV) photons in adipose ($Z_{\text{eff}} = 5.91$) and glandular ($Z_{\text{eff}} = 7.5$) tissue at the scattering angle $\theta$. As the energy of the incident photons increase, the likelihood of scattering in the forward direction also increases. At 140 keV, SPECT $\gamma$-rays are more likely to scatter in the forward direction compared to 36 keV x-rays.

Compton scattering plays a significant role in SPECT-CT medical imaging because of its degradative effect on image quality. For SPECT, the originating photon loses energy with each scattering event. Energy windowing may be used to reject these scattered events, but scattered counts that lose only a small percentage of their initial energy will remain
within the photopeak window, if sufficiently large, and thus still contribute to the image. Positioning errors due to Compton scattered photons lead to a decrease in image contrast [103, 110]. In CT, the current integrating CsI(Tl) detector cannot discriminate between primary and scattered photons, resulting in a redistribution of photons on the detector that can produce cupping artifacts in the reconstructed images and decrease quantitative accuracy of the absolute attenuation coefficient values.

1.3.3.2 Photoelectric Effect

The photoelectric effect describes the process in which an inner shell electron in an atom completely absorbs the energy of an incident photon. The incident x-ray or γ-ray uses all of its energy to free an orbital inner-shell photoelectron. The kinetic energy of the ejected photoelectron ($E_e$) is equal to the incident photon energy ($E_o$) minus the binding energy ($E_b$) of the orbital electron [108]:

$$E_e = E_o - E_b$$

The photoelectric “collision” requires that the incident photon’s energy be greater than the binding energy of the inner shell, and is most probable at the innermost possible shell. The ejected electron leaves a vacancy in the inner shell, which in turn leads to the emission of characteristic x-rays, or occasionally the liberation of another orbital electron (termed Auger electrons). The probability of photoelectric interaction is roughly inversely proportional to the cube of excess photon energy and directly proportional to the cube of the atomic number $Z$ [107]. In other words, the photoelectric effect is most prevalent at lower energies and in high $Z$ materials.
1.3.3.3 Coherent (Rayleigh) Scattering

The third photon interaction is coherent (Rayleigh) scatter, which plays only a minor importance in low-energy CT imaging (accounting for ~10-15% of photon interactions in water at 36 keV). Coherent scattering takes place when a photon interacts directly with an atom as a whole. Due to the large mass of the atom, the photon is re-emitted in a different direction while retaining all of its original energy. No energy is converted into kinetic energy, and ionization does not occur.

Pair production is one other photon interaction that is only important for energies outside of those used in dedicated SPECT-CT mammotomography (> 1.02 MeV). In pair production, a photon interacts with the electric field of a charged particle (e.g., an atomic nucleus or an electron). The energy of the photon creates a positive-negative positron-electron pair. The positron is then repelled from the neighborhood of the positively charged nucleus, and eventually undergoes mutual annihilation with a negatively charged electron, creating a pair of 511 keV annihilation photons that are emitted in opposite directions [103].

1.3.3.4 Attenuation

When a beam of \( \gamma \)-rays or x-rays passes through absorbing materials such as breast tissue, the total number of primary photons is reduced by absorption and scattering. This reduction in primary signal is referred to as attenuation. The total attenuation, or linear attenuation coefficient for a given material, is expressed as the sum of probabilities of each photon interaction. At the energies of our breast SPECT-CT system, 36-140 keV, the linear attenuation coefficient can be calculated as:

\[
\mu_{\text{total}} = \mu_{\text{photoelectric}} + \mu_{\text{Compton}} + \mu_{\text{coherent}}
\] (1.5)
where \( \tau \) and \( \sigma \) are the probabilities of photon interaction per unit path length (cm\(^{-1}\)). Attenuation is also often expressed as a mass attenuation coefficient (cm\(^2\)/g).

The attenuation of \( \gamma \)-rays in breast imaging depends on the distance the rays travel through the breast to reach the detector. For a narrow beam, the reduction in the beam intensity can be described by the Beer-Lambert law [103]:

\[
I_x = I_0 e^{-\mu x}
\]

where \( I_x \) is the beam intensity transmitted through the object of thickness \( x \), \( I_0 \) is the original intensity, and \( \mu \) is the linear attenuation coefficient of the absorber at the corresponding energy. Attenuation degrades the overall image quality of SPECT and CT images and can significantly affect the quantitative accuracy of absolute SPECT activity concentrations in reconstructed images, as discussed further in Chapter 5.

1.4 Dedicated Breast SPECT

The Duke Multi-Modality Imaging Laboratory has developed a novel SPECT system for dedicated emission mammotomography molecular imaging of uncompressed breasts [111] (Figure 1.5). The compact size of the gamma camera and flexible camera gantry allows for innovative 3D breast-imaging trajectories [76, 112-114], as opposed to simple circular orbits, using camera tilt to position and image a greater volume of the breast up to and behind the chest wall, as well as for imaging the medial and axillary nodes.

1.4.1 SPECT Detection

The basic components of any SPECT system are a gamma camera (detector) and a rotating gantry. The gamma camera acquires multiple projection images as it is rotated about
Figure 1.5: Photograph of the independent, dedicated, CZT-based SPECT breast imaging system (major components labeled). The colored arrows illustrate system motions.
the object of interest. Isotropically emitted gamma rays are detected and then reconstructed to form a 3D volumetric estimation of the radiotracer distribution (as described in §1.6).

The two major types of imaging detectors currently used in single photon Nuclear Medicine breast imaging applications are scintillating and semiconductor detectors. The major components of a scintillating gamma camera include: a collimator, a scintillating crystal, a light guide, and an array of photomultiplier tubes (PMTs) (Figure 1.6). Scintillating detectors produce visible light when higher energy radiation interacts within the material, such as commonly used thallium-doped sodium iodide (NaI[Tl]). The amount of light produced is proportional to the energy deposited by the incoming gamma ray. PMTs are used to convert the low-level light into a more useful electrical signal. Amplified signals from the PMTs then proceed to position logic circuits that determine the location of each event in real-time, by calculating the weighted average of the PMT signals. A pulse-height analyzer circuit may also be used to determine whether an event falls within a specified energy window. The valid events are positioned on a 2D grid that represents the accumulating projection image at each view angle.

Semiconductor detectors, including the one in our SPECT camera (Figure 1.7), are solid-state analogs of gas-filled ionization chambers [103]. Whereas scintillating NaI detectors indirectly convert the light produced in them by incoming radiation, semiconductor detectors directly measure an electrical signal proportional to the radiation energy deposited in the detector. The compact gamma camera utilized in the current dedicated breast imaging system is the semiconductor-based LumaGEM 3200STM (Gamma Medica-Ideas, Northridge, CA) originally developed for dedicated scintimammography.
Figure 1.6: Basic components and principles of a NaI(Tl)-based scintillating gamma camera for breast imaging. Adapted from [103].

(Figure 1.7). The 16 x 20 cm² field of view (FOV) detector is made up of a 4 x 5 array of 4 cm long and 4 cm wide by 5 mm thick monolithic cadmium zinc telluride (CdZnTe or CZT) electrically pixelated (5120 total pixels in a contiguous 64 x 80 array) to 2.3 x 2.3 mm² in size, and spaced with a pitch of 2.5 mm.
Incident $\gamma$-rays interact with the CZT crystals via photoelectric absorption and Compton scattering, creating electron-hole pairs along the path of the photon (~31,000 electron-hole pairs produced per 140.6keV photon) [115, 116]. When electron-hole pairs are created by an incoming photon, electrons from the valence band are raised to the conduction band where they migrate to the anode under the influence of a high external voltage potential. The movement of electrons produces a charge at the anode in proportion to the energy of the incident photon. Application specific integrated circuits (ASICs) connected to the anode process the anode signal so that the energy and pixel location of the signal is digitized, buffered, and interfaced to a data acquisition and control computer.

All detected events are also recorded sequentially into a raw list of the uncorrected energies and placement of each detected gamma ray. The full-spectrum list-mode collected
data can then be post-processed to extract energy-windowed projection data of varying widths about the photopeak as used in Chapter 3 to compare varying energy window widths. Each detected event is represented by four values, designated as $X^+, X^-, Y^+, Y^-$. The 2D position $(X,Y)$ is calculated by an Anger logic equation:

\[
X = \frac{X^+ - X^-}{X^+ + X^- + Y^+ + Y^-} \quad (1.7)
\]

\[
Y = \frac{Y^+ - Y^-}{X^+ + X^- + Y^+ + Y^-} \quad (1.8)
\]

where the denominator, the sum of the four signals, is the total energy of the event. These events make up the raw, uncorrected image. List mode processing is discussed in more detail in §3.1.4.

CZT has several advantages over NaI(Tl) detectors including higher stopping efficiency for $^{99m}$Tc gamma rays at 140.6 keV (due to it high atomic number $Z$ and density of cadmium and telluride, $Z_{\text{eff}} = 49.6$, $\rho = 5.78 \text{ g/cm}^3$) along with a better energy resolution of 6.7% compared with 13% full-width at half-maximum (FWHM) [117]. A key advantage of our system is that the elimination of PMTs allows for a more compact detector thickness overall, allowing for closer positioning of the camera relative to the breast and chest wall. Some disadvantages include the small low energy “tail” that is often seen in CZT energy spectra, resulting from charge trapping, imperfect charge collection, and impurities in the crystal [118]. CZT is also more expensive and difficult to produce consistently at a large monolithic size.
1.4.1.1 Energy Resolution

The energy resolution of a detector describes its ability to distinguish between interactions depositing two close-lying energies. Energy resolution for a given energy is generally defined in terms of the FWHM of the photopeak with mean energy ($\langle H \rangle$):

$$E_{\text{RES}}(\langle H \rangle) = \frac{\text{FWHM}}{\langle H \rangle} \times 100\%$$  \hspace{1cm} (1.9)

Energies spaced closer together than the FWHM at a given energy are generally considered unresolvable. For NaI(Tl)-based detectors, the major cause of spectral blurring of the photopeak are statistical fluctuations of light produced in the detector crystal and subsequent photoelectrons produced in the PMT [109]. Other smaller factors include electronic noise and nonuniform light collection. For semiconductor detectors, causes of photopeak blurring include detector leakage current, due to the finite resistivity in the CZT crystals; the empirically determined detector Fano factor, due to energy losses not being purely statistical; electronic noise in the amplifier circuits; and incomplete collection of the charge carriers [119]. Semiconductor detectors generally have better energy resolution than scintillating detectors due to direct energy conversion and a greater number of ion pairs produced per incident photon. In Chapter 3, the importance of energy resolution is investigated for dedicated breast imaging.

1.4.2 Collimator

Collimators are essential to the formation and quality of SPECT images. The collimator, usually made of high-Z lead, helps create an image of the source distribution by allowing only certain gamma rays into the detector, defined by the solid geometry of the
collimator. The SPECT system currently utilizes a parallel-hole, low-energy collimator with 1.22 mm (flat-to-flat) hexagonal hole openings, 0.2 mm septa, and 2.54 cm height as shown in Figure 1.8. The collimator is also a critical factor in defining the system spatial resolution and sensitivity. Collimator resolution is defined as:

\[
R_{\text{col}} = \frac{d(l_{\text{eff}} + b + c)}{l_{\text{eff}}} \tag{1.10}
\]

where \(d\) is the hole diameter (0.122 cm), \(l_{\text{eff}}\) is the “effective length” of the collimator holes, \(b\) is the source-to-collimator distance, and \(c\) is the collimator-to-detector distance (0.25 cm) [103]. The effective hole length can be calculated as:

\[
l_{\text{eff}} = l - 2\mu^{-1} \tag{1.11}
\]
where \( l \) is the length of the holes and \( \mu \) is the linear attenuation coefficient of the collimator material \([103, 120]\). For the lead collimator \((\mu = 22.7 \text{ cm}^{-1} \text{ at } 140 \text{ keV})\) in our system with a collimator hole length of 2.54 cm, \( l_{\text{eff}} = 2.54 - 2 / 22.7 = 2.45 \text{ cm} \).

Collimator efficiency, \( g \), is the fraction of gamma rays passing through the collimator versus the number of gamma rays emitted by the source:

\[
g = K^2 \left(\frac{d}{l_{\text{eff}}}\right)^2 \left[\frac{d^2}{(d + t)^2}\right]
\]

where \( t \) is the septal thickness, and \( K \) is a transfer function having a scalar value of \( \sim 0.26 \) for a hexagonal array of holes.

Collimator optimization is a tradeoff between resolution and sensitivity. As hole size and collimator length decrease, sensitivity increases but resolution decreases correspondingly. Ultimately the collimator should be optimized to the imaging task at hand. Recent commercial SPECT imaging systems utilize automated mechanical collimator changing systems to switch between multiple collimators depending upon the radioisotope energy and imaging task. For low-count, high-noise, dedicated breast-imaging, increased sensitivity may be of higher importance than spatial resolution for lesion detection (as discussed in the results of a limited observer study in §2.2.2.2). For compressed-breast MBI, in particular, the breast is lightly compressed between two opposing detectors and the object of interest is typically within 3–4 cm of either of the opposing detectors; thus, the drop off in resolution with distance is not as critical as in conventional nuclear medicine studies. One MBI group has also investigated matched-collimator designs, in which the collimator holes directly align with pixel elements \([121]\). It remains to be investigated whether our SPECT system would benefit from a more sensitive collimator design. In general, collimator
resolution and sensitivity will be sufficient if parallel holes are utilized, septal penetration is minimized, and the hole separation is less than the intrinsic resolution of the camera [122].

1.4.3 Gantry

The gamma camera is attached to a laboratory jack (model M-EL120, Newport Corp., Irvine, CA) that controls the ROR, and a goniometer (model BGM200PE, Newport Corp., Irvine, CA) that controls the polar tilt of the system. A rotation stage (model RV350CCHL, Newport Corp., Irvine, CA) rotates the system about the breast’s central axis. This gantry system provides the maneuverability for flexible, 3D trajectories traversing a hemisphere about the pendant breast (Figure 1.5). Image acquisition and gantry movement are synchronized and precisely computer controlled. The compact, high-performance gamma camera and positioning gantry allow for fully-3D imaging anywhere within a hemispherical volume about the pendant breast, and they thus overcome several of the physical proximity restrictions of standard clinical gamma cameras.

1.4.4 3D SPECT Trajectories

Until now, contemporary clinical tomographic imaging systems have used horizontal axis-of-rotation camera trajectories to acquire projection images. The patient lies supine or prone on a radiolucent bed while the imaging system rotates around the horizontal axis of the entire patient. This configuration is not optimal for breast SPECT imaging due to significant attenuation and spatial resolution degradation caused by the gamma rays traveling through the entire torso to reach the detector. Background contamination from the normal uptake of radioactive compound in the heart and liver may also obscure the primary signals of interest from the breast. Vertical axis-of-rotation (VAOR) orbits were therefore proposed.
by several research groups, where the gamma camera instead rotates around the vertical axis of a pendant breast \[73, 83, 123\]. The camera can then potentially be kept closer to the breast during the scan, exploiting the fact that photons travel a much shorter distance to the detector. However, due to the fairly large dead edge at the top of most clinical gamma cameras, and the large cameras themselves, the breast tissue immediately anterior to the chest wall is not within the FOV, and the cameras are still not optimally close to the breast.

Orbits that incorporate camera tilt can image farther into the breast near the chest wall. The dedicated breast SPECT imaging system in our lab allows the implementation of unique 3D camera trajectories that can be designed to maximize the imaged breast volume and minimize breast-detector separation, thus improving resolution and image quality in SPECT \[112, 124, 125\]. Three general orbits are used extensively through the experiments in this thesis (Figure 1.9): 1) VAOR, with 0° polar tilt for all azimuthal camera positions; 2) tilted parallel beam (TPB), generally with a fixed 45° polar tilt for all azimuthal camera positions; and 3) complex projected sine wave trajectory (PROJSINE), generally oscillating within a 15°-45° polar tilt range as the system tracks through all azimuthal camera positions. The latter two orbits allow chest wall imaging, with the tradeoff of moderate, well characterized reconstruction distortions in the undersampled regions, as seen in the detailed characterization studies in Chapters 2-4. Currently, the ROR is tailored for each orbit and each object imaged in order to optimize resolution. Chapter 5 discusses developing ROR autocontouring methods for arbitrary SPECT trajectories about any object within the camera’s FOV.
Figure 1.9: Acquisition orbits – VAOR, TPB, and PROJSINE, as indicated – used for SPECT imaging acquisitions throughout this thesis. To the LEFT are visual representations of the 3D orbits of the wire-framed box (camera FOV) about a hemi-ellipsoid, and to the RIGHT are polar plots of camera tilt as a function of azimuthal angle, where the radius refers to polar tilt ($\phi$), and in-plane angular displacement represents azimuth ($\theta$).
Orlov’s sampling criterion states that to accurately reconstruct imaged volume using an infinitely wide parallel beam collimator, the 3D acquisition trajectory must intersect every great circle (i.e. equatorial diameter) on a unit sphere [126]. Thus, a simple VAOR circular trajectory satisfies this criterion for all rows. TPB and PROJSINE orbits, using a far-less-than-infinite parallel hole imaging detector, substantially sacrifice the completeness criterion but also increase the viewable volume. Moreover, with iterative reconstruction algorithms, the data can be reconstructed to yield reasonable likenesses of the object(s) being imaged. Previous studies in the lab found that a PROJSINE orbit with 0-45° polar tilt, which should in principle satisfy the Orlov sampling criterion, actually yielded poorer visualization of chest wall lesions than a PROJSINE with 15-45° polar tilt due to the location of streak-like artifacts, despite the fact that it was more completely sampled [114]. The relaxed angular criterion “pushed” the artifacts deeper behind the breast to a region less important for visualization/detection of lesions in the breast volume itself.

### 1.5 Dedicated CT

The ongoing SPECT imaging system development and research has been enhanced by the parallel development of an independent, cone-beam x-ray CT breast system in our lab [51, 58, 127-130] (Figure 1.10). The CT system complements the functional SPECT images with high-resolution anatomical 3D volumetric images of the breast. Heavy K-edge filtering pre-hardens the x-ray beam to produce a quasi-monochromatic source [52, 131]. A key novelty of the original dedicated breast CT system was its tilting goniometer gantry that allowed for unique 3D trajectories with variable polar tilt. CT tilting trajectories improve sampling and thereby overcome cone-beam image artifacts [51, 132]. CT subsystem tilting
Figure 1.10: Photograph of the original independent breast CT system, including a cone-beam x-ray tube and detector attached to a goniometer and rotation stage allowing fully 3D motion. The goniometer allows for up to $30^\circ$ of system-tilting capabilities, which allows for 3D imaging trajectories that reduce artifacts caused by insufficient cone beam sampling.

Capabilities were removed when the CT system was coupled with the SPECT system onto a common gantry as described in Chapter 6. Future designs of the hybrid system will restore tilting capabilities to the CT subsystem with the design of a more sophisticated hybrid
gantry. Low dose studies with the prototype CT system indicated the feasibility of breast CT imaging with doses lower than those for dual-view mammography, while maintaining the ability to detect soft tissue lesions less than 5 mm in diameter [130, 133, 134]. Pilot observer studies also demonstrated that breast CT outperformed standard mammographic techniques in low contrast, dense-breast cases where overlying structure was an impediment to visibility [130].

1.5.1 X-ray Tube and Filter

The dedicated CT breast imaging subsystem uses a commercially available cone-beam x-ray source (model Rad-94, 0.4 mm focal size, 14° anode angle, Varian Medical Systems, Salt Lake City, UT). The basic functionality of the x-ray producing tube has already been described in §1.3.2. A high-frequency, constant-voltage x-ray generator (model CPX160, Electromed Inc., Montreal, PQ) provides the voltage to the x-ray tube. An ultra-thick (100th value layer thickness or 0.0508 mm at 60 kVp) K-edge filter (Cerium, Z=58, \( \rho = 6.77 \text{ g/cm}^3 \)) is inserted into a custom-built collimator attached to the x-ray source to produce quasi-monochromatic x-rays (tube potential = 60 kVp, mean beam energy \( \approx 36 \text{ keV} \)) which can: (1) improve visualization of tissues with small differences in attenuation coefficients; (2) use minimal x-ray dose; and (3) reduce beam hardening effect [130, 135]. The source-to-image distance is currently 60 cm and source-to-object distance is 38.1 cm, resulting in a magnification of 1.57 for an object located at the system’s center of rotation.

1.5.2 Digital X-ray Detection

The CT tube is paired with a CsI(Tl)-based, amorphous silicon digital x-ray detector (Varian Medical Systems) with an active matrix size of 1920x1536 pixels having 127 \( \mu \text{m} \)
This indirect detector uses CsI(Tl) \((Z_{\text{eff}}=54, \rho = 4.51 \text{ g/cm}^3)\), a scintillating material that converts x-rays into visible light \((\lambda=550 \text{ nm})\) (Figure 1.11) [109].

The number of light photons produced in the scintillating crystal is proportional to the

Figure 1.11: Simplified illustration of CT detection process. Incoming x-rays are converted by the columnar scintillating CsI(Tl) into a fluorescent shower of visible light that induces charge in the photodiodes. The charge is stored in capacitors and read out by ASICs.
integral energy of the incident radiation (66k photons per MeV). The CsI(Tl) scintillator material is connected to or grown directly on the glass substrate of the underlying semiconductor photodiode material, hydrogenated amorphous silicon (aSi:H) [136]. The emitted fluorescent light illuminates the photodiode array and frees up electrons in the photodiode layer, which is sandwiched between two thin electrodes with a small bias voltage applied across it. The electric signal created is stored in capacitors or thin-film transistors at the base of the photodiodes and then read out sequentially by ASICs to the image acquisition controller.

Several detector calibrations and corrections are implemented to minimize image artifacts caused by variations and imperfections in the components, non-uniform x-ray fields due to the heel effect, dark currents, and electronic noise in the detector [137]. The three primary corrections employed in our system are gain, offset, and defective pixel corrections. Gain correction is performed by exposing the detector to a uniform unobstructed field, and then normalizing the sensitivity response of the individual pixels. Offset correction corrects for dark leakage currents in the detector caused by finite conductivity in the semiconductors with a bias voltage applied, which can result in non-zero pixel readings. Offset correction is performed by capturing several images from the detector without any x-ray exposure, and then correcting by subtracting the dark images from the final corrected images. Defective pixel correction is implemented by exposing the detector to a uniform field and replacing pixels that are below or above a certain threshold value with an average of the surrounding pixel values.
1.6 Tomographic Iterative Reconstruction

The fundamental limitation of mammography and other conventional 2D imaging modalities is that the acquired images are 2D projections of 3D source distributions. Acquiring several views from different angles around the breast is one solution to this problem, for example with dual-view craniocaudal and mediolateral oblique mammography). Still, with only a few views, the true distribution remains ambiguous due to overlapping structures. Another solution is tomographic imaging, such as SPECT and CT imaging, where tens to hundreds of equiangular-spaced projections are acquired around the object of interest. Each projection represents line integrals of the emitted radiotracer activity or transmitted intensity, for SPECT and CT, respectively, along a collection of particular ray paths. Mathematical algorithms are used to reconstruct the acquired projections into a 3D volumetric representation of the object. Tomographic imaging and reconstruction allows for better 3D localization, improved contrast by removing overlying and underlying structures, and more accurate quantification of CT attenuation coefficients and SPECT radiotracer activity than with conventional 2D radiographs [138].

The two primary tomographic reconstruction methods are filtered back projection and iterative reconstruction techniques. Godfrey Hounsfield used an iterative reconstruction technique when he was developing the first clinical CT scanner [139]. Filtered back projection, however, became the predominant reconstruction method for clinical CT imaging mainly due to its much shorter reconstruction time and subsequent ability to provide to the radiologists images in a matter of seconds.
1.6.1 The Radon Transform

The basis for filtered back projection is the Radon transform, and the inversion of this transform provides the basis of 3D reconstruction, which utilizes the Fourier slice theory. Johann Radon proved that a 3D object can be reproduced from an infinite number of projections at different angles [140]. The 2D Radon Transform relates the 2D distribution, \( f(x,y) \), to the line integral space, \( R(\theta,s) \), and is expressed by [141]:

\[
R(\theta,s) = \int_{-\infty}^{\infty} \int_{-\infty}^{\infty} f(x,y) \delta(x \cos \theta + y \sin \theta - s) \, dx \, dy \tag{1.13}
\]

where \( s = x \cos \theta + y \sin \theta \). In two dimensions, the x-ray transform is the Radon transform and the transform can be observed in acquired data as the sinogram. However, in fully 3D imaging, the Radon transform integrates \( f(x,y,z) \) across all 2D planes and does not coincide with the 3D x-ray transform exactly [117].

1.6.2 Iterative Reconstruction

Iterative reconstruction is used exclusively for both SPECT and CT imaging in this thesis. These statistical iterative reconstruction methods do not invert the Radon transform, but instead maximize the probability or the likelihood of an attenuation coefficient (for CT) or an activity level (for SPECT) being present in a particular voxel of the reconstructed volume. Iterative reconstruction techniques perform well for count-starved SPECT and low flux CT exposures, with reduced image noise and artifacts for incompletely sampled trajectories. Iterative reconstruction also allows for the complex 3D SPECT trajectories used to acquire projection data.
The iterative reconstructed technique used for SPECT is called Ordered Subsets Expectation Maximization (OSEM). OSEM is an accelerated modification of the Maximum Likelihood Expectation Maximization (MLEM) algorithm [142]. This reconstruction code was coded by Dr. James E. Bowsher at Duke University Medical Center, Durham, NC. In his algorithm, projections are divided into equal image subsets, shortening convergence and computation time. In OSEM the new probability estimate is given by [117]:

\[
\hat{f}_j^{\text{new}} = \frac{\hat{f}_j^{\text{old}} \sum_{i \in S_n} h_{ij} \sum_{i \in S_n} h_{ij} \hat{f}_i^{\text{old}}}{\sum_{i \in S_n} h_{ij} \sum_{i \in S_n} h_{ij} \hat{f}_i^{\text{old}}}
\]

where: \( \hat{f} \) is the emission activity distribution; \( h_{ij} \) is the element of the system matrix representing the mean contribution of the \( j \)th pixel in the object to the \( i \)th pixel in the projections; \( S_n \) is the subset number; and \( g \) is the observed projection data.

For CT, using ordered subsets transmission (OSTR), the new estimate is given by [143, 144]:

\[
\mu_j^{\text{new}} = \left( \mu_j + \frac{M \sum_{i \in S} a_{ij} h_i^{(n)} - \beta \sum_{k=1}^K c_{kj} w_k [C \mu^{(n)}]_k}{d_j + w_j} \right)
\]

where: \( \mu \) is the attenuation value; \( j \) is the voxel; \( M \) is the random variable to denote the number of photons that pass unaffected through the object; \( S \) is the number of subsets; \( a_{ij} \) is the line integral along the \( i \)th ray through the \( j \)th voxel; \( h_i^{(n)} \) is the marginal log-likelihood of the \( i \)th measurement; \( n \) is the iteration number; \( \beta \) is the hyper-parameter that controls the tradeoff between spatial resolution and noise; \( \sum_{k=1}^K c_{kj} w_k [C \mu^{(n)}]_k \) is a penalty function that considers discrepancies between neighboring pixel values; and \( d \) is the curvature of the separable surrogate function.
The optimal choice of reconstruction parameters is a tradeoff between image contrast and SNR and thus depends upon the imaging task. As the number of iterations increases, overall image contrast and spatial resolution increase, but noise also increases and thus SNR decreases. For reconstructions using 8 subsets, previous studies found the optimal stopping points to be at 2 and 10 iterations for SPECT and CT, respectively [76, 145]. For the imaging studies in this thesis, these settings were generally used. However, for patient data, the optimal point for CT was more recently found to be at 30 iterations with 8 subsets.

1.6.3 Image Presentation

Tomographic volumes are generally viewed as a stack of 2D image slices through different planes of the reconstructed volume. Coronal, sagittal, and transverse (axial) image planes are the standard imaging planes, shown in Figure 1.12 with respect to the patient-based coordinate system. Maximum intensity projections (MIPs) are often displayed in SPECT imaging to quickly view the maximum areas of focal radionuclide uptake. Fused volume renderings of the SPECT-CT images can also be useful for registering the functional SPECT images with the higher resolution CT anatomical images (Figure 1.13). For initial hybrid SPECT-CT images, spherical external fiducial markers have been used to scale and register the two modalities.
Figure 1.12: Illustration of the different reconstructed image planes relative to a patient-based coordinate system. The coronal plane is parallel to the left-right and superior-inferior axes. The sagittal plane is parallel to the anterior-posterior and superior-inferior axes. The transverse (axial) plane is perpendicular to the coronal and sagittal planes of the reconstructed images.
Figure 1.13: (TOP LEFT) SPECT and (TOP RIGHT) CT volume rendered images of a 900 mL breast phantom containing multiple CT iodine contrast-enhanced lesions. Note that only the two largest lesions contained $^{99m}$Tc activity. The fused SPECT-CT volume rendering illustrates the value of combining functional and anatomical modalities.
1.7 Challenges of Imaging Uncompressed Breasts

Developing and optimizing dedicated breast imaging systems requires an understanding of the general variability in pendant breast shapes and sizes. Similar to the SPECT-CT imaging procedure in our lab, clinical MRI images are acquired with patients lying prone, and they provide views of a complete 3D, uncompressed breast volume. An IRB approved study (Appendix A) of 103 unique, existing clinical MRI breast data was conducted to obtain several parameters of uncompressed breasts to categorize shape and size. MRI data, provided by Dr. Victoria Seewaldt, were acquired during patients’ regular visits to Duke Radiology, and they represent a random sampling of high-risk breast cancer patients at the Duke University Medical Center. The volumetric data were completely de-identified except for age (Figure 1.14).

![Histogram of the range of ages included in the retrospective MRI study.](image-url)
Using open-source OsiriX imaging software [146-150], the following pendant breast parameters were measured: nipple-to-chest wall distance, medial-lateral distance, and superior-inferior distance (Figure 1.15). From the 103 subjects, a total 202 uncompressed breasts were measured (several women had complete unilateral mastectomies and therefore only the remaining intact breast could be measured). A random sampling of transverse image slices from the study is shown in Figure 1.16 to illustrate the wide variability of breast shape and size.

A 3D surface rendering of the external breast shape was also generated in order to visualize challenges of contouring the breasts (Figure 1.15, BOTTOM) and to generally classify the data according to volumetric shape (Figure 1.17). These MRI breast image sets can thus be used as the digital “phantoms” when utilizing computer models for system development and orbit optimization purposes.
Figure 1.15: Sample breast MRI sagittal (TOP LEFT) and transverse (TOP RIGHT) slices with illustrated nipple-chest, medial-lateral, and superior-inferior measurements. A volumetric rendering (BOTTOM) was also created for each subject.
Figure 1.16a: Randomized montage of MRI slices included in the retrospective study.
Figure 1.16b: (CONTINUED) MRIs from 10 out of the 103 patients included in the study.
Figure 1.17: Representative examples of transverse plane shape labels used to classify each subject. (CENTER) Distribution of general breast shapes over the 103 subjects. The “Other” category includes mastectomy and miscellaneous shaped breasts that did not fit into the other three general classifications.
Estimated volumes of the breasts were also calculated by first thresholding and segmenting the data and then using voxel integration of the MRI images (Figure 1.18). A weighted mean was calculated for each metric.

Results are tabulated in Table 1.1 and the frequency distributions are displayed in Figure 1.19. Moderate compression did occur for some larger breasts due to the fixed size of the MRI breast coil holes, and thus, true dimensions may have been slightly larger than measured. The relevant result is the average breast volume of 720mL (with a somewhat large ±415 mL standard deviation). Prior to this study, most imaging experiments had used breast
phantoms with volumes greater than 1000 mL, which tend to be seen in the FOV of both systems. Based on these results, smaller breast phantoms ranging from 500-1060 mL volumes were used from many of the studies in this thesis, including the SPECT observer studies in Chapters 2 and 4.

Table 1.1: Results for breast sizes obtained from MRI studies

<table>
<thead>
<tr>
<th>Age (Yr)</th>
<th>Nipple-to-Chest (cm)</th>
<th>Medial-Lateral (cm)</th>
<th>Superior-Inferior (cm)</th>
<th>Vol. (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>45.8</td>
<td>8.4</td>
<td>10.8</td>
<td>14.3</td>
</tr>
<tr>
<td>Std Dev</td>
<td>7.6</td>
<td>2.7</td>
<td>2.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Min</td>
<td>23</td>
<td>2.9</td>
<td>5.5</td>
<td>8</td>
</tr>
<tr>
<td>Max</td>
<td>66</td>
<td>19.1</td>
<td>16.9</td>
<td>17.3</td>
</tr>
</tbody>
</table>

This study was helpful in visualizing the challenging variety of breast shapes and volumes to be contoured during the SPECT-CT scanning procedure. The polar tilts possible with our current complex orbits (Figure 1.9) appear to sample adequately the majority of the shapes and volumes observed, but the ROR cannot rely on linearly interpolated points to accurately contour the breast, as is currently the protocol.

While the relatively low number of subjects measured prevents us from making any broad statistical classifications for the general population of women, the minimum, maximum, and mean measurements provide a starting estimate of ROR ranges for the gamma camera in our lab.
Figure 1.19: Frequency distributions of measured breast parameters extracted from 202 individual MRI breast volumes. Breast volumes were estimated using segmentation and mesh volume calculations.
Figure 1.20: Photographs of the incompressible breast phantoms mounted on a chest-plate support, with truncated arm in the lower right corner. The large white ring is a 3 cm diameter sealable insertion port on the chest side of the breast, and the smaller white screw at the phantom’s bottom is a screw port to help top off and drain the phantom (black arrows).

1.7.1 Breast Phantoms

Prior to the retrospective MRI study, six incompressible breast phantoms (Figure 1.20) and one compressible (shown in Figure 2.1) were designed and fabricated to our general specifications by Radiology Support Devices, Inc. (Newport Beach, CA) [151]. These phantoms vary in shape and overall fillable volume, and they were molded to resemble prone pendant breasts. The measured MRI breast sizes from this study retrospectively validate the range of shapes and sizes of these custom shaped, pendant breast phantoms (Table 1.2). The 700 mL compressible phantom dimensions are close to the mean volume and breast
dimensions of the MRI subjects, and the incompressible phantoms allowed us to physically test minimum to maximum extremes. These phantoms were used extensively for evaluating, optimizing, and further developing both the SPECT and CT systems throughout this dissertation.

Table 1.2: Specifications of the molded breast phantoms for transmission and emission imaging.

<table>
<thead>
<tr>
<th>Breast Volume (mL)</th>
<th>Nipple-to-Chest (cm)</th>
<th>Medial-Lateral (cm)</th>
<th>Superior-Inferior (cm)</th>
<th>“Skin” (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incompressible (PETG skin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>240</td>
<td>3.8</td>
<td>12</td>
<td>12</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>325</td>
<td>4.4</td>
<td>13</td>
<td>13</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>470</td>
<td>5.0</td>
<td>15</td>
<td>16</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>935</td>
<td>7.4</td>
<td>15</td>
<td>20</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>1070</td>
<td>12</td>
<td>18</td>
<td>16</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>1730</td>
<td>12</td>
<td>18</td>
<td>19</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Compressible (urethane-based skin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>700</td>
<td>9</td>
<td>12</td>
<td>16</td>
<td>0.16</td>
</tr>
</tbody>
</table>

1.8 Thesis Organization

The remainder of this thesis document is organized into two sections. Chapters 2 - 4 are characterization studies of the independent SPECT subsystem including a direct comparison with 2D imaging, an analysis on the effect of energy window width, and an observer-based study to evaluate the limits of object detectability under various imaging conditions. Chapters 5 - 6 describe enhancements to and evaluation of the combined SPECT-CT prototype system, followed by concluding remarks in Chapter 7.
Chapter 2

Comparison of Dedicated Breast SPECT and Scintimammography

The superiority of 3D SPECT for breast imaging over 2D planar scintimammography is unresolved. While ideal observer studies have demonstrated the advantages of 3D SPECT [69], several studies show less sensitivity for SPECT [82, 152, 153], potentially due to the non-optimized nature of the clinical, whole-body SPECT cameras, acquisitions, and simple back projection reconstruction algorithms. Breast imaging with clinical SPECT cameras is limited by the bulkiness of the large, whole-body cameras, which necessarily result in a larger ROR with the camera’s being placed far away from the breast. Because spatial resolution degrades linearly with increasing distance in SPECT, the larger ROR results in reduced resolution, a fall-off in contrast, and poorer image quality. As one solution, SPECT breast imaging with pinhole collimators has been investigated, increasing both sensitivity and resolution compared to standard parallel-beam SPECT [74, 80, 154, 155]. The emergence of compact, semiconductor-based gamma cameras, with minimal dead space along the camera edge, has lead to more flexible camera positioning at close proximities to the breast, and they have been used for both 2D and 3D breast imaging. One such system was illustrated and described in detail in Chapter 1.

The overall goal of this chapter is to qualitatively and quantitatively compare breast lesion imaging using 2D planar scintimammography imaging of the breast under various degrees of compression with fully uncompressed, dedicated 3D breast SPECT using
contoured acquisition trajectories. A specialized compressible breast imaging phantom was previously developed in order to compare the two imaging approaches (§1.7.1). Two studies are investigated here. Based on the findings of the first quantitative study, a second range of experiments was undertaken and an observer-based study was completed.

2.1 Phantom Development and Initial Quantitative Studies

2.1.1 Methods

2.1.1.1 Gamma Camera

The previously described (§1.4.1) 16 x 20 cm\(^2\) area, CZT-based compact gamma camera with 2.5 mm discrete pixels was used for all imaging studies [113]. A low-energy collimator with 1.22 mm (flat-to-flat) hexagonal hole openings, 0.2 mm septa, and 2.54 cm height was used in both planar and tomographic measurements. General performance characteristics and breast imaging capabilities of this specific camera system were studied previously in detail by Brzymalkiewicz et al [111, 113].

2.1.1.2 Breast and Lesion Phantoms

A specialized compressible, anthropomorphic breast-plus-chest-wall phantom was developed, which could contain lesions of various sizes, in various locations, and of different activity concentration ratios (Figure 2.1, TOP LEFT) [156]. This phantom was derived from a commercially available mammography-training phantom for breast positioning (Radiology Support Devices, Inc., Newport Beach, CA). The original stock phantom was filled with gel to provide realistic compressibility, but for our purposes was left empty to allow for custom lesion insertion and added background of our choosing. The fillable breast volume was 700 mL, and the breast chamber was internally sealed with a bladder to keep the breast volume
constant under various degrees of compression. A ~1.6-mm thick “skin” of an expandable urethane-based compound was stretched over a thick plastic, anthropomorphic chest plate. The dimensions of the breast volume were: nipple-to-chest distance of 9 cm, medial-lateral distance of 12 cm, and superior-inferior distance of 13 cm. On the top surface of the chest wall, there was a 3-cm diameter O-ring sealable port hole, through which lesions could be
inserted (Figure 2.2, TOP RIGHT). Next to the lesion insertion port was an additional needle sized fill port, used to add radioactivity and top-off the breast volume. This phantom is meant to accommodate both 2D and 3D imaging for emission and/or transmission imaging, but also to have physical hindrances similar to those encountered on a human torso that otherwise preclude idealized imaging of an isolated, compressible breast.

Latex-based lesions were adapted from animal catheterization balloons (Harvard Apparatus, Holliston, MA) and filled with radioactive fluids using a micropipettor with <0.30 µL precision. In this way, the lesions’ radioactivity concentration and volume could be precisely controlled, even if there were differences in the actual balloon volumes. The filled-lesion volumes and dimensions are listed in Table 2.1. Since the lesions were not spherically symmetric, it is more appropriate to refer to their volumes rather than effective “diameters.”

Table 2.1: Lesion sizes for the comparative breast-imaging study

<table>
<thead>
<tr>
<th>Volume (µL)</th>
<th>Diameter (mm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short Axis</td>
<td>Long Axis</td>
</tr>
<tr>
<td>40</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>70</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>140</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>300</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>500</td>
<td>10</td>
<td>14</td>
</tr>
</tbody>
</table>

These thin-walled lesions had very little cold (non-radioactive) material around them, given that a large, cold volume near a hot focus can provide an artificial signal enhancement in the image. These balloons were tied with a single knot of silk line on top of a notched, 1.6-mm diameter polyethylene tubing of ~4.5-cm lengths (Figure 2.1, BOTTOM LEFT). For one of the lesion posts, three 140 µL lesions were placed at ~1.5-cm intervals. This post with three lesions was designed to gauge the extent of the breast volume anterior to the
chest wall that could be imaged with the various acquisition trajectories. An x-ray of the inserted lesions is shown within an air-filled, uncompressed breast (Figure 2.1, BOTTOM RIGHT).

2.1.1.3 Scintimammography (Planar) Acquisition Parameters

Lesion-to-background concentration ratios using aqueous $^{99m}$Tc pertechnetate (140 keV photopeak) varied from infinite (no background activity) to 12:1, 7:1, and 3:1 with an absolute lesion concentration of 40 $\mu$Ci/mL, which is roughly a factor of 20 greater than that observed clinically or in other studies [105, 157-159]. This lesion concentration reduced imaging times for the large number of studies performed, and it also helped to ensure low noise quality in the final obtained images. The infinite ratio was used to ascertain the absolute lesion count rates. A ±6% energy window was used for all acquisitions in this chapter [160].

For planar imaging, two 6 mm thick acrylic plates were used to compress the breast (Figure 2.2). The standard marks seen on mammography compression plates were transcribed onto the plates used here. We attempted to use the thinner polycarbonate plates used in x-ray mammography, but with their modification for this nuclear medicine study they deformed substantially when attempting to uniformly compress the breast phantom across the entire field. Furthermore, given the polycarbonate plate geometry that was meant to strengthen it, the gamma camera could not be placed in direct contact with the compression plate to minimize the distance to the breast. The camera-side acrylic plate attenuated the signals from the $^{99m}$Tc by ~11%, but was compensated by the relatively high
activity concentrations. The acrylic plates were secured at each corner by an adjustable slider-clamp, which was used to hold the plates at fixed separation/compression thicknesses.

Initial image acquisitions took 10 min and then increased with compensated times with radioactive decay.

Scintimammograms were acquired for each of the three compression thicknesses: 12 (uncompressed, but with plate between the phantom and camera), 9, and 6 cm (Figure 2.3). More compression was attempted, but since the phantom leaked at an unrelated location, and breasts this large do not usually undergo more compression than \(~6\) cm [63, 161], it was
felt that a maximal compression of 6 cm would be suitable for these studies. Since the balloons on the lesion tree were nearly coplanar and centered along the compression dimension, the distance between the camera face and lesions was nominally ~3 cm under the greatest compression. The views were in a medio-lateral orientation with respect to the pendant breast phantom, affording close imaging coverage of the anterior chest wall. With increased compression, the camera was always moved closer staying in contact with the plate in order to minimize distance from the breast phantom.

2.1.1.4 SPECT Mamnotomography (3D) Acquisition Parameters

To enable 3D SPECT imaging, the gamma camera was attached to a laboratory jack and goniometer that provided the maneuverability for fully flexible, 3D trajectories
traversing a hemisphere about the suspended uncompressed breast [111]. The breast and lesion activity distributions for the SPECT acquisitions were identical to those used for the planar acquisitions, though overall activity was slightly decayed. This was compensated again by slightly increasing acquisition time to obtain similar overall counts in the SPECT images compared to the scintimammograms. Three acquisition trajectories were investigated (described in more detail in §1.4.4 and [114]), including a vertical axis of rotation (VAOR), a tilted parallel beam (TPB) and a 3-lobed sinusoid projected onto a hemisphere (PROJSINE)
(Figure 2.4). For each orbit, the camera system used 360° azimuthal (circular) rotation with 128 projections (angular increments ≤2.8°) over the 10-min acquisition period, as this was shown to yield superior resolution characteristics throughout various breast volumes [112, 114]. For all trajectories, the radii-of-rotation were optimized such that the camera was not more than ~1 cm from the proximal breast surface at any projection view: the VAOR ROR was fixed at 6.6 cm, the TPB ROR was fixed at 5.2 cm, and the PROJSINE ROR varied from 2.8 to 5.2 cm in order to contour the breast closely at all acquisition angles. The vertical height of the breast phantom was adjusted for each trajectory so that the camera system could move unimpeded through a full 360deg azimuth without contacting the chest wall.

The previously described (§1.4.1), ray-driven OSEM algorithm was used to reconstruct the acquired data, with up to 5 iterations and 8 subsets, using a 150 x 150 x 100 grid and 2.5 mm³ voxels [162]. Attenuation correction was also implemented using a calculated uniform attenuation throughout the breast. The final reconstructed data was then smoothed by using a 3D Hann filter with a cutoff at 0.8*Nyquist frequency. ROI data was obtained from the filtered 3rd iteration that has previously been shown to have an optimal trade-off between SNR and contrast in higher-noise conditions [112]. It should be noted that to easily view all the lesions, maximum intensity projection (MIP) images were used in this dissertation for display, but that any quantitative data (ROI values or profiles) are otherwise obtained from single slices of the original 3D data set.

2.1.1.5 Data Analysis

All image analysis to extract ROI data from the mammotomographic images was performed using Matlab (The Mathworks, Inc., Natick, MA) and ImageJ (National Institute of
Health, Bethesda, MA). For the planar scans, ROIs were drawn within the boundaries of the visible lesions, and larger background ROIs were obtained at the same row-level as the lesion ROIs to ensure that the effects from attenuation, scatter and noise were the same as for the lesion signal. Signal was considered as the mean of the lesion ROI, and noise was the pixel standard deviation about the mean, measured in the background region. Signal was considered as the mean of the lesion ROI, and noise was the pixel standard deviation about the mean measured in the background region. Thus, SNR was calculated as the difference in the mean pixel values of the lesion and breast background, divided by the standard deviation of the background:

\[
\text{SNR} = \frac{\text{ROI}_{\text{lesion}} - \text{ROI}_{\text{breast}}}{\sigma_{\text{breast}}}
\]

where \( \text{ROI}_{\text{lesion}} \) and \( \text{ROI}_{\text{breast}} \) are the mean values of the pixels within each respective region, and \( \sigma_{\text{breast}} \) is the standard deviation of reconstructed pixel values in the breast background ROI. Lesion contrast was defined as the signal difference divided by the background signal:

\[
\text{Contrast} = \frac{\text{ROI}_{\text{lesion}} - \text{ROI}_{\text{breast}}}{\text{ROI}_{\text{breast}}}
\]

2.1.2 Results

2.1.2.1 Scintimammography Imaging Results

The projection images are shown in Figure 2.5 and illustrate several clear results. With increased compression (thinner breast thickness), the noise quality becomes more uniform throughout the breast, making it easier to view the individual lesions that are evident in the line profiles. However, due to the limitation of viewable imaging area in a
single planar scan, only the two anterior lesions on the central three-lesion post can be visualized. The lesions also become more difficult to distinguish from one another with increasing breast thickness (decreasing compression), and they are more difficult to see with decreasing lesion:background activity concentration ratios. No lesions are visible at the 3:1 concentration ratio.

Increasing compression yielded improved SNR and contrast for all lesions, as illustrated for the 12:1 activity ratio (Figure 2.6). Overall lesion visibility is still good, with SNR values meeting the minimal Rose detectability SNR criterion of 5 for all but the smallest 40 $\mu$L lesion. SNR and contrast decreased by ~40%, as expected for the more realistic 7:1 ratio (Figure 2.7). SNR and contrast decreased, regardless of lesion volume, with decreased concentration ratios. At 7:1, the 70 and 140 $\mu$L lesions have SNRs below 5 and are correspondingly difficult to discern even in the low-noise scintimammograms. The 3:1 concentration ratio was not quantified due to the low lesion contrast. While SNR and contrast more than doubled with increasing lesion volume from 40 to 70 $\mu$L, and from 140 to 300 $\mu$L lesions, improvements were more modest between 70 to 140 $\mu$L and 300 to 500 $\mu$L (Figure 2.8).
Figure 2.5: Planar scintimammograms compressed to 12-, 9-, and 6-cm breast thicknesses, and lesion-to-background concentrations from 12:1, 7:1 and 3:1. Normalized horizontal line profiles through the two largest 500 µL lesions (at hash marks illustrated in upper left corner image) are shown below each image. The 6-cm compressed breast began leaking at the 3:1 ratio under full compression, so for radiation safety reasons we discontinued scanning that condition. Images are normalized to a global maximum value and are otherwise not cropped in any way.
Figure 2.6: SNR and contrasts plotted as a function of compression thickness for the 12:1 lesion : background concentration ratio.
Figure 2.7: SNR and contrasts plotted as a function of compression thickness for the 7:1 lesion : background concentration ratio.
Figure 2.8: SNR and contrasts plotted as a function of lesion volume for the 12, 9, and 6 cm compression thickness.
2.1.2.2 SPECT Mammotomography Imaging Results

MIP images of the reconstructed data (Figure 2.9) quickly highlight differences between all the image acquisition modes and concentration ratios. For VAOR, there is a clear resemblance to the planar scintimammograms (Figure 2.5), especially in that only two out of three lesions on the central three-lesion post are visualized, whereas all three lesions are seen in images obtained with the other trajectories. Therefore, a smaller breast volume is imaged with simple VAOR acquisition, potentially missing lesions closer to the chest wall. For TPB, while more lesions can be visualized, there is a clear distortion of the breast shape itself and also of the known spherical lesion shapes. The PROJSINE trajectory seems to be a good compromise between a simple circular and tilted acquisition. Not only is there a more faithful breast and lesion shape reproduction, but more lesions are clearly seen in PROJSINE throughout the imaged volume, including the anterior chest wall region (posterior breast). At 3:1, the two largest lesions are still faintly discernable in the images and line profiles. Individual slices with corresponding line profiles of the 12:1 PROJSINE data further illustrate the benefits of SPECT imaging for removing overlapping structures and localizing lesions in 3D (Figure 2.10). Despite qualitative image differences, SNRs and contrasts do not differ substantially between the various acquisition trajectories as long as the lesions are visible (Figure 2.11). A ~40% drop in contrast and SNR was measured again for the 7:1 ratio. Lesion visualization was not quantified for the 3:1 activity concentration. SPECT obtained SNR and contrast increases more linearly with increasing lesion volume (Figure 2.12) compared to the scintimammogram values.
Figure 2.9: MIP images of SPECT mammotomography results acquired using three different trajectories and lesion-to-background concentrations at 12:1, 7:1 and 3:1. Line profiles are shown through the two largest lesions below each image (at hash marks illustrated in upper left image). Images were smoothed using a 3D Hann filter (0.8*Nyquist) and normalized to a global maximum value. Nipple is at image bottom and chest wall is at top.
Figure 2.10: (TOP ROW) Transverse and (MIDDLE IMAGES) coronal slices through the 12:1 PROJSINE collected phantom, and (BOTTOM ROWS) with associated profiles through the (L to R, T to B) 40, 70, 140, 500 and 300 μL lesions.
Figure 2.11: SNR and contrast values determined for each lesion for the 12:1 and 7:1 concentration ratios. Data were obtained from single coronal slices of the specific planes optimized for each lesion ROI.
Figure 2.12: SNR and contrast values determined for each lesion, for each concentration ratio, for the PROJSINE-acquired, reconstructed SPECT slices and 6-cm compressed planar images.
2.1.2.3 Comparison of Scintimammography and Mammotomography

Comparing the best (available) planar imaging cases (6-cm compression) along with the PROJSINE SPECT data indicates that full tomographic imaging yields better SNR and contrast values for the visible lesions (Figure 2.12). In fact, there is nearly a factor of two improvement in SNR and contrast values for mammotomography compared to planar scintimammography, since the results with a lower concentration of mammotomography data (e.g., 7:1) correspond to the next higher concentration scintimammography data (e.g., 12:1). Thus, while the absolute values obtained from scintimammography are quite good and the images of high quality, fully 3D tomographic imaging yields nearly twice as good image parameters in this comparison study. One caveat to this low-noise study is that the SPECT images were post-processed with a 3D smoothing filter that additionally boosts SNR, while the scintimammograms were unaltered (as is generally the case for clinical scintimammography). It is unclear if the scintimammography obtained SNR values would change appreciably if the images were smoothed, though the contrasts, which measure the mean values, should most likely remain unchanged. Scintimammography was more limited in its ability to image the entire breast volume and near-chest-wall activity, which can be reliably imaged with full mammotomography. While this previous study was semi-quantitative in nature, a more comprehensive, quantitative comparison study was further investigated to determine if observers could indeed visually make out differences between the scintimammography and dedicated breast SPECT images.
2.2 Observer Studies

The initial studies in Section 2.1 utilized only low-noise, non-clinical count densities. In this second broader, yet more specific, observer-study based comparison, 3D SPECT and 2D scintimammography were compared by investigating observer detectability limits of various-sized lesions under the following imaging conditions: (1) different lesion:background activity concentrations; (2) low-noise vs. high-noise (clinical count densities); (3) 10-minute vs. 20-minute clinical acquisition times; and (4) uniform vs. heterogeneous breast backgrounds.

2.2.1 Methods

2.2.1.1 Phantom and Lesion Experimental Setup

The same compressible breast phantom (Figure 2.1) was filled with 500 mL of water. Though the leak resulting from over-compression of the breast during the previous experiments was repaired, a small pocket of air was left above the main breast cavity to avoid rupturing the chest-wall skin of the phantom when the breast was under complete compression. The breast cavity was otherwise completely filled. In these experiments, a total of eight balloons were used (ranging from 70 to 500 $\mu$L); two balloons of each volume were distributed at roughly 2 cm arc spacing through small holes made in a 4 mil (0.102 mm), thin plastic (transparency) film that was cut in a semicircle (Figure 2.13). The film was bonded to the fill cap of the breast phantom with clear silicone, such that the plane of lesion phantoms could be suspended vertically medially in the breast phantom. This lesion holder helped gauge the amount of breast volume within the field of view, as well as allow imaging of the smallest lesion detectable under various imaging approaches. The lesions were arranged on
the same plane in an effort to minimize distance dependent effects and thus avoid biasing either modality.

The absolute lesion activity concentration used was 36 $\mu$Ci/mL. Lesion : background concentration ratios using aqueous $^{99m}$Tc pertechnetate were varied from 12:1 to 6:1 to 3:1 by adding additional activity to the background as before. The full-spectral list-mode data for 6:1 and 3:1 were down-sampled such that the total counts per projection were approximately the same for each simulated biological uptake variation.

In initial 3D SPECT images of patients with confirmed cancer, some patients had areas of apparent non-uniform, patchy uptake in the breast background (see ahead to §5.2). To simulate this effect in the breast phantom, small (~1-2 cm$^3$) randomly cut pieces of
acrylic plastic were embedded in various-sized sponges. The sponges, while not seen in the emission images, allowed the plastic pieces to float at various heights in the breast in addition to pooling at the bottom for those pieces not inserted into the sponges, and compressed nicely in the scintimammograms because of their otherwise loose arrangement. With this method we were able to simulate patches of heterogeneous uptake in the breast background. The added material increased the total volume of material + fluid, but the total activity remained the same for both uniform and heterogeneous breast background scenarios. Additionally, for the heterogeneous breast experiments, an 290 mL activity-filled anthropomorphic heart was placed above the chest wall to simulate additional cardiac contamination (Figure 2.14). The heart-to-lesion activity concentration ratio was 1 : 1.

2.2.1.2 Acquisition Parameters

For planar imaging, the same two 6 mm thick acrylic plates were again used to compress the breast (Figure 2.3). Image acquisitions were 10 min (with increased times to compensate for radioactive decay) for both an uncompressed 12 cm plate separation, and a compressed 6 cm plate separation, similar to that for clinical MBI or BSGI acquisitions [62, 63]. Views were again in a medio-lateral orientation with respect to the chest plate of the phantom, with the top edge of the camera placed as close as possible to the chest wall. For SPECT acquisitions, the TPB 45° and 3-lobed PROJSINE (15-45°) trajectories were used (Figure 2.4). The VAOR orbit was not acquired because of its previously discussed chest wall visibility limitations, and to reduce the overall number of imaging studies given to the
observers. Dedicated breast SPECT and scintimammograms were acquired first with a uniform aqueous background. The same experiments were then repeated with added acrylic material to simulate a heterogeneous breast background.
2.2.1.3 Reconstruction and Post-Processing

The ray driven OSEM algorithm was again used to reconstruct the acquired data, using the previously described parameters and grid sizes (§2.1.1.4). For these experiments, attenuation correction or 3D filtering were not implemented for the SPECT images. Scintimammograms and reconstructed SPECT images were instead smoothed with a simple Gaussian blur filter (1 pixel radius) to reduce noise in the images. Image grayscale window and levels were also normalized between data sets in an effort to provide unbiased images to the observers. For the observer study, image data were displayed at the 1st reconstruction iteration to maximize lesion SNR.

2.2.1.4 Clinical Count Densities

The full list-mode emission data from both 2D and 3D modalities were randomly down-sampled such that the lesion activity concentration was effectively near reported clinical count densities of \(~2 \mu\text{Ci/mL}\) (based on pharmaceutical uptake studies) [105, 158]. A sub-aim of this study was to investigate the effect of a 10-min equivalent versus a 20-min equivalent patient scan time on lesion detection for various concentrations. For ongoing dedicated breast SPECT human subject studies in our lab, we have been imaging for 10 min per breast. Scintimammography is often conducted for 10 min per view for a total of 20 min per breast [157]. Here the potential benefit of adjusting our clinical protocol for an increased scan time was examined. Two independent “clinical count” projection data sets were created from each complete “low noise” data set: the first with count levels of a 10 min clinical acquisition, and the second with count levels of a 20 min clinical acquisition.
2.2.1.5 Observer Study & Image Analysis

Seven independent observers, comprised of two nuclear medicine physicians and five medical physicists, participated in a signal known exactly (SKE) contrast-detail observer study. Scintimammograms and contiguous 13-slice SPECT image sets were randomly displayed in a controlled viewing room. The observers marked which of the lesions were visualized for each of the 72 data sets, collected as summarized in Figure 2.15. In this SKE study, the observers were shown the general location and pattern of the lesions prior to viewing the study, and the observers did not adjust the window and leveling during the study. Statistical significance comparing the observer results was computed using paired Student T-tests.

It is important to note that observer contrast-detail analysis has known limitations as it is, by nature, subjective and can be susceptible to observer bias. The SKE setup represents the best-case scenario where visualization of the lesions should be otherwise obvious to the casual observer. This study did not account for false positives that may be expected to
increase in high noise images. Intra-observer variability was also not investigated in these initial observer studies. The following results do, however, provide a quantitative measure of inter-observer variability comparing 2D scintimammography with 3D SPECT, as well as varying 3D trajectory techniques possible with a fully-3D acquisition-positioning system.

2.2.2 Observer Study Results

2.2.2.1 Low Noise Uniform Breast Results

Qualitative side-by-side analysis of the low noise SPECT MIPs and scintimammography projections in Figure 2.16 illustrate that scintimammography is, again, limited in its ability to image the entire breast volume and near chest wall activity, which can be more reliably imaged with full breast SPECT. In the scintimammograms, the largest 500 μL lesion in the upper left hand corner (posterior) of the breast is truncated, and the 70 μL lesion in the upper right corner is completely out of the field of view. A medial-lateral oblique view of the breast may have arguably allowed visualization of slightly more volume in the FOV, as opposed to the medio-lateral view used here. Full breast SPECT incorporating polar tilt, however, consistently images the complete breast volume including the chest wall. Comparing PROJSINE and TPB SPECT images, PROJSINE images are a more faithful reproduction of the real breast shape, and fewer visible distortions are apparent in the lesions as observed previously [77, 114]. Often, this is more evident in individual SPECT slices (Figure 2.17).

Quantitative observer study results are given in Figure 2.18. The standard deviation between observers was relatively small for the low noise case, as may be expected. Intra-observer variability was not examined in this study, but should be in line with the contrast-
Figure 2.16: SPECT MIPs for PROJSINE and TPB trajectories shown together with uncompressed (12cm) and compressed (6cm) scintimammograms acquired of the same breast phantom for varying lesion to background concentrations.
Figure 2.17: Nine sequential sagittal SPECT slices for the low noise breast data. 1st iteration shown with Gaussian smoothing applied. Slice number is indicated for the 12:1 activity concentration ratio and the other ratios follow the same layout.
Figure 2.18: Low noise, uniform breast background observer results viewing the 8-lesion phantom. Error bars represent one standard deviation across the 7 observers. Asterisks indicate statistical significance (p<0.05) between the SPECT and scintimammography results.

Figure 2.19: Uniform breast background observer results for four lesions (highlighted by red dotted line) located within the FOVs (beneath blue dashed horizontal line at phantom posterior) of both modalities. Lesion volumes (mL) and relative locations within the phantom are illustrated. Asterisks indicate statistical significance (p<0.05).
detail observer study discussed in §4.3.1 where intra-observer variability was low (interclass correlation coefficients averaged between 0.8-0.9). For both SPECT trajectories, observers saw a significantly greater \((p<0.05)\) number of lesions at 12:1 and 6:1 than for scintimammography. The observers saw more lesions at 3:1 in images acquired with the TPB trajectory than either planar or PROJSINE acquired images. SPECT and scintimammography were generally equivalent at 12:1 for lesions within the field of view for both systems, as seen in Figure 2.19, where four non-repeated lesions within the FOVs of both modalities were compared. On the whole, more and accordingly smaller lesions were seen in both of the lower contrast SPECT cases; this result was statistically significant. Scintimammography compression (6 cm thickness) had no significant impact on observer performance in the low noise uniform 500 mL breast.

2.2.2.2 Clinical Count Uniform Breast Results

The down-sampled “clinical” count-level image results for simulated 20 and 10 min scans are shown in Figure 2.20 and Figure 2.21, respectively. These images have been moderately smoothed with a Gaussian filter; however, the increased noise is apparent, especially in the 10 min SPECT MIPs (Figure 2.21). Without smoothing or other noise reduction, small lesion detection is much more challenging and could result in more false positives, especially in the count starved individual SPECT slices (Figure 2.22). In scintimammograms, the line integral of all counts projected into a single projection reduces image noise, but also leads to lower image contrast.

There was an overall loss in observer performance between the simulated 20 min and 10 min scans, with an average \(~6\%\) drop in the number of lesions observed for the 10
Figure 2.20: 20-min scans at clinical-count densities of the same uniform breast phantom.
Figure 2.21: 10-min scans at clinical-count densities of the same uniform breast phantom.
Figure 2.22: Three sequential SPECT slices comparing 20-min and 10-min clinical-count density scans of the same uniform breast phantom at a 6:1 lesion:background activity concentration ratio. Line profiles are drawn through the anterior 500 µL lesion (at arrow).
Figure 2.23: (TOP) Clinical 20-minute scan and (BOTTOM) 10-minute scan, uniform breast background observer results viewing 8-lesion phantom. Asterisks indicate statistically significant separation between SPECT and scintimammography at $p<0.05$. Delta indicates statistical differences between the 20-min and 10-min scans.
minute scan (Figure 2.23). The 6:1 ratio exhibited the largest drop for both imaging techniques with an average drop of nearly 20% in observer sensitivity, a statistically significant loss across all imaging techniques. One surprising outlier to this trend was the uncompressed (12 cm) breast, which at 10-min was significantly better than the 20-minute scan (p<0.05). The 20 min and 10 min scans were generated by sub-sampling from different sections of the same original complete list-mode spectrum. This is indicative of the high noise and variability at low count rates. Due to wide error bars, further investigation is warranted at clinical count levels with multiple acquisitions to account for sample variation. The observer results for the 6:1 activity concentration ratio suggest that the increased sensitivity of a 20-min scan may be beneficial for future patient studies in our lab.

2.2.2.3 Low Noise Heterogeneous Breast Results

The addition of sponge-embedded floating cold spots simulates “patchy” radiotracer uptake in the heterogeneous image results (Figure 2.24). The cardiac phantom was placed slightly too high above the chest wall (Figure 2.14), so cardiac activity is only faintly visible at the top of the SPECT images. Plastic pieces intentionally pooled at the anterior breast phantom, creating the heterogeneously “cold” area near the nipple region. After two days of continuous experiments, $^{99m}$Tc appears to have absorbed into the 1.6 mm urethane-based malleable skin, resulting in an abnormally “hot” rim, most pronounced in the 3:1 images acquired later in the scan sequence. The rim appears more pronounced in the SPECT images partially due to the use of MIP images, but is prevalent in the individual slices as well (Figure 2.25).
Figure 2.24: SPECT MIPs for PROJSINE and TPB trajectories shown together with uncompressed (12cm) and compressed (6cm) scintimammograms acquired of the same heterogeneous breast phantom for varying lesion to background concentrations.
Figure 2.25: Three sequential SPECT slices for PROJSINE and TPB trajectories of the same heterogeneous breast phantom for varying lesion : background concentrations. Line profiles drawn through the anterior 70 μL and 500 μL lesions (at arrow) illustrate the effects of background concentration and the “hot” rim at the borders due to $^{99m}$Tc concentrating in urethane-based malleable skin.
Figure 2.26: Low noise, heterogeneous breast background observer results. Error bars represent one standard deviation across 7 observers. Asterisks indicate statistical significance between SPECT and scintimammography.

For both SPECT trajectories, lesions were significantly (p<0.05) more detectable at 12:1 and 3:1 than for scintimammography (Figure 2.26). Compression had a more notable effect on observations in the heterogeneous breast. At 6:1, there was no significant difference between SPECT and compressed breast scintimammography. With compression, the most likely explanation for the improved performance was that the added plastic pieces were compressed close to the lesions, thus raising the relative (apparent) contrast and lesion visibility due to decreased activity along line integrals adjacent to the lesion. This would be consistent with a biologically heterogeneous uptake that may additionally vary based on an individual’s breast density; it is not currently known what the natural variation in tracer
uptake is in these various breast conditions. However, at a 3:1 concentration, compressed breast scintimammography again significantly (p<0.05) underperformed SPECT. TPB and PROJSINE trajectories were more comparable in these low noise heterogeneous studies with now significant differences in performance.

2.2.2.4 Clinical Count Heterogeneous Breast Results

Images from the clinical count heterogeneous breast studies (Figure 2.27 and Figure 2.28) follow similar qualitative trends as the uniform clinical images. Individual SPECT slices are shown in Figure 2.29 The 20 min images show improved noise quality compared to the 10 min images, as evident in horizontal line profiles through the individual slices. The observer study results are shown in Figure 2.30. As before with the uniform breast case, the 10 min scan has considerably larger error bars and the overall performance was poorer. There was no statistically significant difference between the 20-minute and 10 min scans for either the 6 cm compressed breast scintimammograms or SPECT PROJSINE. Because of the wide error bars, no clear conclusion can be made as to whether a 10 minute increase in scan time has significant enough impact on lesion detection to justify doubling the scan time. Scintimammograms with compression can justifiably be acquired for 10 min with less of a performance drop (allowing for two 10-min views of the breast).
Figure 2.27: Clinical count density 20 min scan SPECT MIPs and scintimammograms acquired of the same heterogeneous breast phantom.
Figure 2.28: Clinical count density 10 min scan SPECT MIPs and scintimammograms acquired of the same heterogeneous breast phantom.
Figure 2.29: Three sequential SPECT slices comparing 20 min and 10 min clinical-count density scans of the same heterogeneous breast phantom at a 6:1 lesion:background activity concentration ratio. Line profiles are drawn through the anterior 500 μL lesion (at arrow).
Figure 2.30: (TOP) Clinical 20 min scan and (BOTTOM) clinical 10 min scan, heterogeneous breast background observer results. Asterisks indicate statistically significant separation between SPECT and scintimammography at p<0.05. Delta indicates statistical differences between the 20 min and 10 min scans.
Overall sensitivity for planar scintimammography could be further optimized by reducing collimator length, as well as adding a second camera head (and doubling the cost) which images closer to the distal lesions of the first head, as several groups have already investigated [63, 163]. SPECT imaging could be improved not only by collimator and detector optimization, but also by implementing more comprehensive image corrections (e.g. attenuation, scatter, and modeling of the point-spread function) into the reconstruction process, some of which are investigated in subsequent Chapters here.

2.3 Conclusions

A compressible anthropomorphic breast and chest phantom was developed for use in both uncompressed and compressed breast imaging. This can be useful for both emission and transmission imaging. Quantitative and qualitative comparisons of emission imaging with this phantom under different breast compression thicknesses, along with various 3D tomographic trajectories for uncompressed breast imaging, for lesions ranging from 40-500 μL in volume were shown. There was nearly a factor of two improvement in SNR and contrast values for 3D SPECT compared to planar scintimammography. Due to greater positioning flexibility of the system gantry, dedicated SPECT was able to both image a larger breast volume and view the anterior chest wall, where tumors may be otherwise missed in 2D imaging.

An observer-based direct comparison of 3D dedicated breast SPECT and 2D scintimammography using a single-headed high-resolution gamma camera was also completed. Scintimammograms were noticeably quicker for the observers to read. SPECT
and scintimammography sensitivity were generally statistically equivalent at the highest lesion: background concentration ratio (12:1), except that chest wall lesions were detected in SPECT that were not in the FOV of the scintimammograms. At 6:1 and 3:1 simulated biological lesion uptake, SPECT statistically outperformed scintimammography overall, seeing more and smaller lesions. In the compressed heterogeneous breast, scintimammography was found to be equivalent to SPECT at 6:1 only.

Clinically equivalent count data gave mixed results as to whether a 20 min SPECT scan may be preferable to a 10 min scan, in order to lower noise and boost sensitivity. Presumably, from a lesion detection point of view, this could lower the false-positive rate, though this was not explicitly measured here. The TPB SPECT acquisition trajectory generally outperformed PROJSINE, despite conical distortion in the breast and lesion shape, with the caveat that this was a SKE observer study. The PROJSINE orbit was more consistent, with generally lower variation between observers. Future random lesion placement observer studies are warranted to determine overall sensitivity in lesion detection.

Under a wide range of measurement conditions, significantly (p<0.05) more lesions, smaller lesion sizes, and more (3D) lesion locations can be detected with dedicated breast SPECT than with compressed breast scintimammography. With the implementation of automated breast contouring, attenuation, and scatter correction for the SPECT imaging (Chapter 5) [164], SPECT image quality and observer detectability of smaller lesions would be expected to improve further. Thus, these imaging results support the main hypothesis of this dissertation that 3D molecular SPECT breast imaging has the potential to improve detection and potentially in vivo characterization of small (<1 cm) early stage breast cancer.
Chapter 3

Effects of Energy Resolution in Breast SPECT

When utilizing a SPECT gamma camera for clinical applications, the energy window used to accept events which form the images is an important consideration. The energy window is partly affected by the intrinsic energy resolution, which greatly determines the ability to isolate true events and reject scattered counts. The importance of energy resolution in 2D nuclear medicine imaging has been mildly controversial, with some studies arguing for the importance of good energy resolution in camera selection and lesion detection [165, 166], with other studies concluding that the fraction of scattered events in a 2D imaging, energy-windowed breast image is minimal, and therefore the degrading effects of scatter are insignificant [167-169]. Thus, the objective of this chapter is to determine how energy resolution affects image quality for 3D, dedicated uncompressed breast imaging, which is similar, in principle, to the straightforward study for PET image quality [170].

The relatively fine intrinsic energy resolution of our CZT-based *LumaGEM™* 3200S gamma camera makes this study of various energy windows possible. By post-processing full-spectrum, list–mode-acquired data with various energy windows, the quality of the acquired images can be effectively degraded without changing the other characteristics of the imaging system, such as detection sensitivity or intrinsic spatial-resolution. While this approach is a surrogate to a comparison of various energy resolutions instead of imaging the subject repeatedly, this series of experiments would be more difficult to obtain with systems of worse intrinsic energy resolution. Poorer-energy-resolving systems would be unable to
differentiate events in the photopeak spectra arising from intrinsic statistical limitations (e.g., from poor light collection from small, discrete scintillators, and/or high electronic noise in semiconductors) or truly scattered events from the object being imaged, regardless of the energy window width used with those systems. By using a camera with excellent energy resolution, planar and tomographic data sets of geometric and anthropomorphic phantoms can then be analyzed qualitatively, quantitatively, and in finer increments.

3.1 Materials and Methods

3.1.1 Mini-Cold-Rod Phantom

A mini-cold-rod phantom (model ECT/DLX-MP, Data Spectrum Corp., Hillsborough, NC) placed in a 7.7 cm inner-diameter cylinder was used to characterize the effects of varying energy windows for a known geometric object (Figure 3.1). The 2.6 cm long rods were arranged in six sectors, with inner diameters from 4.7, 3.9, 3.1, 2.3, 1.5, to 1.1 mm, with each rod spaced on a pitch of twice their diameters. 15.8 mCi of $^{99m}$Tc in water filled the interstitial spaces. The phantom was suspended vertically with the mini-rods in the center of the camera’s field of view and parallel to the camera surface.

Three different experimental setups were used (Figure 3.2): first, imaging with a minimal, 4.4 cm ROR about the cold rods; second, imaging with the camera backed away to a 7.0 cm ROR (Figure 3.3); and third, immersing the cold rods in a 13.5 cm diameter, water-filled glass cylinder in order to add an additional scatter medium (Figure 3.4), as would be the case for women with larger breasts.

Data were acquired using a simple 256 projection VAOR orbit over 360°. Acquisition time was adjusted in order to keep nearly equal counts for each experiment and
to correct for decay. Data were acquired using two shorter 360° scans to minimize the effect of decay-reduced counts in later projections, acquiring approximately 55,000 counts per projection in a ±4% energy window, though the projections were all also collected in full-spectral list mode. The total number of events in the energy window after summing the two data sets was approximately 110,000 counts per projection in the complete data set, for each experiment.

Figure 3.1: Photograph of the mini-cold-rod resolution phantom. Rods are spaced on a pitch of twice their diameters.
Figure 3.2: Illustration of cold-rod phantom experimental setup. (LEFT) The camera was brought very close to the cylinder with an ROR of 4.4 cm for the best-case scenario. (CENTER) Camera was backed away to an ROR of 7.0 cm. (RIGHT) A 13.5 cm diameter, water-filled cylinder was secured to the camera, with the cold rods immersed in the center of the cylinder. The ROR remained at 7.0 cm. Arrows indicate the direction of acquisition.

Figure 3.3: Photograph of the cold rod acquisition at the wider 7.0 cm ROR.
3.1.2 Isolated Breast Phantom

The breast phantom experiments were designed to investigate the effects of energy resolution, first in an isolated breast phantom, then also in a breast phantom with torso background (see §3.1.3). Two 1.8 mL balloon lesions (Harvard Apparatus, Holliston, MA) were inserted into a custom 1060 mL breast phantom (Radiology Support Devices, Newport Beach, CA), which was fastened to the patient support bed (Figure 3.5, TOP) [114, 171]. One lesion was positioned in the physical center of the breast and one was glued on the
posterior breast, next to the anterior chest wall. The lesion : breast background activity concentration ratio was 8 : 1, with an absolute lesion activity concentration of 15.5 µCi/mL.

Two acquisition trajectories were used: one simple TPB orbit at a polar tilt of 45°, since untilted orbits (e.g., VAOR) would have precluded imaging of the chest wall lesion; and one complex, PROJSINE trajectory, with polar tilts ranging from 15-45° (Figure 1.9, Figure 2.4, Table 3.1) [112-114]. Projection data were initially acquired for an 11-minute total scan time, with count rates of ~1 kcps per projection, with subsequent scan times increased to account for radioactive decay.

Table 3.1: Parameters Used for Breast Acquisitions over a 360° Azimuthal range

<table>
<thead>
<tr>
<th>Orbit</th>
<th>Num of Prjs.</th>
<th>Polar Tilt, ( \phi ) (Range, min:max [degrees])</th>
<th>ROR (Range, min:max [cm])</th>
</tr>
</thead>
<tbody>
<tr>
<td>TPB</td>
<td>128</td>
<td>45</td>
<td>5.7</td>
</tr>
<tr>
<td>PROJSINE</td>
<td>128</td>
<td>15-45</td>
<td>2.2-6.7</td>
</tr>
</tbody>
</table>

3.1.3 Breast Phantom with Filled-Torso Background

An anthropomorphic torso phantom that included a heart, lungs, and liver (Radiology Support Devices) was placed on the table above the 1060 mL breast phantom with embedded lesions, without disturbing its original location (Figure 3.5, BOTTOM). Volumes for the torso, liver, and heart were 7810 mL, 940 mL, and 290 mL respectively. The lesion : breast : torso : heart : liver activity concentration ratio was 8.1 : 1.0 : 1.0 : 11.6 : 6.5, which distribution was determined according to compiled, published data [105, 113, 123, 158, 172, 173]. Absolute lesion activity concentration remained at 15.5 µCi/ mL and identical acquisition orbits were used as in the breast-only scans. Acquisition times were similar to the isolated breast phantom experiments, with adjustments (increased acquisition times) for decay correction.
Figure 3.5: (TOP) The isolated 1060 mL breast phantom was suspended through the breast opening of the patient bed, with lead aprons for additional shielding. Two 1.8 mL lesion balloons were embedded in the breast phantom (BOTTOM, at arrows). The upper lesion was glued to the chest wall. The radioactivity-filled torso phantom was positioned above the suspended breast on the patient bed.
Figure 3.6: Energy window width count-normalized spectra summed across all projections and detector pixels of resampled, list-mode data for various energy windows about the 140 keV photopeak of $^{99m}$Tc. The total counts in each energy-window width (shaded region) are equal to the number of counts of the narrowest energy window (-3+3%).

3.1.4 Count-Normalized Energy Window Analysis

List-mode resampling has been shown to be equivalent to multiple actual measurements in PET and SPECT imaging systems [174-176], and therefore it was utilized here. The full-spectrum list-mode data was collected and then post-processed to extract energy-windowed projection data of varying widths about the photopeak. For these experiments, cold-rod and all breast-phantom data sets were list-mode post-processed to create new image realizations with symmetrical ±3%, ±4%, ±8%, and asymmetrical -12+6% energy windows (Figure 3.6).
A flow-chart of the data processing is shown in Figure 3.7. To ensure equivalent noise quality between the varying energy windows, the list-mode data were resampled into equal count density windows using a bootstrap resampling method. Total counts per raw projection were reduced to equal the number of counts of the narrowest energy window (±3%) in order to create statistically count-equivalent image realizations. The narrowest window had the fewest overall detected events, and therefore it was the limiting factor for image-count density. All subsequent image corrections to these evaluation experiments were made with the appropriately energy-windowed flood acquisitions.

There is expected inherent statistical variability across multiple acquisitions, and therefore ten-count normalized bootstrap data sets for the listed energy windows were generated for all imaging experiments. The bootstrap resampling method can be useful to generate multiple resampled projections from the original data set when repeated measurements of an object are not practical, for example with a patient study. Each
bootstrap replicate is treated as an individual, independent data set, equally likely as the original to have occurred from the underlying source distribution.

A previously developed custom graphical user interface, LMPro, was used to perform all of the list-mode processing [111] (Figure 3.8). The code was modified for these experiments to enable accurate processing of the high-count cold-rod data. These modifications consisted of incorporating better memory management and implementing a more robust uniform subsampling algorithm based on the Mersenne Twister random number generator [177, 178].

Figure 3.8: Screenshot of the latest custom list-mode processing graphical user interface originally created by Caryl Brzymialkiewicz, based on modified code by Joshua Li (Gamma Medica-Ideas, Northridge, California, USA).
3.1.5 Time-Normalized Energy Window Analysis

In addition to the count normalized energy window comparisons, a time normalized energy window comparison of the data was also evaluated. The original full-spectral list mode data were post-processed to compare images acquired for the same amount of time with varying energy windows. This was achieved by extracting all counts within a specified energy window from the full-spectral file and therewith creating new projection files. Symmetrical ±3%, ±4%, ±8%, ±12%, and asymmetrical -12+6% energy windows were evaluated for both acquisition orbits and breast/torso setups.

3.1.6 Reconstruction and ROI Analysis

Images were reconstructed from list-mode-processed projection data using the OSEM algorithm with ray-tracing capability, with 8 subsets and 5 iterations. Attenuation and scatter correction were not applied. A 13-pixel region of interest (ROI) was drawn in the reconstructed images inside the lesions, and a 216-pixel ROI annulus was drawn circumferentially about both lesions in the breast background (Figure 3.9). ROIs were centered on the lesions’ calculated centroid location for the narrowest (±3%) energy window and thereafter remained fixed for measurements over multiple realizations and varying energy windows.
SNR was calculated as the difference in the mean pixel values of the lesion and breast background, divided by the standard deviation of the background (Equation 2.1). Lesion contrast was defined as the signal and background difference divided by the background signal (Equation 2.2).

3.2 Results & Discussion

3.2.1 Mini-Cold-Rod Phantom

The effects of using varying energy windows are readily apparent in the planar projection data of the mini-cold-rod phantom (Figure 3.10). Planar projection images show visibly increased signal outside of the rod-phantom border, due to the redistribution of
(scattered) events with larger-energy-windowed images’ having otherwise equivalent counts (Figure 3.10, TOP). Vertical line profiles through the planar projections confirm broadened tails at the edge of the phantom in the -12+6% energy window, compared to the -3+3% energy-windowed image (Figure 3.10, BOTTOM). This broadening is most likely due to an increase in scattered counts in the wider energy window.

Iteratively reconstructed images with OSEM also illustrate a qualitative and semi-quantitative difference between narrow- and wide-energy windows (Figure 3.11). Ring artifacts are due to non-uniformities in the pixilated camera. For the smallest ROR scan (Figure 3.11a), there is little difference in spatial resolution with different energy windows, and image contrast of the rods is nearly the same as well. This does not imply that, despite compressed-breast imaging’s having a smaller object-to-camera distance, using a tighter energy window (hence, fine-energy resolution) does not have a role, since these data are tomographic and hence do not have overlapping structures. This result does imply, however, that energy resolution may be less of a concern for tomography of smaller objects, like in small-animal imaging at 140 keV. Non-uniformity-induced ring artifacts are also somewhat more apparent in the tightest energy-windowed reconstructed data when compared to the largest energy window, given the same number of reconstructed counts per projection. Increasing the ROR from 4.4 cm to 7 cm results in comparable image-quality degradation for both energy-windowed data sets (Figure 3.11b). With the additional scatter medium along with larger ROR, the narrower energy-windowed data has better contrast and spatial resolution, as seen both in the images and line profiles through the 3.9-mm rods (Figure 3.11c). This is a clear validation of earlier work in PET [170].
Figure 3.10: (TOP) Planar projection images post-processed using varying energy windows from the mini-cold-rod phantom scans in air with an ROR of 7cm (see Figure 3.2). Each projection image contains ~55,000 counts. Note the increased signal apparently emanating from outside the physical phantom border of the phantom (arrow) in the -12+6% energy window image, most likely due to scattered counts. (BOTTOM) Vertical line profiles, plotted on a logarithmic scale through the planar projections, more clearly highlight the difference in the ‘tails’ of the profiles.
Figure 3.11a: OSEM reconstructed mini-cold-rod image data with the rods in air at the smallest (4.4-cm) ROR. 10th iteration shown with 8 summed slices and an absolute grayscale for both images. Identical line profiles were drawn through the second-largest (3.9-mm) rods in the images. (CONTINUED)
Figure 3.11b: (CONTINUED) Reconstructed images of the mini-cold-rods in air with a wider, 7-cm ROR. Identical line profiles were drawn through the second-largest (3.9-mm) rods in the images as indicated in Figure 3.11a. (CONTINUED)
Figure 3.11c: (CONTINUED) Reconstructed images of the mini-cold-rods in water with a 7-cm ROR. Identical line profiles were drawn through the second-largest (3.9-mm) rods in the images as indicated in Figure 3.11a. Note the moderately improved contrast and spatial resolution using a narrower energy window for cold rods in the water-filled cylinder.
3.2.2 Isolated Breast Phantom

Both lesions are clearly visible in the reconstructed images, as expected with a relatively large 1.8 mL lesion size and 8:1 lesion:background activity ratio (Figure 3.12). Qualitative differences in image quality are subtle, with only moderate differences in line profiles through both lesions. Quantitatively, however, narrower energy windows lead generally to an increased contrast compared to a wider window for both TPB (Figure 3.13) and PROJSINE (Figure 3.14). Variability in contrast increases with each increasing OSEM reconstruction iteration, while variability in SNR decreases. Mean SNR values are about the same for both energy windows, as would be expected for equal-noise distributions. The larger error bars in the chest lesions are likely influenced by reconstruction artifacts due to incomplete sampling near the chest wall.

Over the ten resampled realizations, there is no overlap in the means of the ±3% and -12+6% windows, and minor overlap in standard deviations. The smallest energy window does not always have the best SNR or contrast, seen for example in the insufficiently sampled chest lesion for the TPB orbit (Figure 3.13) and the central lesion for PROJSINE (Figure 3.14, RIGHT). By windowing too tightly, true events may be discarded unnecessarily. There is also less room for error when defining a narrow energy window about the photopeak if the system is not correctly calibrated (e.g., due to energy spectral shifts caused by variability in the imaging equipment). These findings suggest that an energy window slightly larger than the mean intrinsic energy resolution of the camera (~6.7% FWHM at 140keV) will yield optimal lesion contrast. Whether these results would yield differences in observer studies remains to be explicitly investigated.
Figure 3.12: OSEM reconstructed isolated-breast-phantom image data with line profiles through both lesions at two energy windows for two trajectories. Sagittal slices of the second iteration are shown with no smoothing or other correction. MIPs are displayed in order to show both lesions simultaneously.
Figure 3.13: SNR vs. contrast mean-value plots with corresponding error bars for ten realizations of TPB isolated breast phantom data over five reconstruction iterations (numbered for ±3% energy window) and indicated energy windows. Error bars represent one standard deviation between realizations, calculated for each reconstruction iteration. Chest lesion data are in the lower-left corner and central-lesion data are in the upper right.
Figure 3.14: SNR vs. contrast mean-value plots with corresponding error bars for ten realizations of PROJSINE (LEFT) chest-lesion and (RIGHT) central-lesion isolated-breast-phantom data over five reconstruction iterations (numbered) and indicated energy windows. Error bars represent one standard deviation between realizations, calculated for each reconstruction iteration.
Figure 3.15: Photopeak normalized, summed energy spectra for isolated-breast-phantom data compared to breast-phantom-with-filled-torso-phantom data. The threshold at 60 keV is set in the system hardware. Scattered events due to the addition of the torso are clearly seen.

### 3.2.3 Breast Phantom with Filled-Torso Background

The added background contamination from the heart and liver results in a proportionally larger amount of scattered counts in the energy spectra and a correspondingly slightly wider photopeak (Figure 3.15). In the reconstructed images, streak artifacts and additional enhancing regions appear posterior to the breast, due to the cardiac-hepatic activity included in the torso phantom (Figure 3.16). Streaking artifacts are more prominent in the wider windowed TPB images, especially in the posterior-breast (chest-wall) region, where there are a higher number of scattered counts from the torso region.
Figure 3.16: OSEM-reconstructed breast-with-filled-torso-phantom image data with line profiles through both lesions. Sagittal slices of the second iteration are shown with no smoothing or attenuation correction.
PROJSINE line profiles for the 18% window through both lesions also reveal lower relative contrast and increased noise compared to the 6%-energy-windowed images.

Similar to the isolated-breast-phantom data, SNR-vs.-contrast plots of the chest lesion (Figure 3.18) and central lesion (Figure 3.17) for both trajectories show a general improvement in contrast with narrower windows. These measurements can vary depending on ROI size and placement, but the overall trends remain consistent regardless of the acquisition trajectory or ROI metrics. These results reiterate that, although a narrow energy window is desirable to eliminate scattered radiation, losses in performance can appear once the window is below the intrinsic energy resolution of the system (in this case, below ~7%). More useful and true events outside of the energy window are then lost reducing primary signal. In the PROJSINE data, the ±4% energy window showed the highest general contrast and SNR, while the ±3% fell below the ±8% in the chest lesion for some iterations (Figure 3.17, RIGHT).

In summary, given equivalent noise levels, both experiments suggest a definite dependence on the energy window used to obtain the tomographic projections, with a tighter energy window providing increased contrasts up to a window width that is near the width of the intrinsic system energy resolution. SNRs remained relatively constant due to the normalization of counting statistics between energy windows. Further observer studies would be helpful to determine if increased contrast, at the potential cost of a drop in SNR, actually improves lesion detectability.
Figure 3.17: SNR vs. contrast mean value plots of the central lesion with filled-torso background over five reconstruction iterations (numbered) at different indicated energy windows with corresponding error bars for ten realizations of (LEFT) TPB and (RIGHT) PROJSINE.
Figure 3.18: SNR vs. contrast mean value plots of the chest lesion with filled-torso background over five reconstruction iterations (numbered) at different indicated energy windows with corresponding error bars for ten realizations of (LEFT) TPB and (RIGHT) PROJ SIN.
3.2.4 Time-Normalized Energy Window Analysis

To expand this study into a more operator-realistic perspective, comparisons of varying energy windows using a “time-normalized,” full-list-mode data set were compared as well. In these studies the scan time was held constant. As expected, the larger energy windows have moderately improved SNR due to the increased number of counts within the full-energy-windowed data set, and consequently reduced noise, for both TPB (Figure 3.19) and PROJSINE (Figure 3.20) trajectories. Note that the time-normalized parametric plots now represent a single SNR-and-contrast realization calculated using all counts within each window for each iteration, and they therefore no longer have error bars, which previously illustrated the variation over multiple boot-strapped realizations.

For both the TPB isolated-breast phantom (Figure 3.19, RIGHT) and the activity-filled torso (Figure 3.19, LEFT), the ±3% energy window displayed the highest contrast for the central lesion but suffered lower contrast and significantly lower SNR relative to the wider energy windows when measured for the chest lesion. The chest-wall region was undersampled with TPB polar tilt, leading to increased reconstruction artifacts and poorer attenuation and scatter cancellation. Poorer SNR also indicated again that windowing too tightly yields undesirable degradations in performance. The PROJSINE data were clumped more tightly together (Figure 3.20), due most likely to more complete sampling of the complete volume, yet followed a similar distribution, with narrow energy windows providing increased contrast. Here, the 8% and 12% wide windows consistently yielded higher contrasts at a smaller loss in SNR than the 6% window. While it is beyond the scope of this current study to determine whether contrast or SNR has more impact on observer detection,
Figure 3.19: SNR-vs.-contrast plots over five reconstruction iterations at the indicated photopeak window widths for time normalized (LEFT) TPB isolated-breast-phantom and (RIGHT) TPB breast-phantom-with-activity-filled -torso data. Chest-lesion data are in the lower-left region and central-lesion data are in the upper right (as indicated).
Figure 3.20: SNR vs. contrast plots over five reconstruction iterations at the indicated photopeak window widths for time normalized PROJSINE (LEFT COLUMN) isolated-breast-phantom and (RIGHT COLUMN) breast-phantom-with-activity-filled-torso data. The top row shows results from the chest lesion and the bottom row the central lesion.
these quantitative metrics provide insight into which acquisition and reconstruction characteristics could provide higher-quality images for future evaluation.

Figure 3.21 is a plot of only the second iteration of the scan-time-normalized data, in an attempt to analyze the effect of energy window width on SNR and contrast. For these studies the 6%-energy window maximized contrast for the central lesion; the 12%-energy window, however, provided a more balanced tradeoff between increasing SNR (average boost of over 10%) and maintaining high contrast (with only a minimal drop, except for the TPB central lesion) for both trajectories and experimental setups.

As a final characterization, Gaussian curves were fit to horizontal line profiles to measure the spatial FWHM and assess what effect, if any, changing energy windows may have had on image spatial resolution. Line profiles through the central lesion illustrate the increased signal with increased energy-window width, from the increased counts allowed into the image (Figure 3.22). After normalizing the line profiles, it was apparent that there was very little difference between the shapes of the lesion profiles, despite increased scatter content along with the wider energy windows. The 8% and 12% data had the narrowest FWHM measurements, but there was only a 6% difference between all the energy windows. These results fall in line with a previous study comparing the 3D modulation transfer function (MTF) for an 8% versus 6% energy-window width [179]. That study, in concordance with these measurements, showed that there was only a very slight improvement in the MTF using the smaller-energy-window width.
Figure 3.21 Comparison of (TOP) SNR and (BOTTOM) contrast versus energy window width for 2nd-iteration data for (LEFT COLUMN) isolated breast phantom and (RIGHT COLUMN) breast phantom with activity filled torso. Data from Figure 3.20 and Figure 3.19 were replotted to illustrate how contrast (or mean value) degrades, and SNR generally improves for increasing window widths.
Figure 3.22: (TOP) Time-normalized, PROJSINE individual sagittal slices of isolated-breast phantom for five energy-window widths. (MIDDLE) Original and (BOTTOM) normalized line profiles through the central 1.8-mL lesion (at arrow) in 2nd-iteration data. FWHM measurements show only minor difference between the energy windows.
3.3 Conclusions

A narrow-energy-resolution CZT camera was used in a variety of imaging situations for multiple, noise equivalent realizations of list-mode post-processed data to determine the effect on image quality of various energy window widths about the photopeak, as a surrogate for comparing multiple systems having poorer intrinsic energy resolution. Results with a mini frequency-resolution cold-rod phantom under various image degradative conditions illustrate qualitative and semi-quantitative relative improvement of contrast resolution with a narrower energy window, especially under high-scatter conditions (as would be the case when imaging women without breast compression). At a close ROR, energy resolution may be less of a concern for tomography of smaller objects. Using a wider energy window led to apparent counts outside the object in projection images. Quantitative comparisons with lesion and isolated-breast-phantom activity indicate higher contrasts with narrower energy windows. Quantitative comparisons of multiple realizations with lesion- and breast-and-torso-phantom background activity indicate overall better imaging performance with a 6-8% energy window as well.

While there was no test for statistical significance between the different windows, the general trends indicated that under the various measurement conditions and lesion locations, a window just slightly larger (8-12%) than the intrinsic energy resolution of the imaging system (6.7%) yielded the best performance metrics across all studies. In these studies, the 8% and 12% wide windows consistently yielded higher contrasts at a smaller loss in SNR than the 6% window. A future research area might be to dynamically select the energy window based on real-time analysis of the energy spectra (e.g. select a dynamic window with
a cutoff governed by the FWHM or FWTM of the photopeak). While it is beyond the scope of this current study to determine whether contrast or SNR is more important from an observer-detection perspective, these quantitative metrics provide insight into which acquisition and reconstruction characteristics could provide higher-quality images for future evaluation. A 12% energy window is recommended as general-purpose energy window to maintain high SNR and contrast. For studies where quantitative accuracy is of most importance, an 8% energy window may be more appropriate for increased scatter rejection. Overall, the use of narrower energy windows along with a camera having fine intrinsic energy resolution are highly recommended for uncompressed mammotomography imaging.
Chapter 4

Observer Detection Limits

With the implementation of a novel, 3D dedicated breast SPECT imaging system, it is necessary to evaluate and characterize system performance to provide substantial motivation for further clinical testing of this paradigm. Lesion detectability for varying lesion sizes and contrast ratios has previously been evaluated using quantitative SNR and contrast measurements (Chapters 2 and 3, [112, 113, 180]). However, an observer study is desirable to further characterize the system for an object-detection imaging task. This study builds on the limited observer study in Chapter 2 (§2.2), providing a more comprehensive and detailed look into inter- and intra-observer variability across a wide range of imaging conditions for dedicated SPECT breast imaging.

Contrast-detail observer studies are commonly used for comparing varying imaging systems and techniques and have been regularly used for nuclear medicine tomographic and planar imaging systems [65, 181]. The goal of this phantom-based study was to compare the multiple 3D SPECT imaging trajectories possible with our system, and to evaluate the minimum object size under a variety of “hot” and “cold” signal-to-background contrast ratios since early- and late-stage, and more- and less-aggressive cancers take up varying amounts of tracer compounds [105, 158]. Hot contrast ratios can be defined as having a greater accumulation of radioactivity than the background, while cold can be defined as the absence of radioactivity. Imaging hot objects is appropriate because most cancerous lesions
are more metabolically active than the surrounding normal tissue. Cold imaging is also appropriate because, as cancers become more advanced, they may contain necrotic cores that do not take up or concentrate radioactive tracers. Object size (detail) is also important as
early detection of smaller lesions potentially increases survival rates by allowing more and earlier patient treatment options.

4.1 Materials and Methods

4.1.1 Contrast-Detail Phantom Design

A custom geometric contrast-resolution phantom was developed that could be used for both positive (hot) and negative (cold) contrasts (Figure 4.1). The frame was designed using Autodesk Inventor software and then constructed using high-resolution 3D stereolithography (American Precision Prototyping, Tulsa, OK) using a water-resistant resin (DSM Somos® 11120, density ~1.12 g/cm³). Stereolithography is an additive manufacturing process using liquid photopolymer resin and a UV curing laser to build 3D parts one layer at a time. The 3D CAD model is exported as an STL file, which describes only the surface geometry of the 3D object. This model is read into the rapid prototyping machine and, layer by ~0.05 mm layer, the laser beam traces the part cross-section pattern on the surface of the liquid resin. Exposure to the UV laser light solidifies the pattern traced on the resin and adheres it to the layer below.

The 3 cm-long, thin-walled polytetrafluoroethylene (PTFE, density ~2.2 g/cm³) plastic tubes (Small Parts, Inc., Miami Lakes, FL) of varying inner diameters (6.2, 5.0, 4.0, 3.1, 2.3, and 1.1 mm with equal wall thicknesses of <0.25 mm), on a pitch of twice their inner diameter were arranged in six sectors. This 2X pitch positioning is due to the Nyquist sampling criterion for detectability. We considered building the entire tube phantom using solid stereolithography, but the minimum wall thickness was ~1 mm, so we instead opted for the thinner-walled PTFE tubes. The tubes were glued into place using a cyanoacrylate-
based adhesive (i.e. “super glue”), using modeling clay on some tube ends in order to seal leaks at the edges. For the three smallest-diameter sectors, two additional tubes were spaced at three times their inner diameter in order to evaluate if those rods would be visible at all, regardless of spacing them at the Nyquist sampling rate. Tubes were independently filled using equal concentrations of radioactivity and then sealed on their open ends with thin plastic tape.

Though loosely based on a commercially available mini-cold rod phantom we use regularly in the lab (model ECT/DLX-MP, Data Spectrum Corp., Hillsborough, NC), this newly developed phantom can be used for any combination of concentrations, both for hot- and cold-rod imaging, while also varying the background activity and fluid density composition. The thin wall of the tubes was intended to minimize scatter and partial-volume sampling effects due to minimal introduction of a cold region between the tube interstitial space and the remainder of the phantom, although the higher density of PTFE could play a degradative role as well. The axially symmetry of the rods allow for summing multiple planes to reduce image noise, but are admittedly less clinically realistic than the ellipsoidal lesion balloons used in Chapter 2.

4.1.2 Phantom Setup and Acquisition Parameters

The first set of contrast-detail imaging experiments was designed to optimally image the cylindrical geometric rod phantom using a close ROR of 4.3 cm and moderate scatter conditions. The phantom was placed in a 7.7 cm-inner-diameter cylinder, and the background volume was filled with 215 mL of water (Figure 4.2). The tubes were individually filled with aqueous $^{99m}$Tc-pertechnetate radioactivity with an absolute
Figure 4.2: Contrast-detail phantom in water-filled cylinder imaged using a simple circular scan at a close radius of rotation. Food coloring was added to the fluid inside the tubes for better visibility.

A concentration of 10 $\mu$Ci/mL, approximately five times the lesion uptake found in biodistribution data obtained via pharmaceutical uptake studies [105, 158]. The background activity concentration was varied by systematically adding additional activity, resulting in tube:background ratios of infinity (only water in background), 10:1, 5:1, 2.5:1, 0.4:1, 0.2:1, and 0.1:1 (with ~5% error caused by variations intrinsic to the dose calibrator). The varying contrast ratios in this study are modeled after clinical findings that $^{99m}$Tc-estamibi concentrates in breast tumors with a mean contrast ratio of 5.6:1 compared to the surrounding normal tissue, varying from 2.6:1 up to 8.7:1 [105],[158]
A vertical axis of rotation (VAOR), 360-degree circular acquisition orbit was used to acquire a total of 128 projections. Scan times were initially ~11 minutes (5 seconds per projection) and subsequently lengthened to account for radioactive decay. The initial count rate was ~300 counts per second (cps) for the 10:1 contrast ratio, thereafter increasing proportionally with the added background activity to ~2400 cps for the 0.1:1 contrast ratio. Exploiting the excellent energy resolution of the semi-conductor-based CZT gamma camera, and incorporating the lessons learned earlier about the most appropriate energy window for dedicated breast SPECT (Chapter 3), an 8% (+/- 4%) window about the 140 keV photopeak was used for this and all of the following studies.

In the second set of experiments, the contrast-detail phantom was removed from the cylinder and placed inside a non-uniformly shaped breast phantom [182], giving more clinically realistic attenuation and scatter characteristics (Figure 4.3). The dimensions of the breast phantom were approximately 7 x 17 x 14 cm (nipple-to-chest depth, medial-lateral width, superior-inferior height, respectively), which corresponds to the mean values measured in a human subject study at Duke (see §1.7, [183]). The breast phantom was only partially filled with 500 mL of water in order to avoid paralyzing the detector with the continually added background activity added to vary the concentration ratios, but sufficient to completely submerge the contrast-detail rod phantom. Scans were obtained using both a TPB and a complex 3D PROJSINE trajectory [114] (Table 4.1, Figure 1.9). Absolute activity was again 10 µCi/mL in the tubes, and activity was continually added to the background to generate the same contrast ratios as for the cylinder experiments. Scan times were initially ~11 minutes (5 seconds/projection over 128 projections) and then subsequently adjusted during the acquisition sequences to account for radioactive decay. The initial count rate was
~480 cps for the 10:1 contrast ratio, which was larger compared to the cylinder experiments due to the cumulative volume in the breast background.

Figure 4.3: The rod phantom submerged in 500 mL of water within a breast-shaped phantom. An inverted plastic cup, acrylic sheet, and tape were used to keep the phantom from floating.

Table 4.1: Parameters for Breast Experiment Acquisitions over a 360° Azimuthal range ($\theta$)

<table>
<thead>
<tr>
<th>Orbit</th>
<th>Num of Prjs.</th>
<th>Polar Tilt, $\phi$ (Range, min:max)</th>
<th>ROR (Range, min:max [cm])</th>
</tr>
</thead>
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<tr>
<td>VAOR</td>
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<td>0°</td>
<td>4.3</td>
</tr>
<tr>
<td>TPB</td>
<td>128</td>
<td>45°</td>
<td>6.3</td>
</tr>
<tr>
<td>PROJSINE</td>
<td>128</td>
<td>15-45°</td>
<td>3.3-7.6</td>
</tr>
</tbody>
</table>

During data acquisition, the expected emission counts from the tubes was kept constant for each contrast ratio by adjusting the scan times for radioactive decay, yielding an
estimated constant noise quality from the tubes in reconstructed images. The continually
added activity to the background, however, resulted in a greater number of overall acquired
counts and therefore yielded improved noise quality for the background. This was especially
true for the cold tube:background contrast ratios (0.4:1, 0.2:1, 0.1:1, which correspond to
1:2.5, 1:5, and 1:10, respectively). To account for this count-biased discrepancy in the
observer study, a separate set of count-normalized “high-noise” images was generated by
randomly down-sampling the breast projection data such that the background noise quality
was approximately uniform for each concentration ratio. The total targeted counts in each
down-sampled projection image were randomly determined using a Poisson distribution
with a mean based on the number of counts in each corresponding 10:1 concentration ratio
projection image. The rationale is that the background count rate should be near-constant,
and it’s the rod of interest whose count rate will vary.

8 reconstruction subsets and 5 iterations were used to reconstruct the data. The
reconstruction grid size was 160 x 160. For the breast phantom images, the reconstructed
volume was rotated in 3D slightly so that the tubes were vertical in the sagittal plane, and
therefore multiple slices could be combined to enhance image quality. This rotation
definitely incurs smoothing due to interpolation in the rotation and regridding of the data.

4.1.3 Initial Observer Study

Summed slice images were generated for each experiment set by summing planes
where rods where present (fourteen 2.5 mm-thick slices) and then smoothing the planar
image using the uniform smoothing filter in ImageJ, which replaced each pixel with the
average of its 3×3 neighborhood. The images were also rotated so that the largest diameter
rods were in the same position for both the cylinder and breast experiments for the observer study.

The resulting 2D images of the rods in the cylinder and breast phantom (Figure 4.4) were evaluated in random order, in a controlled environment by five independent medical physicists (all non-radiologists) and one inexperienced lay observer, who were each tasked with identifying the smallest distinguishable rods (details) for all concentrations, noise levels and experimental setups and acquisitions. The initial results (presented in [184]) concluded that the mean detectable size was \(~3.1\) mm at 10:1 ratio, degrading to \(~5.5\) mm with the 2.5:1 concentration ratio. Using paired Student t-tests as a metric, it was perhaps overconfidently concluded that there was little statistically significant difference (\(p<0.05\)) between cylinder vs. breast, simple vs. complex trajectories, or whether the rods appeared hot (10:1) or cold (1:10), indicating that data acquisition with the mammotomography system was quite robust. A more rigorous analysis, presented in the next section and published in Physics in Medicine and Biology [185], showed more subtlety in the details.

### 4.1.4 Follow-up Observer Study

After submitting the original results for peer review, one of the reviewers was concerned with the large variation between observers, and the fact that we had not addressed intra-observer variation or sample variation. To provide valid data, it was recommended that the observer study be repeated, replicating the images a number of times and averaging across the replications. Following the reviewer’s suggestions, we repeated the study and reprocessed the original data to improve image quality.
Figure 4.4: Reconstructed summed coronal-slice images for rod:background concentration ratios ranging from 10:1 down to 0.1:1 (effectively 1:10) for VAOR scans about the cylinder, and two trajectories about the breast phantom. Down-sampled reconstructions for the TPB orbit (only) are shown on the bottom row, where projection count densities were normalized to the 10:1 concentration case.
The original raw data were reconstructed again, this time implementing calculated attenuation correction ($\mu = 0.1545 \text{ cm}^{-1}$) and then additional post-processing with a 3D Hann filter with a cutoff of 1.4 cycles/mm, which is 0.7 times the Nyquist frequency of 2 cycles/mm. Originally, the data had no post-processing other than the simple 2D smoothing filter. The 3D filter improved the contiguous slice SPECT data considerably (Figure 4.5), so multi-slice image stacks were included into the new observer study along with the summed planar data. For the high-noise down-sampled data, the sub-sampling process was repeated twice for each method to average the error due to sample variation in the count-skimming process.
Please place an X in the appropriate numbered field on the spreadsheet for each sector where you can separate individual rods.

Figure 4.6: Instruction sheet used in limited observer study.
The resulting reprocessed summed slice and contiguous 14-slice SPECT image sets were evaluated in random order, in a controlled environment by five independent observers (four medical physicists and one nuclear medicine radiologist). The observers were again tasked with identifying the smallest distinguishable rods (details) for all concentrations, noise levels, experimental setups and acquisitions. The instruction sheet used to show observers the location and pattern of the rods prior to viewing the study is shown in Figure 4.6. Three training images were displayed prior to beginning the study (see ahead to Figure 4.8 and Figure 4.9 for representative images). One challenge for the reader was to determine whether the randomized images had hot (10:1, 5:1, or 2.5:1 ratios) or cold contrast (e.g. 0.4:1, 0.2:1, and 0.1:1 ratios). Ambient lighting remained low and the observers could not adjust the window or leveling during the study. Summed images were read three times in randomized presentation order to assess intra-observer variability. A combined total number of 145 summed slice images and stacks were viewed by each observer, summarized in Figure 4.7 (in comparison, only 30 images were viewed in the original study). The time for each observer ranged from 30-60 minutes depending on how quickly they read the images. For each test, results were averaged over the multiple readings.

We consulted with Dr. Huiman Barnhart, from the Duke Department of Biostatistics and Bioinformatics to analyze the data for statistical significance. Intra-observer variability was examined by computing the repeatability coefficient (RC) and intra-class correlation coefficient (ICC1) based on the one-way analysis of variance (ANOVA) model. The RC provides the difference expected for 95% of the contrasts between any two replicated readings. Inter-observer variability was examined by the intra-class correlation coefficient (ICC3) from the two-way ANOVA model with interaction [186]. The ICC3 value
Figure 4.7: Summary matrix of the 145 total image data included in the observer study.

describes the inter-observer agreement between the five observers based on their single readings, and it takes intra-observer variability into account. The resulting data were examined by plotting contrast against the average results for each experimental setup. If the reader could not see any rod at all, a value of 7.0 mm was assigned for these analyses. Depending on the best fit to the averaged data (over the multiple readings) from the five observers, linear or quadratic regression was used to model the data from the five observers. The linear lines or quadratic curves were compared between experimental setups by testing the equality of the coefficients from the linear or quadratic functions. Hot and cold contrast curves were analyzed separately. All statistical tests were computed using *SAS* (version 9.2) statistical analysis software, and a p-value less than or equal to 0.05 was considered to be statistically significant.
4.2 Results and Discussion

Contrast-detail analysis has known limitations as it is, by nature, subjective and can be susceptible to observer bias. The SKE setup represents the best-case scenario where visualization of the rods should be obvious to the casual observer. Since nuclear images are routinely filtered and smoothed in the clinic, a modest amount of smoothing was used, as described, on all image sets. This study did not account for false positives that may be expected to increase in high-noise SPECT images. Readers did not give confidence levels for their decisions as they would in a full ROC observer study. The following results provide a quantitative measure of observer variability in defining the detection limits, comparing varying orbit techniques possible with a fully-3D acquisition-positioning system as well as hot versus cold imaging for a dedicated breast imaging system.

4.2.1 Summed-Slice Images

Reconstructed images of low-noise $\infty:1$ and 1:10 rods illustrate the best-case examples of rod visualization for these experiments (Figure 4.8). Due to the vertical geometry and axial symmetry of the phantom, the vertical axis of rotation scan optimizes distance-dependent spatial resolution for the rods at all acquisition angles. The increased background volume of the breast phantom creates an additional and non-uniformly varying scatter medium about the rods, visually apparent in the reconstructed images (Figure 4.9). Contrast-detail observer study quantitative results demonstrate an expected trend that finer resolution is observed for higher contrasts (Figure 4.10). For the phantom in the cylinder using the VAOR trajectory, the mean observed detail ranges from $\sim$2.8 mm in the infinite:1 case, which degrades to $\sim$5.2 mm for the 2.5:1 setup. The inverse then occurs from $\sim$3.8 mm for
Figure 4.8: Reconstructed images (5th iteration, 8 subsets, 14 summed slices, calculated attenuation correction, post-reconstruction 3D Hann smoothing applied at 0.7*Nyquist to reduce noise) of the phantom in the cylinder for \( \propto:1 \) (LEFT) and 1:10 (RIGHT) concentration ratios. Rod sizes are indicated in mm. Note that three additional cold spots are seen at right (2 (at arrow tip), 6, and 10 o’clock) due to the 5 mm-diameter posts holding the tube alignment layers together.

The mean detectable rod size averaged over all the breast acquisitions was \( \sim 3.5 \) mm at the 10:1 concentration ratio, which degraded to \( \sim 5.5 \) mm at the 2.5:1 concentration ratio. For cold contrasts, the average rod detected was \( \sim 4.5 \) mm at 0.4:1, improving to \( \sim 3.5 \) mm at 0.1:1. Hot and cold contrasts of equivalent ratios (e.g. 5:1 vs. 0.2:1), generally agreed within \( \pm 0.75 \) mm of each other, except for the lowest contrast ratios where 0.4:1 was significantly better than 2.5:1. The mean system-detection limits observed in this study are approximately in-line with the calculated and previously measured spatial resolution for the SPECT system [113, 179]. The system in-plane spatial resolution is determined heavily by the distance-dependent collimator resolution as well as the intrinsic resolution of the camera, in this case the size of the individual 2.5 mm CZT detector elements.
Figure 4.9: Reconstructed summed coronal-slice images for rod:background concentration ratios ranging from 10:1 down to 0.1:1 (effectively 1:10) for VAOR scans about the cylinder, and two trajectories about the breast phantom. Down-sampled reconstructions for only the TPB orbit are shown on the bottom row, where projection count densities were normalized to the 10:1 concentration case.
Comparative test results for statistical significance are summarized in Tables 4.2a-4.3d. For cold-rod imaging, VAOR exhibited the best results of the three acquisition trajectories. For hot contrasts, TPB outperformed both VAOR and PROJSINE. Observer performance for the contrast-detail phantom in the non-uniformly shaped breast was overall close to that of the rod phantom in the uniform cylinder. These studies may have benefitted from the placement of the contrast-detail phantom near to the nipple, thus decreasing the camera ROR and improving resolution, in contrast to placement near the chest wall where TPB would have performed more poorly [179]. A larger breast, having increased scatter and
a necessarily larger imaging ROR, would also likely have degraded images and yielded poorer observer results.

Intra-observer variability results are summarized in Table 4.3, including RC, ICC1, and 95% confidence limits for the five observers. For example, if a repeatability coefficient is 0.7 mm, the expected difference between any two replicates is ±0.7 mm in 95% of experiments. For ICC values, 1.0 indicates perfect agreement and, generally, an ICC value of 0.8 or greater is considered very good agreement. VAOR scans in the cylinder had the lowest average repeatability coefficient, as might be expected. The intra-observer ICC1 values averaged between 0.8 and 0.9 for all of the methods except for the noisy down-sampled TPB data.

Inter-observer variability (ICC3) values are reported in Table 4.4. There was poorer agreement between observers for VAOR and TPB than for PROJSINE acquisition data. Generally, the complex PROJSINE orbit had the best overall agreement among and within observers for all of these studies.

<table>
<thead>
<tr>
<th>Methods</th>
<th>TPB vs. PROJSINE</th>
<th>VAOR vs. PROJSINE</th>
<th>TPB vs. VAOR</th>
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<tr>
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<td>.0001</td>
<td>.0074</td>
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### 4.2C: SUMMED VS. STACKS

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#### 4.2D: ORIGINAL VS. DOWN-SAMPLED

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<td>Hot</td>
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Table 4.3: Summary of Intra-observer Variability results

<table>
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<th>Method</th>
<th>Observer</th>
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<th>ICC1</th>
<th>95% Lower Confidence limit (LCL)</th>
<th>95% Upper Confidence Limit (UCL)</th>
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Table 4.4: Summary of Inter-observer Variability results

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<td>TPB</td>
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<td>Down-sampled TPB</td>
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</table>

4.2.2 Contiguous-Slice Stacks

Contiguous, 14-slice stacks of the same data were also included in the study to investigate any perceived differences compared to viewing the reduced-noise summed slices alone (Figure 4.11). The resulting curves in Figure 4.12 follow the same general trends as the summed-slice data, but with an apparent degradation in observed detail of up to ~1 mm for the cold-rod images, as well as a slight improvement for the higher (10:1, inf:1) hot-rod contrasts. Notably, for the infinite:1 ratio, the average reader values were 2.2 mm for multi-slice images, versus 2.8 mm for the summed images. Readers appeared more able to separate the 2.2 mm rods when scrolling through multiple slices, which may have blurred together when the slices were summed due to inter-slice misalignment in the rods.

Linear regression of the three methods indicate that for contiguous-slice stacks, the TPB acquisition method yielded the best results for cold contrasts but no significant difference between TPB and VAOR scans for positive contrasts (Table 4.2b). When testing for statistical significance between summed versus stacked data, observers saw significantly smaller objects for summed data for PROJSINE and VAOR, but no significant difference for TPB for cold-contrast ratios (Table 4.2c). Conversely, for hot-contrast ratios there were no significant differences between summed images and slices for PROJSINE and VAOR.
Figure 4.11: Example contiguous slices of the reconstructed rod phantom for three concentrations (TOP) in water using VAOR (no background activity), and (MIDDLE and BOTTOM) in the breast using a TPB acquisition.
but there was a significant difference for TPB. For all of the breast phantom experimental conditions, the TPB acquisition method demonstrated significantly (p<0.05) superior observer results than for data acquired with PROJSINE. This is likely due to the fact that the TPB acquisition orbit contained many views at a closer proximity to the phantom, while PROJSINE moved farther from the rods due to variations in both polar angle and ROR (Table 4.1). One important caveat is that TPB demonstrated higher intra- and inter-observer variability compared to PROJSINE (Tables 4.3, 4.4). The PROJSINE trajectory has been shown to have more complete sampling throughout the breast volume compared with TPB [114], and the symmetry of the rods in the phantom should have yielded a consistent trend
in observer detection. With development of automated object contouring on the SPECT system (see Chapter 5, [183]), we would expect better and more uniform overall resolution through the object of interest. Such improvement can be inferred from the high (> 0.8) ICC3 value for the PROJSINE acquisitions (Table 4.4). The overall more constant performance of PROJSINE corroborates with the results of both the limited observer study in Chapter 2 and the energy window experiments in Chapter 3.

4.2.3 Down-sampled Images

Down-sampled data sets suffered from a lower number of total counts (Figure 4.13), and observer detection performance correspondingly degraded with decreasing contrast and increased noise. Figure 4.14 compares both contiguous and summed acquisition down-sampled data with the original data. As mentioned earlier, if the reader could not see any rod at all (an infrequent occurrence), an estimated value of 7.0 mm was assigned. Thus, values located above the dotted 6.2 mm line are estimates, indicating that some of the observers saw no rods at all under those conditions. An estimated value of 8.0 mm was also tested to assess the statistical sensitivity of the assigned value, with no substantial changes to the regression results in Tables 4.2a-d. For higher-noise data at low contrasts, further experiments are warranted to verify the true lower limit of detectability.

The gap between the full data and count-skimmed data is much wider for cold contrasts, because a greater number of counts were skimmed in order to normalize to the 10:1 contrast data. Count normalization additionally results in lower relative signal-to-noise ratios because, in the cold contrasts, counts are spread across the background instead of concentrating in the rods as they are in the positive contrasts. PROJSINE and TPB
acquisitions followed a similar trend. TPB was prone to larger observer variability for the high-noise data, demonstrated by the lowest repeatability coefficients and ICC values (Tables 4.3-4.4). Though a definite separation in mean values between original and high-noise data sets exists, the overall observer study results are still promising for clinical detection applications where detected count densities are more similar to the high-noise data.

Figure 4.13: Total counts in the original versus the down-sampled PROJSINE projection data. The down-sampled data were normalized to the number of counts at 10:1 for each individual projection.
Figure 4.14: Contrast-detail plot of means and standard deviations for (TOP) TPB and (BOTTOM) PROJSINE orbits for contiguous-slice and summed-slice images, original and high-noise down-sampled data. The upper limit of the phantom (6.2 mm) is indicated with a dotted line. No lesions were seen in the down-sampled slices at a 2.5 activity ratio.
4.3 Conclusions

The observer detection limits using a high-performance clinical imaging system for dedicated SPECT breast imaging were successfully evaluated with a newly designed and constructed contrast-detail phantom under various imaging conditions. The average detail in a moderately-sized 500 mL breast volume under relatively low-noise conditions at 10:1 activity concentration ratio was \(~3.4\) mm, degrading to \(~5.2\) mm at a 2.5:1 ratio. While far from the fine resolution of radiographic imaging techniques, the spatial resolution of the system is better than clinical SPECT and PET systems and comparable to other dedicated nuclear-medicine-based detectors [187]. Compact CZT-based pixilated cameras are recently commercially available with even smaller pixels than those used on our current camera. Decreasing pixel sizes results in a further drop in sensitivity and increase in noise, which could potentially also affect lesion visibility for low-contrast, low-count (high-noise) lesions. For example, More et al. found that a larger pixelated (3.2 mm) NaI(Tl) camera coupled with a high-resolution collimator was better suited for 2D breast imaging than a smaller, 1.4 mm pixilated NaI(Tl) camera [65]; this finding corroborates our previous similar conclusions with NaI(Tl)-based pixelated systems for 3D breast imaging between 2.0 and 1.3 mm pixel sizes [180]. Hruska et al. have used a high-resolution, 1.6 mm pixilated CZT gamma camera, but have increased their overall sensitivity by optimizing (reducing) collimator length as well as adding a second camera head imaging closer to the distal lesions of the first head [63, 121]; they are also only imaging in 2D, however. Thus it remains unclear if smaller pixels would benefit dedicated, fully-3D breast imaging. If noise could be normalized between 2D and 3D imaging, for example, then one of the main advantages of 3D imaging, then the inherently
increased signal contrast due to the removal of overlapping tissues still obtains. Additional advantages of fully-3D imaging include potential for quantification as well as localization for targeting.

Overall, these observer study results are promising, demonstrating the potential of detecting sub-centimeter objects of various biological uptake, a critical target for effective functional breast imaging. For improved accuracy, a larger sample set of images is needed to better characterize the limits of detectability for this system. More realistic, 3D spherical lesions should also be evaluated at various contrasts for a variety of breast sizes in a broader observer study, since there are some advantages in using the axially symmetric rods here. Summing multiple planes to reduce noise improved detectability by ~1 mm smaller object visualization compared to objects in smoothed-slice-stacks, except for the highest hot contrasts (>10:1), where multi-slice stacks yielded improved visualization of the smallest rods. The use of a low-pass 3D Hann (smoothing) filter remarkably improved the image quality of otherwise-noisy SPECT slices. Degrading spatial resolution correlated with the radius of rotation of the camera, highlighted, for example, by the observed finer resolution for TPB vs. PROJSINE scans, because TPB contained more views at a closer proximity to the phantom. PROJSINE data, however, had the most consistent combined intra- and inter-observer results, making it the best imaging approach for consistent results, including consistency with earlier results on energy dependence in 3D imaging (Chapter 3), and thus the acquisition trajectory that would be recommended for clinical imaging.
Chapter 5
Enhancing Spatial Resolution and Quantitative Accuracy in Clinical SPECT Imaging

The prototype dedicated SPECT-CT hybrid imaging system has shown promising results in initial characterization studies [4, 188, 189] (Chapters 2-4). Still, there are system improvements that can be made in order to make a large-scale clinical trial more feasible and effective. This chapter outlines several enhancements and optimizations made to the SPECT system. First, a prototype patient bed was designed for the dedicated breast SPECT system. Shortly thereafter, our first clinical patient study was carried out. Based on the results of this study, two major improvements to the SPECT system were identified: 1) to enhance and automate the SPECT subsystem with the ability to dynamically contour non-uniform breast shapes and sizes; and 2) to increase the SPECT system’s diagnostic power through the development of absolute quantification methods.

5.1 SPECT Patient Bed

The integration of a patient bed with the SPECT imaging system presented a significant engineering challenge. Ideally, the patient bed should be comfortable and allow views of the breast beyond the chest wall, while still preventing collision with the imaging equipment. The first patient bed was a curved radiolucent nuclear medicine imaging palette composed of a thin aluminum-walled shell with a foam core (Figure 5.1). Curved Plexiglass sheets were cut and added to the head section of the bed to support the patient’s raised arms. A thin lead lining was placed on the top surface of the bed, covered by foam and bed
Figure 5.1: Photographs of the raised independent SPECT subsystem underneath the original curved patient palette and positioning system.
sheeting. The bed was modified by making a large cut-out at the left superior edge for the patient’s pendant left breast. The bed was attached to a positioning system (model 830-058, Biodex Medical Systems, Shirley, NY) with five degrees of computerized displacement freedom (forward-back, left-right, up-down, roll, and pitch) [190]. This system allowed for flexible 3D positioning of the pendant breast and compensation of any bowing that might occur due to the weight of the patient [191]. With the hole cut to the side, the original bed design only allowed for imaging of the left breast. Another disadvantage was that with a moderately thick curved bed, the SPECT camera was restricted in how close it could be positioned relative to the patient’s chest wall. Imaging with the CT system was also impossible without the imaging instrument colliding into the bed. A separate patient bed was subsequently designed for the hybrid SPECT-CT system, as discussed in detail in §6.1.

An unforeseen consequence of adding the prototype patient positioning system was that even with the bed at its lowest vertical position, the SPECT system gantry platform was too short to allow the camera to reach the bottom surface of the bed. This configuration would have resulted in truncation of the posterior breast for VAOR orbits, and unnecessarily large RORs with corresponding spatial resolution loss for orbits incorporating polar tilt (e.g., PROJSINE and TPB). As a temporary solution prior to hybrid system integration and for the initial clinical SPECT study, the SPECT gantry base was raised 11 inches to restore full 3D camera positioning flexibility. The raised platform allowed for flexible placement of the bed to optimize the breast volume in the FOV for each SPECT orbit (Figure 5.1, TOP).
5.2 Dedicated SPECT Patient Study

The first IRB-consented SPECT patient volunteer was a 55yr-old, post-menopausal, 59kg woman with biopsy-confirmed adenocarcinoma in her left breast (Figure 5.2). Approximate nipple-to-chest and superior-to-inferior dimensions of her left breast (obtained from photographs with rulers) were ~15 cm and ~8 cm, respectively. She was injected with 17.8 mCi (660MBq) of $^{99m}$Tc-sestamibi.

The patient was first scanned using a 15-45° three-lobed PROJSINE orbit, followed by a TPB trajectory with 45° polar tilt over 128 projections. ROR contouring was implemented by manually measuring breast-to-camera distances at six different 3D positions and then using these values to linearly interpolate the other RORs around the breast. The average counts per projection were 1800 and 500 counts for the TPB and PROJSINE acquisitions, respectively. Iterative SPECT reconstruction parameters were 2 iterations, 8 subsets, a 150x150x100 reconstruction grid, and 2.5 mm³ voxel size. SPECT data were post-processed with a 3D Hann smoothing filter with a cutoff at 1.4 cycles/mm (0.7*Nyquist).

Reconstructed images from the dedicated SPECT study are shown in Figure 5.3. There was a clear signal-enhancing, ~2 cm diameter volume of tracer anterior to the chest wall, which corresponded to that seen in the contrast enhanced MRI scan performed earlier in the day. This lesion is only partially viewable in the PROJSINE images because the patient was positioned too high above the SPECT system, placing the lesion near the edge of the defined reconstruction volume [111]. The TPB trajectory allowed views well above the chest wall, but with the drawback of imaging out-of-breast activity that results in increased image artifacts.
Figure 5.2: IRB approved photographs of the first patient scan using the independent SPECT imaging system. Camera-breast separation distances were not optimal for the PROJSINE scan (LOWER RIGHT).
Figure 5.3: Reconstructed images of the patient volunteer’s breast acquired with PROJSINE and TPB trajectories. Images smoothed with a 3D Hann filter. Confirmed lesion just below the anterior chest wall is indicated by intersection of the green hash marks. The TPB orbit clearly imaged a greater volume of the breast, allowing greater conspicuity of the lesion, with the tradeoffs of increased artifacts due to cardiac and hepatic uptake of the tracer, as well as introducing the well-known conical distortion of the breast shape.

While out-of-field-background activity was partly reduced by use of the radio-opaque pre-prototype bed, direct views of the heart and liver resulted in streak artifacts and additional enhancing regions that appeared in the bottom left of the coronal view and upper left of the transverse view [192]. Shape distortions were partially due to the incomplete sampling of the TPB acquisition trajectory, which are consistent with our previously published results on breast phantoms [114]. In future clinical studies, better patient
positioning should allow more of the breast into the FOV for the PROJSINE orbit, which is otherwise known to have improved sampling characteristics.

5.3 Automated Dynamic Sensor-Guided SPECT Contouring

A key novelty of the dedicated breast SPECT imaging system is its ability to image the breast using unique 3D camera trajectories [112, 124, 125]. These 3D trajectories can be designed to maximize the imaged breast volume and minimize breast-detector separation, thus improving resolution and image quality in SPECT. Initial studies (Chapters 2-4) have involved rigid, geometric breast phantoms for which the trajectory could be exactly tailored to contour the breast. The first clinical SPECT study highlighted the time-consuming and user-dependent nature of manually calculating the ROR. The breast-to-camera ROR was often greater than 2-3 cm in the PROJSINE scan due to the linear interpolation between manual measurements. Defining the initial breast measurements for clinical scans was also stressful for the operator, while the nervous subject waited for the scan to commence. This lead to overly conservative ROR measurements and bed positioning, resulting in decreased resolution along with truncation of the breast in the PROJSINE scans (Figure 5.3, TOP). Manually calculated RORs are not rapidly adaptable to different breast shapes and sizes. A robust, fully automated solution to realize high resolution, routine human SPECT imaging given the vast array of breast shapes (see §1.7) in healthy and diseased women is needed. This section seeks to transition to a more efficient and robust automated contouring solution for routine patient SPECT imaging.

The primary design objective was a solution that would allow automatic close contouring of any breast size or shape, i.e., would keep the camera positioned approximately
1 cm away from breast at all projection angles during the scan. Like most engineering challenges, there is more than one solution to the problem. Reflected light, ultrasonic distance ranging, and video tracking methods were all considered, but they generally have poor accuracy and high divergence at close range. The limited available space on the SPECT-CT system also required that the sensor implementation be compact. Ultimately, a dual-layer “light curtain” optical barrier was chosen as the most straightforward and practical solution. A single optical barrier only reports that the barrier is compromised, without any knowledge of how close an object (e.g., breast surface) is. Having a second layer at a known small distance from the camera face provides information that the object has penetrated the first layer, and is therefore within some distance to the camera, but that it has or has-not penetrated the second, more proximal layer (Figure 5.4).

5.3.1 Dynamic Laser-Guided Contouring

Commercially available, low divergence, ribbon laser feedback sensors (Keyence, 3.5 cm wide lasers (model LV-51M) and detectors (LV-H300)) were obtained to implement this dual-layer light curtain design (Figure 5.5). The dual-layer light curtain design was successfully bench tested with the ribbon lasers, measuring a change in beam intensity even using clear breast phantoms (Figure 1.20). 3D computer models of the sensors were also generated to experiment with various sensor configurations before developing the appropriate mounting hardware (Figure 5.4). The upper layer consists of independent ribbon lasers that help identify the region on the camera face that has been penetrated (superior, medial, inferior), while the lower layer consists of a single, multiply reflected beam defining a virtual plane.
Figure 5.4: (TOP) CAD rendering of an automated breast surface contouring implementation using a dual-layer, low-divergence, ribbon laser feedback sensor system mounted along the edges of the SPECT camera. The upper sensor layer (shown in red) consists of three laser-detector pairs that identify the region on the camera face that has been penetrated, while the lower layer (shown in blue) consists of a single, multiply reflected beam defining a virtual plane. (BOTTOM) Top-down view of the SPECT camera with breast penetrating the upper optical sensor plane.
In both layers, a receiver senses the signal intensity drop when the path of the beam is interrupted. The relative location along the camera face, and distance to the camera face (within 1 or 0.5 cm), of the breast can be continuously monitored. Changes in ROR to keep the camera close can thus easily be made, in principle.

A working prototype of an autocontouring system was then assembled, beginning with the design of a circuit to power the sensor amplifiers (Figure 5.6) and to channel the output receiver voltages (feedback) into the analog-to-digital converter of the ESP7000 (Newport Corp., Irvine, CA) motion controller (Figure 5.7). The electronics and the amplifiers were housed in custom enclosures (Pac Tec, Concordville, PA). The data acquisition and motion control software was then modified to read in the digitized signals, and new algorithms were created to position the camera based on the feedback from the lasers. The major additions to the motion control DLL are included in Appendix B. A diagram of the major system components and data flow for the laser autocontouring system is shown in Figure 5.7.
Figure 5.6: Circuit diagram for the laser DC power (LEFT) and readout interface between the amplifiers and the Newport analog to digital converter (RIGHT).

Figure 5.7 Illustration of the laser contouring electronics and data flow. Sensors provide feedback to the acquisition software via the motion controller ADC, and the computer adjusts the ROR accordingly.
The camera radius can thereby be adjusted to keep the camera face as close to breast in a contoured trajectory.

For the initial prototype, a 2x2 array of transmitter-receiver laser pairs was mounted on a thin (6 mm) piece of acrylic plastic, effectively creating two virtual planes with independent posterior and anterior breast positional data in each plane (Figure 5.8, TOP). After bench-top tests, this plastic sheet was adhered to the face of the SPECT camera, allowing functional scans with little (11%) additional attenuation due to the sheet. Using the functional prototype, we were able to automatically contour the 700 mL urethane breast phantom with a PROJSINE 15-45° trajectory with no setup time besides centering the phantom in the FOV (Figure 5.8, BOTTOM). Trajectory repeatability for a fixed breast phantom was found to be very high, with only a few slight differences of less than 1 cm over multiple measurements. The phantom was tested in multiple arbitrary positions with respect to the SPECT camera to ensure the robustness of the system to contour different surfaces.

Compared to a manually defined ROR contour, the automated approach with the lasers kept the camera on average 0.9 cm (±0.8 cm) closer during the scan (Figure 5.9). The “jaggedness” of the contouring was due to two factors: 1) there was a small amount of lag after sending a stop signal to the ROR lab jack motor; and 2) there was a 1 cm distance between the upper and lower laser ribbon planes. When the first plane is interrupted, the camera ROR does not move until the second plane is broken, because the camera is in the
Figure 5.8: (TOP) Top-down view photograph of the prototype dual-layer ribbon laser contouring system attached to the face of the SPECT camera. (BOTTOM) Separate 35mm wide top-layer ribbon laser beams are seen on the compressible breast phantom skin, as the camera dynamically contours at a minimal radius of rotation.
desired safe zone. With the relatively large 1 cm gap between sensor layers, the ROR remains in the safe zone for 1-2 projections resulting in the “jagged” ROR contour. Note that this has a more significant effect when the camera is backing out (larger ROR) than moving in (smaller ROR), i.e., the path is more jagged as the ROR gradually increases (Figure 5.9). Decreasing the separation distance between sensor planes should result in a smoother and more accurate contour. Automated orbits both simplify and significantly expedite the overall SPECT imaging process (Table 5.1). Contoured acquisition times take slightly increased due to longer gantry motion times resulting from: 1) the increased range of ROR motion, and 2) the ROR motor’s waiting for the sensors to be tripped instead of immediately moving to a preprogrammed position. Increasing the physical speed of the ROR jack motor, and incorporating smarter software algorithms to “anticipate” the next ROR position, could potentially compensate for sensor delays. For example, a prediction of the next ROR position could be made using basic assumptions of breast shapes (§1.7), positional information from the upper sensor plane, and the current polar tilt of the system; thus, initiation of immediate ROR motion between acquisition steps is feasible. Feedback from the sensors would then correct for any estimation errors. The elimination of manual orbit setup time will more than make up for the minimally increased scan time of automated contouring.

Table 5.1: Effect of Automated Contouring on Total Imaging Time

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<td>11 min</td>
<td>17-19 min</td>
</tr>
<tr>
<td><strong>With Lasers</strong></td>
<td>0 min</td>
<td>11-13 min</td>
<td>11-13 min</td>
</tr>
</tbody>
</table>
Figure 5.9: Radii-of-rotation in cm increments as a function of azimuthal position moving clockwise from 0 to 360°, for SPECT 3-lobed PROJSINE trajectories about a 700 mL breast phantom. Laser-guided contouring (solid line) kept the camera on average 0.9 cm (±0.8 cm) closer to the breast during the scan, compared to the manually contoured orbit (dashed line).

After prototype testing, a more compact, vertically mounted laser hardware implementation was designed and constructed in an effort to reduce obstruction of the protruding sensors and decrease the distance between the light curtain layers. The hardware was first conceptualized using 3D computed-aided design software (*Autodesk Inventor Professional*) (Figure 5.4). All of the fabrication was completed in the newly opened Duke student
machine shop. The majority of the laser and mirror mounting hardware were manufactured from acrylic using a computer-guided Universal Laser System. Aluminum braces to mount the lasers to the system and housings for the electronics were fabricated on a milling machine. Front surface reflecting mirrors (Edmund Scientific, Tonawanda, NY) were cut by hand and adhered to the acrylic. The assembled hardware was tested on the bench-top and then, after several iterations, secured to the SPECT camera (Figure 5.10 - Figure 5.11). In this design, the height of the mirrors can easily be adjusted to change the desired patient-camera separation distance.

Overall, a working prototype autocontouring system using the commercially available laser ribbon sensors was successfully implemented. While functional, the vertical ribbon laser design had several drawbacks that made it less than optimal. First, the three 35 mm ribbon laser beams comprising the top layer did not provide complete coverage for the 16 x 20 cm detector face, leaving the gaps seen in Figure 5.11. In initial tests, these gaps did not pose an issue. The largest diameter of the breast is generally near the upper half of the camera, so these gaps could potentially be minimized by arranging the sensors closer together near the top of the camera. Using more mirrors for reflection or diverging optical lenses to increase the width of the laser beams could also solve this limitation.

The second drawback with the prototype laser system was that the reflecting mirror mounts were difficult to keep aligned and thicker than desirable. The lasers and receivers were oriented vertically on the side of the camera, in order to save space and to allow adjustment of the separation width between the top and bottom light curtain planes. In a tradeoff between rigidity and size, the extra thickness (5-6mm) of the acrylic mirror mounts
Figure 5.10: (TOP) Clear acrylic vertical laser supports with laser engraved lab logos. (BOTTOM LEFT) The height of the mirrors can be adjusted to vary the separation between the camera and breast. (BOTTOM RIGHT) A custom housing encasing the amplifiers is mounted at the bottom of the camera, providing numerical beam intensity read-out.
Figure 5.11: (TOP) Side view of the breast penetrating both layers of the 35 mm wide ribbon laser beams. (BOTTOM) Top-down photo of the finished prototype autocontouring system, with anthropomorphic breast penetrating both planes of lasers. (cf. Figure 5.8).

unfortunately negated the space saved. These difficulties could again be solved with a more sophisticated mechanical mounting design using thinner and stiffer materials. However, an overall simpler optical method was implemented instead, as discussed in the next subsection.
5.3.2 Infrared Sensor Contouring

5.3.2.1 Device design

The difficulties in building a robust mirror alignment system motivated the design of an alternative contouring solution. Commercial whole-body SPECT systems have also
implemented contouring systems on the face of their gamma cameras. *Siemens*, for example, uses infrared (IR) dual-layer light curtains, i.e. rows of infrared transmitters and receivers that form two virtual planes (Figure 5.12). Commercially available IR light curtain safety products were investigated before the ribbon lasers were designed and implemented, but there were no models compact enough for our SPECT camera. Difficulty in the lasers’ implementation prompted a reinvestigation of the LED-based light curtains, including a custom design of the circuitry to power and readout the sensors.

A dozen 3 mm diameter infrared (940 nm peak wavelength) LEDs (model LTE-4206, *Lite-On*) with mechanically and spectrally matched phototransistors (model LTR-4206E, *Lite-On*) were obtained for bench-top testing. These inexpensive LEDs were selected due to their relatively narrow ±10° illumination angle (Figure 5.13, LEFT), ideal for avoiding cross-illumination between phototransistors along and between planes. LEDs with even narrower illumination angles are available at a significantly higher cost, but the LTE-4206s,
coupled with moderate collimation (~4 mm hole length), proved sufficient to the task (Figure 5.14).

The IR autocontouring design was based on the same dual-layer light curtain concept as with the lasers, though replacing the lasers with IR emitter-sensor hardware. The transmitter LEDs were soldered into serial sets of three to lower the number of resistors needed and to normalize their relative brightness (Figure 5.13, RIGHT). Fifteen LEDs (5 sets of 3) make up each of the dual layers for a total of 30 LEDs. The phototransistor detectors were also soldered in series, initially also in matching sets of three, for a total of 30 phototransistors.

The complete IR circuit is shown in Figure 5.15. Light sensitive silicon phototransistors operate similarly to standard bipolar transistors, but the detected light drives the input to the transistor base. Light photons generate electrons in the base-collector junction, resulting in a rise in current proportional to the amount of light received until it reaches saturation. This is nearly identical to the operation of the gamma ray sensitive semiconductor CZT SPECT camera, though for visible light. A quad voltage comparator (model LM339N, *Fairchild Semiconductor*) is used to detect the change in voltage across the sensors, which indicates that a beam has been blocked. In empirical tests, a comparative voltage set at ~60% of the DC voltage (5V) provided a good crossover point. A potentiometer could have been substituted for the 6.8 kΩ (‘6.8K’) resistors to make the crossover point variable, but a set hard-wired approach was more desirable for this implementation. The 33 kΩ (‘33K’) resistors determine the sensitivity of the phototransistors. Selecting a higher value resistor increases sensitivity if needed, for example if the dimensions of the collimator decreased.
In this straightforward design, the IR transmitters are continually on. Serially pulsing the LEDs reduce IR crosstalk within and between layers, essentially improving the spatial resolution of the sensors, but this approach was not implemented here. It was found in initial tests of the IR autocontouring system on the SPECT camera that sensors at the top of the camera (posterior breast) were generally engaged more than the anterior sensors.
Figure 5.15: Circuit diagram for the IR sensor assembly with clusters of LEDs indicated to illustrate how the light curtain was divided up into regions along the camera face.
The phototransistor detectors were thus rearranged from equal serial groups of three into groups of 2, 3, 3, 3, and 4 detectors from posterior to anterior, respectively, as shown in Figure 5.15 and Figure 5.17. This arrangement allowed use of the same circuitry with 10 signal outputs, but with optimized relative sensor position. The more frequently used breast-posterior phototransistor pairs have increased sensor resolution and response time, but the less frequently used breast-anterior quad grouping still adequately functions if any of the sensors are blocked.

Mounting hardware to support, align, and collimate the transmitters and receivers was milled out of wood (solid poplar) for ease of machining (Figure 5.14 and Figure 5.16, BOTTOM). The collimator holes were chosen to match the 3 mm diameter of the photodiodes and the hole length was initially 8 mm (~2x the length of the phototransistors). This was shortened to 4 mm to allow for the LED leads to be enclosed completely in the backside of the sensor housing. Both hole lengths were efficient in empirical tests, but further optimization of collimator hole length and diameter may be desirable. The two optical layers are centered on a 5 mm pitch, with a 2.5 mm gap between the 3 mm layers. In future designs, 3-5 mm spacing between the light curtain layers may be more optimal to avoid the breast’s immediately tripping both layers, while avoiding the jagged contouring seen with a 10 mm layer separation with the initial laser prototype (Figure 5.9). The sensors on the top and bottom layers are laterally offset 3 mm from each other in an additional effort to avoid crosstalk between the top and bottom layers.

The individual sensors are linearly spaced 12 mm apart to give full coverage across the camera face (Figure 5.13, Figure 5.17). An acrylic back plate, with an additional coating of paint to block out light, covers the back end of the sensors and wiring. The back plate is
Figure 5.16: Photographs of the SPECT-CT system with IR sensors mounted along the edge of the SPECT camera. In their current optimized height, the sensor assembly extends ~1.5 cm above the face of the camera and can be adjusted 1.5 cm in either direction (e.g., flush with the SPECT camera face when not in use).
Figure 5.17: (TOP) 30 IR LEDs mounted on the edge of the SPECT camera create two light curtain planes for dynamic breast contouring, photographed with an IR-sensitive digital camera. (MIDDLE) X-ray projection image of the phototransistor detectors. (BOTTOM) A custom housing encasing the power and multiplexing circuitry provides visual feedback to the operator of the relative position of the breast to the camera face. Green and red LEDs indicate which sector of the upper and/or lower planes, respectively, has been interrupted.
positioned parallel to either side of the camera by two screws and an aluminum 90° edge, which in turn is firmly secured to the SPECT back plate using the existing bolts. The sensors can be positioned as high as 3 cm above the face of the camera, down to completely flush with the face of the gamma camera when not in use. A ruler (mm) is engraved into the back plates to enable accurate positioning. Ideally, the sensors are positioned with the central ray of the top plane at 1.0 cm above the camera face (with the top of the sensor array ~1.5 cm above the detector). For quick positioning reference, in this position, the bottoms of the sensor blocks are aligned with the collimator gap line on the camera (Figure 5.16, BOTTOM). A 1/8” thick red IR-transparent window covers the front of the collimators, mainly to block out dust, but additionally minimizing visible light that could potentially cause false positives in the phototransistors. An even thinner window may be desirable in the future to minimize unwanted divergence of the IR light. Each individual phototransistor also has a factory-supplied visible-light-reducing purple coating.

The ten outputs from the phototransistor detectors, as well as power and ground, feed to the electronics housing mounted at the base of the imaging system (Figure 5.17, BOTTOM, Figure 5.18). The 5 green LEDs and 5 red LEDs in the electronics control box correspond with the output signals from the upper and lower sensor layers respectively. When the IR sensors are aligned, with nothing in the FOV, the LEDs are all off. When IR light of a sensor band is blocked, the corresponding LEDs illuminate. This provides the operator visual feedback of the relative position of the camera as they’re positioning the patient. Because only 6 of the 8 ADC inputs on the ESP7000 are currently functioning, only the top 2 (posterior) signals are read out directly to the ESP7000. The remaining 8 are multiplexed together using an 8-input 4-output NAND chip (model CD74HCT30E, Texas
Figure 5.18: Photographs of (TOP) the backside and (BOTTOM) front of the analog circuit board that controls the IR transmitters/receivers and feeds the output back to the motion controller.
Instruments). This effectively provides three positional information bands, increasing in width from posterior to anterior sides of the camera. Currently this positional information is not incorporated in the software, treating the inputs as a single virtual plane. A true multiplexor could easily be added to the circuit to read out all of the sensor signals in series if desired.

5.3.2.2 Imaging Experiments

To test the IR autocontouring system, we acquired images of an open breast phantom containing 700 mL of background activity and four lesions: two acrylic lesions (0.3 mL and 0.4 mL) and two balloon lesions filled with 0.15 mL and 1.7 mL (Figure 5.19). Four drops of blue coloring were added to the background volume to allow use of the IR sensors with the otherwise-light-transparent breast phantom (see ahead to Figure 5.23). Lesion volumes were determined by comparing the weight of the filled lesions with the empty lesions. The lesion: background ratio was approximately 10:1, with an absolute activity concentration of 48 μCi/mL in the lesions.

A three-lobed PROJSINE orbit with polar tilts ranging from 15-45° was used for all acquisitions (Figure 1.9). Projection data were initially acquired for an 11-13 minute total scan time (5 seconds plus variable gantry movement time for each of the 128 projections), with count rates of ~3 kcps per projection. Trajectories were first acquired without contouring at a constant 9.54 cm ROR (system maximum), then at a constant 6.07 cm ROR (1 cm from the breast surface at the top of the first lobe [polar tilt of 15°]). A manual ROR contour was then created by measuring three camera-breast distances at 15 degrees polar tilt and three measurements at 45 degrees polar tilt, and interpolating between these
5.3.2.3 Evaluation

For these experiments, IR-sensor-guided contouring kept the camera an average of 0.6 (± 0.6) cm closer to the breast during the scan compared to the manually contoured orbit, keeping the camera within 1 cm of breast for all projections. Overall the contour was much smoother than with the prototype laser system (Figure 5.9), due the smaller 2.5 mm separation gap between the upper and lower sensor planes.
Figure 5.20: Comparison of radii of rotation (cm) for 4 three-lobed PROJSINE orbits with the same 15-45° polar tilt ranges (TOP RIGHT) plotted over 360° about a breast phantom. IR-sensor-guided contouring kept the camera an average of 0.6 (±0.6 cm) closer to the breast during the scan compared to the manually contoured orbit. Jagged contours around 0 degrees azimuth were due to padding protruding through the bed that was accurately avoided with the use of the light curtain.
Figure 5.21: Horizontal line profiles through the 0.4 mL acrylic-walled lesion embedded in the 700 mL breast phantom. Images were acquired using PROJSINE trajectories of varying radii of rotation. FWHM measurements were calculated by fitting Gaussian curves to the line profiles. The IR sensors provide the closest contour resulting in the highest resolution (smallest FWHM). Profiles across the larger 1.8 mL lesion are shown later in Figure 5.26.

To characterize the improvement in resolution, horizontal line profiles were drawn through the 0.4 mL acrylic lesion (Figure 5.21). FWHM measurements were calculated using *Kaleidagraph* software by fitting Gaussian curves to the line profiles. The IR sensors clearly demonstrate the finest resolution (smallest FWHM). It should be noted that resolution recovery was not incorporated in the reconstruction, which might minimize the difference.
between the FWHM measurements. In this dynamically contoured acquisition, however, the
data is measured as accurately as it can be.

5.3.3 Dynamic Contouring Conclusions

A compact dynamic autocontouring system, which both simplifies and expedites the
overall SPECT imaging process, was successfully implemented. Automated trajectories were
tested and found again to be highly robust and improve overall image quality. The IR
autocontouring system was built at a fraction of the cost of the laser system and provided
the same functionality along with a more compact and reliable form factor. By decreasing
the separation distance between the light curtain layers, the contour was much smoother
with increasing RORs.

One suggested enhancement to the current autocontouring system is the addition of
a dedicated microcontroller with an onboard multichannel ADC (e.g. the inexpensive
Arduino microcontroller series) instead of relying on the ESP7000’s limited ADC. A
dedicated microcontroller could also be used to control the movement of the ROR lab jack,
allowing the autocontouring system to function independently or in parallel with the
acquisition software. This could additionally allow full-time automated collision avoidance
when moving the camera to its initial position, and would allow the freedom to acquire
continuous-movement SPECT acquisitions. Another area for improvement is accelerating
the ROR autocontouring algorithm by predicting the next ROR position, using locational
information from the sensors.
5.4 Development of Absolute Quantification Methods

The power of Nuclear Medicine molecular imaging is derived from direct, quantifiable correspondence between the signal in an image and the actual number of molecules being imaged. This allows in vivo quantification, without disturbing the biological system being interrogated. Quantification of absolute in vivo radiotracer uptake is not common for routine clinical SPECT imaging, but has been widely researched for many years [193-198]. Recently, quantification has become a topic of interest for other groups investigating single photon-based breast imaging [199-201]. Relative quantification comparing lesion signals in well-defined ROIs has been an effective evaluative tool for our early studies using the SPECT subsystem. Thus, the next goal is to develop a protocol for absolute quantification of SPECT measurements of the uptake of distributed radiopharmaceutical to arrive at absolute activity concentrations (μCi/mL) in tissue.

Updates in the last few years to the iterative reconstruction algorithms in the workhorse SPECT-MAP software, developed by Dr. James Bowsher, improve overall the ability to have quantitative accuracy. The enhanced SPECT-MAP algorithms integrate modeling of collimator and gamma camera efficiencies, as well as attenuation and scatter corrections during the reconstruction. With the proper implementation of these corrections as inputs to the reconstruction code, SPECT-MAP computes the reconstructed voxel values in μCi/mL, corresponding to the expected activity per unit volume.

Precise quantification is dependent on an accurate model of the geometric sensitivity of the collimator and detection efficiency of the CZT camera, as well as precise corrections for attenuation, scatter, and radionuclide decay. The implementation and optimization of
these corrections could be studied as a doctoral thesis in and of themselves; the primary goal here, however, is to investigate how accurately we can quantify absolute activity using established correction methods.

5.4.1 Absolute Quantification Methods

Figure 5.22 displays a flow chart of the preliminary absolute quantification protocol, which is described in more detail in the following sections.

5.4.1.1 Uniformity Correction

Before the pixilated CZT gamma camera can provide quantitative data, it must be properly and accurately calibrated. Indeed, this procedure is routinely performed on the MMI Lab camera system. A flood-field phantom, completely covering the face of the detector, was used to generate a uniformity correction table (UCT) for correction of the sensitivity uniformity. The UCT is dependent on the collimator, radionuclide energy, and energy window, thus a new UCT must be calculated for each collimator-isotope combination. For these experiments, 9.8 mCi of $^{99m}$Tc-pertechnetate was added to the flood phantom and imaged for a total of 10 M counts (equivalent to 2.2% statistical error per pixel). A follow-up quality control scan of 3 M counts (or 4.1% statistical error per pixel after calibration) with the newly calculated UCT was acquired for the 8% energy window. Generally if the quality control scan has a uniformity of <5%, the camera is considered to be within calibration by the manufacturer.

5.4.1.2 Center of Rotation Correction

The center of rotation (COR) correction determination is a critical parameter in the orbit file and reconstruction algorithm. An improperly defined COR will result in an
Figure 5.22: Flow chart of absolute SPECT quantification methods.
inaccurate count density distribution and ring-like blurring artifacts in the reconstructed image. With a single parallel head collimator and relatively large 2.5 mm pixels (compared to the CT detector), defining the COR is straightforward. A small balloon lesion (∼40 μL) containing 68 μCi of activity was used as a point source. A simple VAOR scan at a minimal ROR was acquired using 128 projection angles. We reconstructed the point source data for a range (∼1-3 mm) of COR parameters about the previously defined COR, and selected the COR that yielded a minimum FWHM of a horizontal line profile drawn through the source. Generally, the COR remains constant for the SPECT system unless the system has been significantly displaced.

5.4.1.3 Dose calibrator scaling coefficient

Despite accurate system modeling and corrections for estimated photon interactions, the resulting total quantified activity in a reconstructed image may still be off by a scaling factor $c$ from the reference dose calibrator. This reconstruction scaling coefficient, $c$, was measured in air using the same 68 μCi source scanned for the COR correction. Data were reconstructed to 20 iterations (using 8 subsets) to approach convergence. A large volume of interest (VOI) containing all events in the image was drawn, and total activity was determined by:

$$A_{\text{tot}} = V \sum_i (A/V)_i$$  \hspace{1cm} (5.1)

where $A_{\text{tot}}$ is the total activity (μCi) in the cumulative volume of interest, $V$ is the reconstructed voxel size (mL), and $(A/V)_i$ is the reconstructed value (μCi/mL) at each voxel $i$ within the VOI. For these experiments, using a 0.25 x 0.25 x 0.25 cm voxel size, $V$ was 0.0156 mL. The reconstruction scaling coefficient was then determined by calculating the
ratio of the measured activity concentration in the image to the dose calibrator measured activity, adjusting also for the known 10% offset between the dose calibrator in the lab and the “gold standard” radiopharmacy dose calibrator.

5.4.1.4 Acquisition parameters

Our preliminary absolute quantification protocol was evaluated using the same 700 mL phantom with four embedded lesions as described in §5.3.2 (Figure 5.19 and Figure 5.23). Two imaging trajectories were used: 1) a VAOR orbit to ensure complete sampling of a suspended volume, and 2) an autocontoured three-lobed PROJSINE with 15-45 degrees of polar tilt, which generally provides better coverage of the chest wall [114]. The breast was suspended completely within the FOV of camera at all projection angles for both trajectories. All acquisition times were 5 seconds per projection over 128 projections (~11 min). An 8% energy window was used for all acquisitions.

The phantom was first imaged with no background activity in the breast phantom (in air, Figure 5.19). Second, 700 mL of water was added as a scatter and attenuating medium. Four drops of blue food coloring were added so that the IR sensors could be used for dynamic ROR contouring (Figure 5.23). Finally, $^{99m}$Tc-activity was added to the background to create a lesion:background ratio of approximately 10 : 1, beginning with an absolute lesion activity concentration of 48 $\mu$Ci/mL.

5.4.1.5 Scatter Correction

Scatter correction was implemented using a stationary assumption dual-window technique [202], where a lower second energy window is used to estimate the scatter fraction in the photopeak, scaled by a proportionality constant, $k$. The scatter window was twice the
width of the 8% (~11 keV wide) photopeak window, ranging from 113 to 133 keV and directly abutting the lower side of the photopeak window. Kristy Perez from our lab had previously iteratively empirically determined an estimated scatter fraction proportionality $k = 0.16$ for an 8% energy window about 140 keV [203]. Briefly, this was measured by comparing planar and SPECT images of a line source in air and in water [202]. The 20 keV scatter window was created by resampling the list-mode projection data, after applying the appropriate uniformity correction for the scatter window. The resulting scatter distribution, i.e., the expected number of scattered photons at each detector bin, and the scaling coefficient $k$ are input parameters to the OSEM reconstruction algorithm described in detail in [204]. It should be noted that for these experiments the scatter map was neither filtered
nor smoothed, but other groups have reduced noise by additionally filtering the scatter map [205]. Given that scatter presents as a smoothly varying low frequency background, it is understandable how smoothing the scatter images could provide corrected data which is less influenced by individual noisy voxels.

5.4.1.6 Attenuation Correction

For these controlled phantom studies, attenuation correction was implemented using a uniform attenuation coefficient. A mask of the breast volume was created by thresholding images that were reconstructed to the first OSEM iteration (8 subsets, 2.5 mm$^3$ voxels, 150 x 150 x 150 grid). For these experiments, pixels greater than 0.8 $\mu$Ci/mL were assigned a constant attenuation coefficient at 140 keV for water, 0.1545 cm$^{-1}$; all other pixels were set to zero. This effectively creates a binary attenuation coefficient mask of the breast boundaries for every projection. Separate masks were created for each imaging trajectory. The breast with hot background attenuation mask was also used for the breast with cold background to properly define the breast volume.

5.4.1.7 Reconstruction Parameters

The calculated attenuation and scatter correction maps were included in the iterative reconstruction algorithm. Collimator septal penetration was also taken into account in the reconstruction by calculating the effective collimator hole length [120] (Equation 1.11). Gamma camera geometry, efficiencies of the detector, radiopharmaceutical branching ratio, and half-life were also included as input parameters (Table 5.2). 8 subsets were used and data were reconstructed up to 100 iterations. The reconstruction grid size was 150x150x150 voxels and the cubic voxel size was 0.0156 cm$^3$. 
Table 5.2: SPECT-MAP Reconstruction Input Parameters for Quantification Experiments

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.79</td>
<td>Distance from patient-side surface of collimator to image plane (cm)</td>
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<tr>
<td>0.88</td>
<td>Efficiency of (CZT) detector for this photon energy</td>
</tr>
<tr>
<td>2.475</td>
<td>(Effective) length of collimator hole (cm)</td>
</tr>
<tr>
<td>0.122</td>
<td>Diameter of collimator hole (cm)</td>
</tr>
<tr>
<td>0.02</td>
<td>Septal thickness (cm)</td>
</tr>
<tr>
<td>128</td>
<td>Number of projection angles</td>
</tr>
<tr>
<td>80</td>
<td>Number of slices</td>
</tr>
<tr>
<td>80</td>
<td>Number of bins per slice</td>
</tr>
<tr>
<td>0.25</td>
<td>Width of (square) projection bins (cm)</td>
</tr>
<tr>
<td>0.262</td>
<td>Dose calibrator scaling factor (see §5.4.1.3)</td>
</tr>
<tr>
<td>0.88</td>
<td>Isotope branching ratio</td>
</tr>
<tr>
<td>21636</td>
<td>Half-life of radiopharmaceutical (seconds)</td>
</tr>
<tr>
<td>0.16</td>
<td>$k$ coefficient for scatter images (+/- 4% energy window)</td>
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</table>

5.4.1.8 Quantitative Analysis

Quantification accuracy was first analyzed on a voxel-by-voxel basis in the reconstructed data by drawing line profiles through the lesions and comparing the activity values with the expected activity concentration per unit volume used to fill the lesions. All quantified data were (radioactive) decay corrected in order to compare the scans. Next, total lesion activity was quantified for each of the known lesion volumes using the reconstructed data with all corrections applied. VOIs were defined by manually drawing 2D ROIs on a slice-by-slice basis and then summing multiple ROIs to generate a VOI. Using the air scans as a guide, four slices were used for the smallest three lesion volumes and eight slices were used to evaluate the largest (1.7 mL) lesion. For the lesions in air and water (with no additional background activity), VOIs with a generous margin were used to capture all of the activity for the known volume. For the data with added background activity, quasi-ellipsoidal VOIs were manually drawn by combining multiple 2D ellipses that closely matched the lesion margins. All data were quantified at 20 iterations, using the lower noise 1st and 2nd
iterations to guide VOI placement for the smallest lesions. The lesions were evaluated for
the accuracy and bias associated with the estimation of total lesion activity and lesion
volume.

5.4.2 Absolute Quantification Results and Discussion

As iterative reconstruction is a nonlinear process, we investigated quantitative
accuracy versus the total number of iterations, as shown in Figure 5.24. For the phantom in
air, both trajectories yielded values that converged to within 0.2 μCi of each other, and well

![Figure 5.24: Plot of activity concentration as a function of reconstruction iteration for a VOI within the 0.4 mL lesion. The dose calibrator measured activity concentration was 48 μCi/mL (±5% accuracy). Convergence measurements are sensitive to VOI size and placement, but in general the data nears convergence by iteration 20.](image)

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within the dose calibrator margins of error. This result is consistent with a previous study that demonstrated that PROJSINE and VAOR trajectories provided comparable quantitative accuracy [203]. The mean activity concentration within the 0.4 mL simulated lesion phantom was sensitive to VOI placement, but in general converged by twenty iterations using subsets. For these controlled low-noise experiments, all data were analyzed at 20 reconstruction iterations (Figure 5.25), although the mean reconstructed values were already within 96% of the converged value after only two reconstruction iterations.

Horizontal line profiles through three averaged coronal slices demonstrate the relative scaling effects of attenuation and scatter corrections on the absolute activity
concentration values for the largest 1.7 mL lesion in air (Figure 5.26, TOP). With all corrections applied, the mean values at the center of the lesion in air were within ±5% of the measured dose calibrator value. The mean activity concentration values at the center of the lesion drop slightly (2-3 μCi/mL) with added scattering water medium, and a greater amount (5-8 μCi/mL) with added background activity (Figure 5.26, BOTTOM). The drop in voxel-by-voxel quantitative accuracy is plausibly due to both imperfections in the corrections for the physical processes (scatter and attenuation) and due to the inherent variability between multiple acquisitions. Overall the mean values of the 1.7 mL lesion for both acquisition trajectories were within 15-20% of the dose calibrator, in line with a previous study in our lab [203].

Partial volume effects, i.e., a voxel contains a mixture of the surrounding voxel values, also significantly affect the quantitative accuracy of the SPECT system. Partial volume effects result from the finite spatial resolution of the SPECT system and have been previously shown to cause a loss in counts for smaller objects [194, 206]. These effects are evident for the smaller lesions in these studies, as demonstrated by line profiles through the 0.4 mL lesion (Figure 5.27). Here, the maximum values through the center of the lesion are ~20 μCi/mL below the expected 48 μCi/mL concentration at which all lesions were filled. Without resolution and partial volume compensation, quantification has been shown to be unreliable for objects smaller than about three to four times the system FWHM [194]. Hence, for our system with 2.5 mm intrinsic resolution, accurate quantification of <1 cm diameter lesions will likely prove difficult. The use of resolution recovery in the reconstruction code and additional partial volume effect compensation methods may improve this accuracy for smaller lesions.
Figure 5.26: Horizontal line profiles measuring activity concentrations across the 1.7 mL lesion (TOP) imaged in air with and without corrections, and (BOTTOM) with all corrections applied in air, water, and added background activity. Three coronal slices were averaged to reduce noise. Thick shaded bar represents dose calibrator value of 48µCi/mL (+/- 5%).
Figure 5.27: Horizontal line profiles measuring activity concentrations across the 0.4 mL lesion imaged in air, water, and added background activity. Three coronal slices were averaged to reduce noise. The thick shaded bar represents dose calibrator value of 48$\mu$Ci/mL ($\pm$ 5%).

Total activity measurements with all corrections applied and using a large VOI (320-500 voxels) to encompass all events surrounding a lesion, provided consistently accurate results in air and in water-only for both VAOR (Figure 5.28A) and PROJSINE acquisitions (Figure 5.28B, Table 5.3). The average difference between quantified total activity and the mean dose calibrator was 6.9% $\pm$5.6% for VAOR and 3.5% $\pm$3.1% for PROJSINE in air and water with no background activity. The smallest lesion was the least accurate for both trajectories, as might be expected. While activity per unit volume did not scale correctly in the smaller lesions (Figure 5.27), total activity for the known volumes could still be accurately determined with a large VOI.
Figure 5.28A: Comparison of dose calibrator measurements versus quantified total activity measured in VOIs from reconstructed SPECT breast phantom data acquired using the VAOR orbit. Four embedded sphere-like phantoms were imaged first with no background medium (AIR), with 700mL of added fluid (WATER), then with activity added to the background (ACTIVITY). Error bars represent 5% variability in dose calibrator. (CONTINUED)
Figure 5.28B: (CONTINUED) Comparison of dose calibrator measurements versus quantified total activity measured in VOIs from reconstructed SPECT breast phantom data acquired using the PROJSINE orbit. Conditions are the same as in 5.28A.
Table 5.3: Comparison of Dose Calibrator Measurements versus Quantified Total Activity

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<tr>
<th>Background Composition</th>
<th>Trajectory</th>
<th>Lesion Vol. (mL)</th>
<th>Calibrated Activity (µCi)</th>
<th>Quantified Activity (µCi)</th>
<th>Error (voxels)</th>
<th>VOI size (mL)</th>
<th>VOI / Lesion Ratio</th>
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<tr>
<td>Air</td>
<td>PROJSINE</td>
<td>1.7</td>
<td>81.6</td>
<td>84.7</td>
<td>3.7%</td>
<td>496</td>
<td>7.8</td>
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<td>88.7</td>
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<td></td>
<td></td>
<td>0.3</td>
<td>14.4</td>
<td>12.9</td>
<td>10.6%</td>
<td>320</td>
<td>5.0</td>
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<td></td>
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<td>0.15</td>
<td>7.2</td>
<td>6.8</td>
<td>6.2%</td>
<td>320</td>
<td>5.0</td>
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<td>Activity</td>
<td>PROJSINE</td>
<td>1.7</td>
<td>81.6</td>
<td>79.5</td>
<td>2.6%</td>
<td>326</td>
<td>5.1</td>
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<td></td>
<td></td>
<td>0.4</td>
<td>19.2</td>
<td>19.7</td>
<td>2.7%</td>
<td>86</td>
<td>1.3</td>
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<tr>
<td></td>
<td></td>
<td>0.3</td>
<td>14.4</td>
<td>13.7</td>
<td>4.9%</td>
<td>112</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.15</td>
<td>7.2</td>
<td>7.7</td>
<td>6.7%</td>
<td>54</td>
<td>0.8</td>
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<td></td>
<td>VAOR</td>
<td>1.7</td>
<td>81.6</td>
<td>80.0</td>
<td>1.9%</td>
<td>463</td>
<td>7.2</td>
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<td></td>
<td></td>
<td>0.4</td>
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<td>17.4</td>
<td>9.4%</td>
<td>144</td>
<td>2.3</td>
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<td></td>
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<td>0.3</td>
<td>14.4</td>
<td>13.8</td>
<td>4.3%</td>
<td>120</td>
<td>1.9</td>
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<td></td>
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<td>0.15</td>
<td>7.2</td>
<td>7.4</td>
<td>2.6%</td>
<td>54</td>
<td>0.8</td>
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With added background activity, quantification is highly dependent on VOI placement and size. The manually drawn VOIs in this study are adequate for the ellipsoidal lesions in air and water, but not optimal when background activity is also present. The results in Figure 5.28a-b and Table 5.3 represent a “best-case” scenario for manually drawn ellipsoidal VOIs with prior knowledge of the lesion location. Figure 5.29 shows the variation in total activity versus VOIs of increasing size for the PROJSINE orbit. These results
indicate that a VOI of roughly 3-4 times the actual volume of the 1.7 mL was needed in
order to match the total measured activity from the dose calibrator. The results in Table 5.3
indicate that for the smaller lesions, a VOI 5-6 times the actual volume was needed largely
due to partial volume effects. Further investigation is warranted as to whether resolution and
partial volume corrections might be applied to the SPECT data in order to properly scale the
data such that the total activity per unit volume is more accurate.

Figure 5.29: Total activity as a function of VOI volume measured about the 1.7 mL lesion in
air, water, and background activity, shown with and without scatter and attenuation
corrections applied. The thick green bar represents the dose calibrator measurement of 81.6
μCi (+/- 5%).
5.4.3 Quantification Conclusions

The choice of VOI size and volume estimation is both important and sensitive for quantitative measurements. Thresholding the SPECT voxels with values above a discrete value (determined empirically based on measurements of image contrasts) to obtain the volume of the simulated breast lesion may be one feasible approach [207]. Thresholding, however, is difficult for lower contrast, high-noise lesions, as one might expect to see in clinical practice. These low contrast lesions could either be large lesions of low biological uptake, or smaller lesions with larger uptake whose signal is diminished by partial volume and other uncorrected effects. More investigation is warranted to refine VOI selection techniques presented in this feasibility study.

At the time of these experiments, the CT subsystem was under repair. The use of the CT system to define volumes and create attenuation masks could be essential for accurate patient quantification. Subsequent absolute radionuclide concentrations (μCi/mL) should be evaluated using a relatively large ROI surrounding the volume image of the source object to determine the total activity in the source object. This value will be divided by the estimated source volume, determined using the CT breast data obtained with the hybrid system. Measurements of volume obtained with CT are expected to be more accurate than those obtained from SPECT due to the intrinsic resolution differences, which are far better with CT. To avoid ambiguity of where the breast “ends” posteriorly, the CT images of the breast and anterior chest wall could potentially provide those anatomical limits.

In the future, image segmentation of the reconstructed CT images using thresholding on the quasi-monochromatic x-ray acquired data could be used to more accurately define the borders of different density components, and hence 3D volume, of the VOI. A very recent
update to the reconstruction algorithm incorporates resolution recovery modeling for the SPECT reconstructions, which may also improve the distribution accuracy of emission events. Quantification for patient images is also expected to be more accurate using scaled non-uniform attenuation maps derived from the reconstructed CT images. It is anticipated that CT images should increase quantitative accuracy especially in a clinical setting. These initial results using the SPECT system alone demonstrate both the weaknesses in quantifying radionuclide concentrations for small lesions due to partial volume effects, and the more promising results with on average 93-97% accuracy for low-noise, high-contrast lesions.

5.5 Conclusions

The first 3D dedicated breast SPECT patient study was successfully completed with promising results. A ~2 cm biopsy-confirmed lesion located close to the patient’s chest wall was clearly visible in the SPECT images. The TPB trajectory afforded the best lesion visualization for this patient and also allowed views well above the chest wall, but with significant streaking artifacts from cardiac and hepatic uptake. In future clinical studies, better patient positioning should allow more of the breast into the FOV for the 3D PROJSINE trajectory, which has improved sampling characteristics. The initial patient bed was adequate for left-breast imaging with the stand-alone SPECT subsystem, and a new patient palette was developed for imaging with the hybrid SPECT-CT system in order to avoid collisions with the CT tube and detector (see §6.1).

Two autocontouring hardware solutions for the SPECT system were successfully implemented. The first used visible ribbon lasers in a custom hardware arrangement. To overcome some optical hardware issues, a second, a more compact, less costly, and easy to
implement IR sensor-guided SPECT contouring solution was conceived, designed and built. This straightforward and effective dual-plane method for automated breast contouring was shown to both simplify and expedite the overall SPECT imaging process. Autocontouring orbits are highly robust and improve overall image quality. The implementation of automated ROR contouring should facilitate a smoother scanning process for ongoing clinical patient studies in the Duke Multi-Modality Imaging Laboratory.

Finally, absolute quantification capabilities were implemented using features in the SPECT-MAP reconstruction algorithm, allowing the calculation of \textit{in vivo} total lesion activity. Initial feasibility studies show promising results with total activity agreement well within 10\% of the dose calibrator values in controlled, low-noise experiments. Further work is needed to incorporate the added information from the CT imaging system, and to develop sophisticated VOI selection methods for quantification purposes. Absolute SPECT quantification methods could greatly enhance the diagnostic power of the hybrid imaging system.
Chapter 6

SPECT-CT System Integration

The current overall focus of the Duke Multi-Modality Imaging Laboratory (MMIL) is on the development of high-performance, dedicated breast imaging technology that benefits both patients and physicians. Towards that end, a goal of this thesis is to develop, evaluate, and optimize a dedicated 3D hybrid SPECT-CT breast imaging system. The hybrid system is simultaneously capable of functional emission and anatomical transmission imaging of a pendant, uncompressed breast and its associated axilla. This chapter details several of the engineering challenges and tradeoffs involved in integrating the independent SPECT and CT imaging subsystems onto a unified positioning gantry, as well as in integrating two separate acquisition procedures into a single imaging protocol. Specifically, limited-angle tomography acquisitions for both SPECT and CT, and modifications of the custom patient bed are investigated in an effort to increase the breast volume imaged within the FOV. Interleaved, near-simultaneous SPECT-CT acquisitions are also tested. Finally, the results of our initial hybrid patient imaging studies are presented.

6.1 Hybrid Patient Bed Design

The current patient bed (Figure 6.1) was custom designed by Dr. Dominic Crotty [133] in our lab to overcome many of the limitations of the pre-prototype curved SPECT patient palette (Figure 5.1) [208, 209]. The latest patient bed is comprised of 1/8” thick
Figure 6.1: Photograph of the custom steel patient palette designed for the prototype SPECT-CT system. Feet are at photograph bottom and the head is positioned at top of photo; the center hole is for the pendant breast. A thin layer of lead has since been added to the surface of the bed to reduce background contamination from the torso into the CT detector. The hole in the center is coupled to a removable, rigid octagonal insert.

stainless steel, along with a 1/8” thick lead lining adhered on the upper patient side for patient protection from scattered x-rays and for reducing emission contamination from the heart, liver, and other organs on the transmission images. Previous phantom studies showed that such a lead lining could effectively reduce the background torso contamination from the heart and liver in the reconstructed images for both modalities [171, 210]. The new bed is mounted on the same Biodex flexible positioning system used previously (§5.1). A central opening for a single pendant breast can thereby be optimally positioned over the common FOV of both imaging subsystems. The bed is angled at the waist in order to provide comfort and promote chest protrusion, in an attempt to increase the viewable breast volume hanging through the opening. During patient imaging, the head side of the bed (at top of
photograph) is additionally supported to minimize bed vibration and motion. The current design is not without challenges, as discussed later in the Chapter, but has successfully allowed for initial clinical testing of the SPECT-CT breast imaging system.

6.2 System Integration onto a Unified Imaging Gantry

A tremendous amount of collaborative work was put into planning, designing, assembling, and assuring a successful marriage of the independent SPECT and CT subsystems. While little personal credit can be taken for these efforts, the integration methods and results are briefly described in this subsection for completeness of the thesis.

The prototype SPECT-CT imaging system was first digitally modeled using computer aided design (CAD) software (Autodesk Inventor Professional, Autodesk Inc., San Rafael, CA). Each system component was modeled either by downloading component 3D CAD files directly from the manufacturer or by manually creating models using datasheets and manually measured dimensions. Using these models, a base plate was designed by Dr. Priti Madhav to secure the SPECT and CT systems onto a unified rotating gantry [188]. The ¼” aluminum base plate was designed to support the asymmetric load of both the SPECT and CT systems on the common gantry, with holes for multiple CT system positions to vary the source-to-image distance (SID) and source-to-object distance (SOD). The base plate was reinforced with metal bars to negate bowing from the weight of the individual SPECT and CT components, and it was then mounted on a high-load rotation stage (model RV350CCHL, Newport Corp., Irvine CA). The integrated CT system was initially mounted with its COR laterally offset by 5 cm to accommodate larger breast sizes [211], while the
Figure 6.2: The independent (TOP LEFT) SPECT system and (TOP RIGHT) CT system are combined onto a (BOTTOM) unified rotational gantry under a custom patient bed. In the prototype SPECT-CT gantry, the CT system sacrifices dynamic polar tilt abilities, though there are still several degrees of freedom for static positioning (blue arrows). The SPECT system retains all three dynamic degrees of motion (orange arrows).
integrated SPECT system was mounted to align its center with the COR of the rotation stage.

The independent SPECT and CT imaging systems were then integrated onto the common gantry as shown in Figure 6.2. Based on the results of a previous investigation into minimizing the cross-contamination of the emission image by the x-ray transmission source [212], the SPECT system was positioned directly orthogonally to the central x-ray axis of the integrated CT system. While the integrated SPECT system retained its full 3D positioning capability, the integrated CT system was constrained to simple circular orbits about the common system vertical axis of rotation at a fixed height with respect to the central ray.

Although the integrated system design had been precisely modeled prior to assembly, some of the system components were modified post-assembly in order to optimize imaging with the new constraints of the common gantry. One substantial modification required adjusting the height of the SPECT camera relative to the CT tube and detector height (Figure 6.3). In the initial hybrid design, the center of the SPECT camera's 16 x 20 cm² FOV was centered with the central ray of the CT cone beam at the system COR. It was so designed in an effort to align the iso-centers and FOVs for both systems as much as possible. In practice, this resulted in a maximum height of the SPECT camera being several centimeters lower than the top of the CT tube in its vertical position (0 degree polar tilt). While this orientation was perfectly adequate for imaging patients using a VAOR scan, it was less than optimal for the more complex PROJSINE and TPB that incorporate polar tilt. For these orbits, the patient bed should be positioned lower to keep a greater volume of the breast within the FOV at all angles and to contour the breast more closely. Thus, in the initial hybrid geometry, the obstacle of the directly coupled CT tube and detector prohibited
Figure 6.3: Lateral view of the SPECT subsystem with (TOP) no vertical shift and (BOTTOM) with the SPECT camera shifted up 5 cm (blue arrow). The static SPECT FOV (green) illustrates the increased breast volume gained by shifting the SPECT camera. Changing the ROR would only affect the distance from the breast, not the FOV.
bed positioning flexibility. The SPECT camera was therefore shifted vertically upward 5 cm (by adding additional holes to the existing aluminum camera back plate) (Figure 6.3).

The vertical shift of the SPECT system must be accounted for in the reconstruction algorithm. Fortunately, this was easily implemented by changing the third column in the SPECT orbit definition files from 0.0 to -5.0 (cm) for all projection angles. With the SPECT camera slightly higher than the CT system, the patient could now be flexibly positioned for
both CT and SPECT scans with the caveat that the bed height should be adjusted between acquisitions.

Other modifications, discussed in more detail by MMIL lab colleagues [133], included removing unnecessary degrees of freedom in the CT detector and tube gantry designs that were leading to source-detector misalignment and image reconstruction artifacts. After an SID of 60 cm had been determined to be optimal [133], a thick C-arm support was added to ensure accurate alignment of the CT source and detector and to reduce error due to motion and vibration (Figure 6.4).

6.3 Limited Angle Studies

A major engineering challenge with the integration of the SPECT-CT and patient bed was the difficulty of creating an imaging geometry where we could reliably image the entire breast volume (at least up to the chest wall). The physical limitation of the CT tube beneath the custom patient bed, combined with the dead edge at the top of the CT detector (i.e., between the focal spot and top of the housing), prevented a full 360 degree dual-modality scan while the bed was low enough for the breast to be fully in the cone-beam CT FOV (Figure 6.5, TOP).

To increase the volume of the breast in the FOV, the bed was lowered and projection images were acquired with a reduced number of angles (~294 degrees) about the
breast, in order to avoid colliding with the headrest of the patient (Figure 6.5, BOTTOM). The directly coupled SPECT subsystem is therefore also limited in motion if the scans are taken simultaneously in the common FOV. Alternatively, following a reduced angle CT scan, a separate SPECT scan can be made by positioning the top of the SPECT camera higher than the CT subsystem (as discussed in §6.2) and raising the bed to allow a 360° clearance of the CT tube and detector.

Reduced or limited angle tomography has been investigated for both emission and transmission breast imaging [38, 39, 74, 80, 214, 215]. These studies usually involve limited
circular imaging trajectories of less than 180°. The objective here is to examine the tradeoffs of removing a much smaller portion of the full 360° azimuthal imaging arc. The SPECT component of our system also introduces the question of how reduced angle tomography affects complex 3D imaging trajectories [113, 114].

6.3.1 Geometric Phantom Study

To characterize fundamental image degradations intrinsic to reduced angle tomography for both the SPECT and CT subsystems, a geometric mini-cold rod phantom (§3.1.1, Figure 3.1) was imaged with 9.5 mCi of ⁹⁹ᵐTc-pertechnetate in water filling the interstitial spaces. The phantom was suspended vertically with the mini-rods in the center of the camera’s FOV and parallel to the SPECT camera surface. Projection data were acquired on the independent SPECT subsystem using a simple 128 projection VAOR trajectory over 360°, acquired for 27 seconds per projection. This yielded a count rate of ~3.5 kcounts/sec or approximately 95k counts per projection (in a ±4% energy window). List-mode data from the full 360° acquisition were then post-processed by removing projections to simulate reduced angle acquisitions of 180°, 240°, and 300°. The list-mode projection data were also truncated such that the total number of counts over the entire acquisition remained the same for each angular acquisition sequence in an effort to make a normalized noise comparison of the various reduced angle trajectories. OSEM reconstructions were performed using a 2.5³ mm³ voxel size on a 150x150x150 matrix grid, using 8 subsets and 20 iterations.

For the reconstructed SPECT data, resolution is distance dependant. Even though the cold rods are theoretically fully sampled with 180° of rotation, objects far from the
camera will encounter degraded resolution. Hence, a 360° scan will have improved image resolution. This is semi-quantitatively seen in the SPECT mini-cold rod reconstructions and line profiles (Figure 6.6). The full 360° images have the highest contrast resolution. Resolution near the edge of the phantom progressively degrades with decreased angular sampling on that side, as seen in the profiles through the largest 4.7 mm rods. Prior to integration of the SPECT and CT subsystems, initial studies found that a centrally aligned CT cone beam (Figure 6.7, LEFT) can result in truncation of larger breasts (>15 cm in diameter). Therefore, a 5 cm offset cone beam (Figure 6.7, RIGHT) was implemented in order to acquire data for larger breast volumes while maintaining the air gap and magnification needed for scatter reduction [130, 211]. This lateral offset geometry posed a potential challenge when imaging with a reduced number of angles, due to undersampling of the breast.

To investigate whether reduced angle tomography is a viable option with an offset CT geometry, two scans were performed with the geometric phantom: one with the central ray of the cone beam intersecting the axis of rotation, and one with the central ray offset 5 cm laterally from the axis of rotation. Data were acquired over 360° in 1.5° increments. Limited angle CT realizations of 180°, 240°, and 300° were created by removing raw data projections, though unlike for SPECT, there were no other noise normalizations employed. CT data were reconstructed using the OSTR iterative algorithm [144]. Reconstructions were performed on 4x4 pixel binned image data (having a 0.508 mm voxel side size) on a 350x350x384 reconstruction grid, using 16 subsets, and 10 iterations.
Figure 6.6: OSEM reconstructed SPECT mini-cold rod images. Normalized line profiles are shown below, drawn identically through each of the largest 4.7mm rods as indicated.
Reconstructed CT slices of the mini-cold rod data where the central ray was aligned with the COR show minimal distortion even with 180° of projection data removed (Figure 6.8). The smallest sector of rods (1.1 mm) is still resolvable, along with minor cone-beam sampling artifacts that begin to appear on the left edge. Line profiles in the tangential and radial directions were nearly identical for all the limited angle and full scans.

Cone-beam data insufficiency and severe aliasing artifacts from the increasingly missing projections are much more visually pronounced when the central ray is laterally offset 5 cm from the COR (Figure 6.9). Undersampled or even unsampled regions imaged with <360° acquisition become radially blurred or completely truncated with insufficient limited angular sampling. With only 180° sampling, the image appears to have the classic “tuning fork” artifact due to insufficient sampling. Despite severe distortions of nearly half of the outer rim, the smallest rod sector was still resolvable, even with 180 degrees removed.
Figure 6.8: (LEFT) OSTR reconstructed single coronal slice CT cold rod data acquired with the central cone-beam ray aligned with the COR. Even with 180 degrees of information removed, the smallest sector of rods (1.1 mm) is still resolvable with the high contrast rod phantom with minor cone-beam sampling artifacts (at white arrow). Line profiles corresponding to the yellow hash marks are drawn (TOP RIGHT) tangentially through the smallest 1.1 mm rods and (BOTTOM RIGHT) radially through the largest 4.7 mm rods, with nearly identical results with full and limited angle scans.
Figure 6.9a: (LEFT) OSTR reconstructed CT cold rod data acquired with the central cone-beam ray offset 5 cm from the COR. With 60° of projection data removed in the offset cone-beam geometry, the 300° limited angle acquisition undersamples the object, resulting in significant artifacts in the reconstructed image. Line profiles corresponding to the yellow hash marks drawn (TOP RIGHT) tangentially through the smallest 1.1 mm rods and (BOTTOM RIGHT) radially through the largest 4.7 mm rods illustrate these aliasing artifacts. (Continued…)}
Figure 6.9b: (…Continued) (LEFT) OSTR reconstructed CT cold rod data acquired with the central cone-beam ray offset 5 cm from the COR. Limited angle acquisitions were simulated by removing an increasing number of projections from the full data, resulting in significant artifacts for the offset geometry as seen in both (LEFT) images and (RIGHT) line profiles drawn through the indicated yellow hash marks.
6.3.2 Breast Phantom with Homogeneous Background

This next experiment investigated reduced angle tomography in a more clinically relevant breast phantom, with the objective of analyzing how artifacts seen in geometric phantom are represented in a non-uniformly shaped breast phantom with embedded spherical lesions. A 900 mL, water-filled anthropomorphic breast phantom with three lesions (2.7 cm, 1.6 cm, and 0.8 cm outer diameter, with corresponding 2.3 mL, 1.0 mL, and 0.35 mL volumes) were acquired on the SPECT and CT sub-systems. Each lesion was filled with $^{99m}$Tc, with an absolute ratio of 20 $\mu$Ci/mL, and ~50 $\mu$L of a CT contrast agent, Gastrografin with iodine (I$_2$). The lesion:background concentration ratio was 10:1. SPECT projections were acquired using a three-lobed PROJSINE [111] with polar tilting range (sinusoidal amplitude) from 15 to 45° and CT images were acquired using a fixed 6.2° tilt. The breast was imaged without the physical challenges of the patient bed so that the phantom could be optimally placed in the center of the FOV for each subsystem. A ±4% energy window symmetric about the 140keV photo peak was used for the all of the SPECT projections in these studies. Total scan time was ~10 minutes. List-mode data from the full 360° acquisition were again count normalized between the scans and cropped to create SPECT acquisitions of 180°, 240°, and 300°. Correspondingly limited angle CT data sets were also created by removing the corresponding raw data projections. SPECT reconstruction parameters were set to 3 iterations, 8 subsets, and 2.5 mm$^3$ voxel size in a 150x150x150 reconstruction grid. CT reconstruction parameters were set to 5 iterations, 16 subsets, and 508 $\mu$m$^3$ voxel size in a 350x350x384 reconstruction grid.
SPECT resolution degradation is not immediately apparent in the profiles drawn across the high-contrast 2.3 mL lesion of the 900mL breast phantom with a uniform background (Figure 6.10). Relative background noise especially on the outer edge of the breast does, however, increase with fewer projections and decreased angular sampling. Both the cold-rod and breast data indicate that removing ~66° of SPECT azimuthal data does not significantly reduce image quality.

Reconstructed CT breast images again illustrate artifacts due to incomplete angular sampling (Figure 6.11). A distinct loss of attenuation value on the side where there was no data collected can be measured across the sagittal and coronal slices. In addition, the cylindrical artifacts in the center due to the offset cone beam and misalignment become more prominent with decreasing azimuthal acquisition angles.

It is evident from the images of the mini-cold-rod and breast phantoms that the 5 cm lateral CT offset geometry of the initial implementation of the hybrid system is increasingly penalized when using reduced angle tomography. A centrally aligned cone-beam geometry is better suited for reduced angle tomography; thus, the current hybrid system has been moved to this centered geometry. Disregarding issues of increased scatter, a larger centrally aligned detector may be a worthwhile solution to avoid truncation of larger breasts for limited angle CT.
Figure 6.10: OSEM reconstructed SPECT breast phantom coronal slices. 2nd iteration shown with 3 summed slices. Normalized line profiles are shown through the 2.3 mL lesion.
Figure 6.11: Reconstructed CT (TOP) sagittal slices and associated profile through indicated hash mark, and (BOTTOM) coronal slices. The complete 360° data are compared with reduced angle scans using 300°, 240°, and 180° of angular sampling. The central cone-beam ray was laterally offset by 5 cm, resulting in truncation artifacts seen in the areas where projection views were not collected.
6.3.3 Breast Phantom with Heterogeneous Background and Patient Bed

The next experiments investigate acquisition techniques in a simulated clinically realistic scenario, now including use of the custom rigid steel patient bed, with the overall goal of maximizing breast imaging volume in the hybrid system common FOV with minimal loss in image quality. Small, 1-2 cm randomly-sized acrylic pieces (see also §2.2.1.1) were added to the 900 mL filled breast to simulate non-uniform uptake in the breast background (particularly in the nipple region), and to add clinically realistic attenuation and scatter characteristics (Figure 6.12). Each lesion was again filled with $^{99m}$Tc, with an absolute ratio of 21.8 $\mu$Ci/mL and $\sim$50 $\mu$L of CT contrast agent (Gastrografin). The top of the open breast phantom was covered with static cling plastic wrap and the breast was suspended through the rigid hole of the patient imaging bed (Figure 6.13). An activity-filled anthropomorphic heart was also placed several centimeters above and to the right side of the (left) breast to simulate cardiac uptake as a background contaminant in the projection data. The lesion:background : heart ratio was 10.8:1:6.1. Approximately 60 kgs of lead weights were placed on the bed to simulate the bowing of the bed from an actual patient (Figure 6.13, TOP). Four 6.0 mm diameter nylon spheres (Small Parts, Inc, Miramar, FL) were soaked in concentrated aqueous $^{99m}$Tc-pertechnetate and taped to the exterior surface of the breast phantom to act as fiducial markers for registration purposes.

Two dual modality acquisition sequences were tested with the filled breast phantom: 1) reduced azimuthal angle CT and SPECT acquisitions at a single bed height, and 2) separate, full $360^\circ$ CT and SPECT acquisitions, each at varying bed heights. For the first
Figure 6.12: Photograph of the 900mL filled breast with three embedded lesions (highlighted with blue food coloring) and acrylic pieces of random sizes to simulate non-uniform uptake in the breast background.

imaging sequence, the bed was lowered to the minimal height where the CT tube and detector could still pass beneath the torso section of the patient, thereby maximizing the breast volume in the FOV for the rigid bed design. At this height the CT scan was limited to 294° by the head trough of the bed (Figure 6.5), and from earlier studies it was known that there would be only minimal distortion for this angular range. CT projections were acquired in 1.5° increments. Reduced angle SPECT data were then acquired using three trajectories (Figure 6.14, RIGHT COLUMN): a tilted-parallel-beam with 45° polar tilt (TPB45), a “saddle” orbit with a 15-45 deg polar range, and a 3.5-lobed PROJSINE.

With the bed at the minimal position for the reduced angle CT scan, the SPECT polar tilting was limited to the range from 30° to 45° before touching the bed. The azimuthal
Figure 6.13: (TOP) Photograph of the activity-filled anthropomorphic heart placed above the suspended breast phantom. Lead bricks were also used to simulate bowing in the bed due to the weight of a patient. (BOTTOM) View of the pendant breast phantom experimental setup suspended through the rigid opening of the patient bed. Plastic pieces are clearly seen in the nipple region of the phantom.
Figure 6.14: SPECT acquisition trajectories for the heterogeneous breast phantom studies. (LEFT COLUMN) 3D illustrations of the camera motion. (RIGHT COLUMN) Polar camera tilt as a function of the azimuthal angle is shown for reduced angle orbits and (CENTER COLUMN) full 360° scans.
position of the polar lobes for the reduced angle saddle and PROJSINE orbits was unfortunately slightly out of phase with the full scans, due to an imperfect modification of the orbit creation software to allow reduced angle scan creation. In the future, such a phase shift could be easily accommodated. In fact the most important feature of this acquisition angle sequence is that there be fewer views with direct views of the heart and/or liver above and behind the breast [192]. Reduced angle acquisitions were made with 119 projections over 294° with a total scan time of ~11 minutes per acquisition. Subsequent scans were increased to account for decay.

In the second imaging sequence, the patient bed was raised a few centimeters to allow the tube to rotate fully underneath the head of the patient, and CT data were thus acquired over the full 360°, in 1.5° increments. The patient bed was then raised again to allow optimal placement for acquisition of full 360° TPB45, saddle, and PROJSINE SPECT scans (Figure 6.14, CENTER COLUMN). Orbits were acquired with 128 projections over 360° and the total scan time was again ~11 minutes. All other system and reconstruction parameters remained the same as above. SPECT and CT image sets were registered and fused using open source AMIDE software [216, 217].

The reconstructed SPECT images yielded several evident differences in image quality between the limited angle and full scans (Figure 6.15). Line profiles indicated a slight increase in background noise for the limited angle scans. With a limited 30-45° polar sampling range, the breast and the heart appeared to run together even though there was a known finite air gap between the two. The greater polar range of the camera in the full scans allowed fewer views of the heart, resulting in less cardiac contamination and a more defined separation between breast and heart for the saddle and PROJSINE trajectories. In fact, the limited
Figure 6.15: Sagittal slices of reconstructed SPECT limited angle (TOP) and full 360° acquisitions (BOTTOM). 2nd iteration is shown with 3 summed slices. 2.3 mL lesion is near the center in the breast and 1.0 mL lesion is closer to the bottom. Horizontal line profiles are shown through the 2.3 mL lesion.
polar sampling had more degradative effects on image quality than did reducing the azimuthal sampling. Cardiac activity was also more pronounced in the 30-45° polar range scans than in the 15-45° scans due to more direct views of the heart; in subsequent studies, the locations of the peaks and valleys in the PROJSINE can be created to minimize vantages of the heart [Kristy’s IEEE ref]. Star patterns, evident in both the full and limited TPB images, most likely due to incomplete polar sampling were another indication that background activity from the heart needs to be accommodated. Truncation artifacts at the anterior (nipple) region of the breast in limited angle scans could be avoided in the future by removing the current 5 cm vertical offset of the SPECT gamma camera.

These results highlight the inherent difficulties in positioning the bed and pendant breast within the two systems’ FOVs such that the acquisition is simultaneously optimized for both imaging systems. Currently, a single bed height limits the positioning freedom of the SPECT camera; for example, the 45° TPB orbit is better placed with the bed at a lower position than at that for a 15-45° PROJSINE. Given that a universal patient bed height for all of the scans is more desirable than scanning with bed motion between sequences due to inherent errors due to the bed motion itself [190], the SPECT camera needs to be repositioned farther down on the goniometer such that the camera can attain at least a 15° polar tilt at the fixed bed height.

6.3.4 Modifying the Custom Patient Bed

A novel feature included in the patient bed design was the removable rigid inner octagonal section of the bed (Figure 6.16) [209]. In an effort to present more of the breast
and anterior chest wall in the common FOV, as well as facilitate full 360° acquisition, this center was removed and replaced with a flexible sheet of neoprene, layered with a leaded radiographic apron. The weight of the patient naturally pushes more of her breast into the FOV, and the flexible neoprene increases patient comfort by creating a cushioned hammock. Full 360° dual modality SPECT and CT scans of the same 900 mL breast with heterogeneous background were now possible without the rigid centerpiece (Fig. 6.17, TOP), and so those breast imaging studies were repeated. Lesion-to-background concentration ratios were approximately 10:1, and there was no additional cardiac activity used in this measurement.
Figure 6.17: Breast phantom positioned (LEFT COLUMN) using the rigid insert with the bed high enough for 360° clearance, (MIDDLE COLUMN) with bed lowered, limiting the scan to 294°, and (RIGHT COLUMN) with flexible center allowing clearance over a 360° acquisition. Estimated CT cone beam FOVs are illustrated in blue. Corresponding (MIDDLE ROW) CT projection data and (BOTTOM ROW) reconstructed, fused SPECT-CT volume renderings are shown below each system photo. There was no heart activity used in the neoprene study. Data are volume rendered giving rise to hollow-appearing centers in the fiducial markers and lesions.
Reconstruction parameters were consistent with earlier parameters, and the resulting volumes were registered and fused using AMIDE.

In summary, Figure 6.17 shows photographs of the phantom, projection views, and fused reconstructions of all three patient bed-positioning strategies. The CT reconstructions illustrate a 2-3 cm increase of breast volume in the field of view for the reduced angle scans (Figure 6.17, MIDDLE) vs. the rigid bed 360° scans (Figure 6.17, LEFT). The patient bed revised with a larger central hole covered with flexible neoprene center clearly allowed a dramatic increase (4-7 cm) in breast volume in the FOV compared to the rigid steel centerpiece, while regaining the ability to rotate 360° around the breast (Figure 6.17, RIGHT). The reconstructed CT data illustrates the entire breast volume, including the air gap above the aqueous activity (Figure 6.17, RIGHT). Fusing the reconstructed images of the SPECT and CT data illustrates the benefits of combining functional and anatomical information. With the larger neoprene opening of the modified bed, the CT cone beam could potentially image through the anterior chest wall depending on the positioning and flexibility of the patient. The natural weight of the patient extends the breast farther into the common FOV.

With this revised arrangement, the need to image with reduced angle scans may be alleviated, although continued efforts are being made to improve the breast volume seen by the CT system through the use of novel CT orbits and more sophisticated bed and hardware designs [133, 218]. Future iterations of the CT subsystem will increase the imaged breast volume by replacing CT components with less dead space between the top of the CT tube and the focal spot and at the edge of the digital detector.
6.4 Initial Investigation of Interleaved SPECT-CT Acquisition Sequences

Originally, combining the two subsystems aimed to have simultaneous, or near simultaneous, emission and transmission data acquisition for the SPECT and CT to minimize any differences between the data collected at a given projection angle. Other benefits of near simultaneous or interleaved SPECT-CT imaging included potentially shorter overall imaging times (no interscan delay), simpler inherent image registration, and more straightforward SPECT attenuation correction using the corresponding CT data. Currently the hybrid imaging protocol uses two independent consecutive scans, consisting of a shorter CT scan followed by the SPECT scan. Consecutive scans benefit from the elimination of emission contamination of the CT images by acquiring the CT scan prior to radionuclide injection of the patient [210], although alternative approaches include CT scanning after radionuclide injection and before specific uptake accumulation.

An investigation of interleaving the SPECT and CT acquisition sequences into a single scan was undertaken as a qualitative feasibility study. The acquisition software for both systems was modified such that two rapid CT projections were taken at different projection angles between every 5 sec SPECT acquisition (Figure 6.18). Thus, the 3-lobed PROJSINE SPECT orbit was sampled in 3° increments, while the CT was sampled in 1.5° increments, over the 360° scan. SPECT camera motions along the ROR are somewhat slow, and so the camera was not backed away from the breast after SPECT projection acquisitions and during CT shots. Because the SPECT camera sometimes obscured a small corner of the breast in the cone-beam CT projections, ~2 cm was cropped from either side of projection data (Figure 6.18, at dashed lines), effectively removing the corner where acquired data was
obscured. Both uncropped and cropped data were reconstructed using previously described methods. It is important to note that when the data are collected consecutively, the SPECT camera can be withdrawn to its maximum ROR, and it therefore does not impede the CT projection image.

Figure 6.18 Sample CT projection and timing scheme of the near simultaneous interleaved SPECT-CT scan. Dashed lines approximately illustrate where CT projection data were cropped 2 cm on both sides to reduce artifacts from the SPECT camera in the reconstructions (see Fig. 6.19).
Interleaved SPECT-CT acquisition sequences can speed up and simplify overall scan time, but potentially limit the positioning freedom of the contoured SPECT orbits due to the fixed patient bed height. The close proximity of the orbiting SPECT camera obscured CT views of the breast and thus created artifacts in the CT images that were reduced and nearly eliminated by cropping the projection data to minimize the overlap region for shifted CT. The potential quantitative losses in this interleaved scan were not, however, investigated in this initial qualitative study. Separate sequential CT and SPECT scans are currently still
preferred because the time saved from the interleaved scan did not justify the artifacts in the CT image and limited positioning freedom of the SPECT scan.

6.5 Hybrid SPECT-CT Patient Studies

The first patient volunteer imaged with both modalities on our system was a 45 year-old, 93kg woman with biopsy-confirmed breast cancer. Three hours prior the first scan, she received an injection of 29 mCi (1073 MBq) of $^{99m}$Tc-methylene diphosphonate (MDP) as part of a Nuclear Medicine whole-body bone scan. While $^{99m}$Tc-MDP is mainly used to detect bone metastases, its use in early scintimammography studies [106] has demonstrated far less accumulation in soft tissue tumors. To eliminate additional radiation dose to the patient, however, the patient was not injected with the more appropriate $^{99m}$Tc-sestamibi for the dedicated breast SPECT scan. Four 6 mm diameter nylon balls (with hollow centers), soaked in diluted $^{99m}$Tc-pertechnetate solution, were taped to the exterior surface of the patient’s left breast at 3, 6, 9, and 12 o’clock positions for fiducial markers (Figure 6.20). Starting at 12 o'clock on the subject's superior-posterior breast, they were arranged in a clockwise spiral ending at the 9 o'clock anterior most position.

Using the bed’s positioning system, the newly implemented shielded bed was angled slightly upward to compensate for minor bowing due to the subject’s weight, and thereby allow the CT tube to pass underneath at a minimal bed height (Figure 6.21). The modified patient bed with the neoprene inner lining allowed the subject’s breast and chest wall to naturally protrude farther into the common FOV. Once the breast was positioned on the COR of the hybrid system, with the aid of a laser crosshair guide, an 11-minute 360° CT scan was acquired. While the subject lay comfortably on the bed, there were no gross
Figure 6.20: Four dual-modality fiducial markers were taped in a spiral pattern at 12, 3, 6, and 9 o’clock, from the subject volunteer’s superior-posterior breast anterior to her nipple. The fiducials consisted of 6 mm nylon balls soaked in dilute $^{99m}$Tc-pertechnetate solution, sandwiched between medical tape, and they are thus easily seen by both imaging modalities.

Figure 6.21: Photograph of the first hybrid study patient volunteer. The SPECT camera (CENTER) is positioned at 55 degrees during the CT scan to avoid obstructing the CT cone beam. Note that the flexible shielded neoprene chest support was used, allowing more of the subject’s chest into the CT FOV.
movements that would have introduced large motion artifacts, besides her natural heart rhythm and breathing; the subject was quite calm and nearly napping. CT images were acquired at 60 kVp and 2.5 mAs exposure/projection with a standard circular orbit. With these settings, the estimated total CT dose to the patient is less than that of dual view mammography (<6 mGy) [134]. Iterative CT reconstruction parameters were 30 iterations, 16 subsets, and 508 μm³ voxel size on a 350x350x384 reconstruction grid.

After a short break, an 11-minute SPECT scan using a PROJSINE 15-45° trajectory was performed (5 seconds per projection over 128 projections, with additional time for gantry movement). The automated contouring sensors (discussed in detail in §5.3) were only in an early prototype stage at the time of this clinical scan; thus ROR contouring was implemented manually by interpolating between six scout measurements (Figure 6.22). A SPECT scan of the asymptomatic right breast was subsequently acquired using a fixed 45° TPB scan only. SPECT reconstruction parameters were 2 iterations, 8 subsets, and a 2.5 mm³ voxel size in a 150x150x100 reconstruction grid. SPECT data were post-processed with a 3D Hann smoothing filter with a cutoff at 1.4 cycles/mm (0.7*Nyquist).
Figure 6.22: Polar plots of SPECT imaging trajectories used to image the first hybrid patient volunteer. (LEFT) ROR and (RIGHT) camera tilt are plotted as a function of azimuthal angle where in-plane angular displacement represents azimuth.
Figure 6.23: Reconstructed SPECT sagittal images of the patient’s left and right breasts acquired with PROJSINE and TPB, respectively. A post-reconstruction Hann filter was applied with 15 slices summed (≈3.75 cm of breast slab). In the PROJSINE reconstruction there is an apparent increase in tracer ($^{99m}$Tc-MDP) uptake in the anterior portion of the breast, where she had post-surgically confirmed cancer.

Reconstructed SPECT and CT image sets were manually registered and fused using the open source AMIDE software. The reconstructed SPECT patient breast images showed little focal uptake of the tracer in the individual slices due to its low accumulation in tumors and soft tissue, and also perhaps to the radioactive and biological decay between the times of her bone study and dedicated breast SPECT scan. After summing multiple slices, however, the lower portion of the left breast with confirmed cancer does appear to have greater uptake than the right, otherwise asymptomatic breast (Figure 6.23).

Manually registered and fused left breast results of our first hybrid subject study are shown in Figure 6.24. The large bright yellow spheres in the SPECT coronal images are the relatively high-activity and blurred fiducial markers. Clearly a smaller amount of activity should be used to soak the nylon fiducials, or if they had a different emission energy, they could be windowed out of the $^{99m}$Tc-radiotracer images.
Figure 6.24: Reconstructed patient (TOP) SPECT, (MIDDLE) CT, and (BOTTOM) manually registered and fused SPECT-CT images. Green crosshairs are centered on the suspected, and post-surgically confirmed lesion, with no apparent focal activity ($^{99m}$Tc-MDP) uptake in the SPECT images other than a general concentration in the lower half of the transverse and sagittal SPECT images. The large bright yellow spheres in the SPECT coronal images are the relatively high-activity ($^{99m}$Tc-pertechnetate) and substantially blurred fiducial markers.
Fiducial marker activity levels were not measured explicitly but, based on past experiments, were at least 20-30 μCi, which is over ten times the magnitude of sestamibi lesion uptake seen clinically [111, 158]. The green crosshairs highlight an area in the breast suspected to be the lesion due to its increased brightness in the CT images than the surrounding glandular tissue, but a mammogram or MRI was not available for confirmation. There was post-surgical confirmation of adenocarcinoma, however, which corresponded to the region of increased CT brightness in that subject. Overall, the patient CT data allows for excellent contrast and visualization due to the removal of overlapping structures, seen especially clearly in this especially-glandular, dense breast. While ~9 cm of the pendant breast is viewable within the CT images, ~14 cm of the breast and chest wall is viewable in the SPECT images due to the use of tilting 3D orbits. The neoprene opening certainly aided in visualization of increased breast volume, although there is potential for increased breast volume with even better patient positioning.

The fourth subject, and latest hybrid imaging patient volunteer to date, was a 54 year-old, 96 kg patient with biopsy-confirmed DCIS anterior to her chest wall (Figure 6.25). The patient was first injected with 17.8 mCi (660 MBq) of $^{99m}$Tc-sestamibi. After the breast was positioned on the COR of the hybrid system (Figure 6.26), an 11-minute 360° CT scan was acquired. Following the scan, the patient readjusted herself, and an 11-minute SPECT scan using a PROJSINE 15-45° trajectory was performed. Because the contouring sensors were not finished at the time of the study, ROR contouring was achieved by manually measuring the camera ROR at six different azimuthal positions and then linearly interpolating between points (Figure 6.27).
Figure 6.25: Photograph of the latest patient volunteer imaged on the hybrid system to date.

Figure 6.26: The measuring tape and laser crosshairs, aligned near the top of the CT cone beam, illustrate that roughly 1-2" (3-5 cm) of the breast are above the CT FOV.
Figure 6.27: Polar plots of SPECT imaging trajectories used to image the latest hybrid system subject volunteer. (LEFT) ROR and (RIGHT) camera tilt are plotted as a function of azimuthal angle where in-plane angular displacement represents azimuth.

Reconstruction parameters were the same as those used for the previous patient. The registered reconstructed SPECT-CT images in Figure 6.28 illustrate the power of fusing functional SPECT information to localize the lesion not easily seen in the anatomical CT images. The surgically confirmed DCIS anterior to the patient’s chest wall is not readily
Figure 6.28: Reconstructed subject breast images from (TOP) SPECT, (MIDDLE) CT, and (BOTTOM) registered and fused SPECT-CT images. Green crosshairs are centered on the suspected lesion. A biopsy clip is seen in upper-left region of sagittal slice (posterior-medial breast, at yellow arrow), just posterior to the sestamibi uptake. Note that for the fused images, activity outside the breast (using the CT image as the boundary) was windowed wider in an attempt to reduce the displayed size of the fiducial markers. SPECT hot spots outside the breast are due to the fiducial markers and those posterior to the CT-visible breast are from myocardium.

visible in the CT images. SPECT signal enhancement (at green crosshairs) that corresponds to the suspected regions from her diagnostic MRI scan (as confirmed by Dr. Terrence
Wong) are just anterior to her biopsy confirmed lesion, indicated by the clip near the top of the sagittal CT image (at yellow arrow). The post-surgical DCIS plus abscess size was determined to be 4.9 x 2.3 x 3.0 cm³ in extent, roughly corresponding with the signal enhancement seen in the fused SPECT images. Other enhanced regions in the SPECT images outside and anterior or lateral to the breast are fiducial markers, and signals posterior to the breast are from myocardial uptake, which is also seen in and consistent with previous patient SPECT images.

These pilot studies demonstrate the feasibility of the dual-modality SPECT-CT system. Contrast and detail in the CT images are fairly good when considering the notable patient motion seen in the sinogram data during the relatively long 11-minute scan [219]. In the time since the initial patient studies were performed, the CT acquisition time has been decreased from 11 to 6 minutes. The investigation of patient motion correction algorithms for both the SPECT and CT images may further improve overall image sharpness and contrast. Future patient studies will also benefit from the now-implemented SPECT autocontouring system (see §5.3), eliminating manual ROR setup time.

6.6 Conclusions

A prototype dedicated SPECT-CT hybrid imaging system with promising imaging capabilities was successfully implemented, and initial patient results have been obtained. Using a rigid stainless steel bed intended to minimize radioactive cross-contamination while protecting and supporting a patient, reduced angle tomographic acquisitions were shown to be useful for imaging close to the chest wall. Both the mini-cold rod and breast phantom studies initially indicated that removing 60° of azimuthal SPECT projection data does not
significantly reduce image quality, though there is observable resolution degradation with decreased angular sampling. CT images were also minimally affected if the cone beam was centrally aligned with the COR and data collected with 180 deg acquisition. But there was dramatic degradation due to <360 deg sampling with the laterally offset cone-beam set-up. A centrally aligned cone-beam geometry with a larger detector (to avoid truncation of larger breasts) would be a more ideal solution for reduced angle CT with respect to resolution and image quality retention. There may still be issues with interference from the SPECT camera due to the magnification with the cone-beam geometry, however, and CT scatter issues may also play a different role in image quality with centrally or offset cone beam geometries.

The latest modification to the patient bed design, a flexible center, allows more of the breast into the common imaging devices’ FOVs due to the larger hole in the bed and natural extension by the weight of the patient. This change permits full 360° dual modality imaging close to and even slightly into the chest wall. A critical focus for future system design should be decreasing the dead space between the top of the CT tube and the focal spot, as well as the dead space at the edge of the digital detector, to increase the breast volume in the FOV. These design criteria are most likely subject to restrictions by the various manufacturers.

Given the hardware restrictions and the implemented designs to try to overcome them, nevertheless, two preliminary subject volunteer SPECT-CT imaging studies were successfully completed. The first study demonstrated the value of fusing anatomical CT images with functional SPECT information by localizing a lesion not easily identified in the SPECT images. The reciprocal was true for the second patient study, where the lesion was more apparent in the SPECT images, but anatomically localized with the corresponding CT images. The SPECT images illustrated the increased ability to image up to and past the chest.
wall, while visualization of the chest wall in the CT images remained limited. Patient comfort and image quality can be improved in the future by decreasing the CT scan time. Patient motion during the scan results in image blurring. Since the initial patient studies were performed, the CT acquisition time has been decreased from 11 to 6 minutes. Further enhancements to the gantry motion hardware and software should allow this time to be reduced even further.

Further investigation of appropriate multi-modality fiducial markers is warranted as well (Figure 6.20). In the initial two studies, the uptake of the fiducial markers was orders of magnitude higher than the cumulative uptake in the breast. This discrepancy resulted in the fiducial markers’ oversaturating the patient images and making interpretation of the images more difficult. Possible solutions are to soak the balls in a much lower activity level solution (µCi vs. mCi), possibly with a different radionuclide of a different energy (e.g., In-111, I-123, or Tl-201) such as is routinely done in dual-isotope SPECT imaging [220-223]. A higher energy radionuclide for the fiducials would be preferred since it would only minimally affect the 99mTc signals, and not be affected by them at all. The latter solution would effectively allow the fiducial markers to be turned “on” and “off” in the image by simple energy windowing of the signal. Once SPECT fiducials obtained at one energy are registered with the CT images, the same rotation, translation, resizing parameters could be applied to the SPECT breast data for accurate registration of the breast SPECT and CT datasets. As patient scans times decrease, especially with the CT component, and the geometry of the hybrid-system becomes finalized, the fixed registration between the systems should also become easier and more clearly defined. The ultimate goal is to automate the registration
procedure completely and thus eliminate the need for fiducial markers, similar to commercial-grade, whole-body SPECT-CT systems.

Overall, these initial studies have proven the effectiveness and feasibility of the hybrid SPECT-CT breast imaging system. Further breast patient imaging studies have been planned to evaluate imaging performance and variability of the hybrid system in preparation for a larger scale clinical trial.
Chapter 7

Concluding Remarks

Through the course of this dissertation work, the dedicated SPECT mammotomography system has matured from an independent prototype system into a clinically-viable dual-modality SPECT-CT imaging system, capable of quantitative hybrid breast imaging (Figure 7.1). The integrated subsystems allow fully-3D, dual-modality uncompressed breast imaging, providing co-registered anatomical and functional images. A great deal of effort has been spent on system-level characterization and enhancement of the SPECT subsystem in preparation for a full-scale clinical trial. The results of these studies largely support the original hypothesis that 3D SPECT-CT breast imaging, with the ability to dynamically contour any sized breast, could potentially improve detection and diagnosis of sub-centimeter breast lesions.

A critical specification for system development and verification is the expected variability in pendant breast shapes and sizes. Thus, early on in this work, a retrospective investigation of existing MRI data of pendant breasts was carried out to analyze breast shape and size variants that might be encountered in otherwise routine clinical imaging. The resulting minimum, maximum, and average breast measurements proved useful in design decisions for the patient bed and hybrid gantry. A key finding was that the average breast volume was 720 mL (±415 mL standard deviation for the 203 breasts categorized). Breast phantom studies had previously focused on volumes greater than 1000 mL, which can to be
SPECT and CT images are fused together to form a fully-3D volume of complementary functional and anatomical information for enhanced lesion diagnosis.
Figure 7.2: Comparison of imaged breast volume for (LEFT) SPECT using a PROJSINE trajectory, (MIDDLE) 2D scintimammography, and (RIGHT) x-ray CT. A known, small lesion just anterior to the chest wall (surrounded by dashed circle in SPECT image) is beyond the FOV of both CT and scintimammography.

seen in the FOV of both systems. Based on these results, smaller breast phantoms ranging from 500-1060 mL volumes were largely used in the various image characterization studies.

A direct quantitative and observer-based comparison was made between the dedicated 3D SPECT system and its 2D analog, scintimammography. Quantitative measurements of SNR and contrast in SPECT data yielded values nearly a factor of two higher compared to planar scintimammography for varieties of lesion sizes and simulated biological uptake ratios. Due to greater positioning flexibility of the system gantry, dedicated SPECT was able both to image a larger breast volume and to view the anterior chest wall, where tumors can be otherwise missed in 2D imaging (Figure 7.2). Since breast cancer is known to occur at the chest wall ~24% of the time, it is important to be able to image the anterior chest wall.

Future studies could investigate breast imaging with higher sensitivity collimator geometries, and the implementation of resolution recovery modeling in the reconstruction code. Overall, under a wide range of measurement conditions, statistically significantly (p<0.05) more lesions and smaller lesion sizes were detected by independent observers with
dedicated breast SPECT than with compressed breast scintimammography. Future random lesion placement observer studies are warranted to determine overall sensitivity in lesion detection.

The effect of energy window width for uncompressed SPECT breast imaging was also investigated. Spatial resolution was only minimally affected by the choice of energy window, while contrast was boosted with narrower windows at the tradeoff of fewer counts and therefore a decreased SNR. Quantitative comparisons over multiple image realizations clearly illustrate both visual and quantitative differences between the various energy windows, with energy windows slightly wider (8-12%) than the system resolution (6.7% at 140 keV) having the best image contrast and quality. For the system in our lab, a 12% energy window is recommended as general-purpose energy window to maintain high SNR and contrast. For quantification studies, an 8% energy window may be more appropriate for increased scatter rejection.

A second observer-based contrast-detail study was performed in an effort to evaluate the limits of object detectability under various imaging conditions. Identical to the previous observer study, the TPB SPECT acquisition trajectory statistically outperformed (p<0.05) PROJSINE, with smaller detail observed despite the conical distortion present due to the incomplete polar sampling. The complex PROJSINE acquisition, however, had the most consistent combined intra- and inter-observer results, making it potentially the best imaging approach for consistent clinical imaging. A full ROC study (using either simulated ideal observers or actual observers) is warranted to more comprehensively characterize the sensitivity and specificity of the SPECT mammotomography system.
At the genesis of this dissertation work, novel 3D camera trajectories had already been implemented with the SPECT system [111]. The manual setup for these orbits was time consuming and not quickly adaptable to different breast shapes and sizes, and it therefore was cumbersome during clinical imaging. The vast array of breast shapes seen in healthy and diseased women necessitated the design and implementation of real-time, automated robust 3D contouring for quick, highly adaptable patient setup and close-proximity, high-resolution molecular imaging. Automatic ROR contouring was implemented using a dual-layer light curtain design, ensuring that an arbitrarily shaped breast is within ~1 cm of the camera face, but no closer than 0.5 cm, at every projection angle of a scan. The initial visible ribbon laser prototype had the nice feature of providing additional visual feedback on the subject’s breast, but it was ultimately replaced by a more compact and practicable IR design. The implementation of this IR-based autocontouring system now enables simplified routine scanning using complex 3D trajectories, without the need to carefully measure a subject’s breast boundaries through scout positions. Overall image quality is improved with closer camera placement.

Absolute quantification capabilities were also integrated into the SPECT system, allowing the calculation of \textit{in vivo} total lesion activity. Initial feasibility studies in controlled, low-noise experiments showed promising results with total activity agreement on average within 93-97\% of the dose calibrator values. A large amount of work will be needed before this can be used with confidence in a clinical setting. The effect of VOI size and selection will need to be better characterized to see if there is a repeatable scaling coefficient. A VOI of roughly 3-4 times the actual volume of a 1.7 mL lesion was needed in order to match the total measured activity from the dose calibrator, while a VOI 5-6 times the actual volume...
was needed for lesions <1 mL largely due to partial volume effects. Resolution recovery modeling and partial volume corrections might be applied to the SPECT data in order to properly distribute reconstructed counts such that the total activity per unit volume is more accurate. Both the simple attenuation and scatter corrections implemented could be improved with robust corrections. In the future, image segmentation of the reconstructed CT images using thresholding on the quasi-monochromatic x-ray acquired data could be used to define more accurately the borders of different density components, and hence 3D volume, of the VOI. It is anticipated that CT images should increase quantitative accuracy especially in a clinical setting.

Initial human subject studies have demonstrated the clinical feasibility of imaging with the hybrid SPECT-CT breast system (Figure 6.28). The reconstructed SPECT-CT images illustrate the power of fusing functional SPECT information to localize lesions not easily seen in the anatomical CT images. The use of a 3D Hann filter was found to beneficial to smooth high-frequency SPECT background noise in both phantom and patient images (Figure 7.3).
Figure 7.3: Comparison of (LEFT) unaltered SPECT slices and (RIGHT) with a 3D Hann filter applied (cutoff at 1.4 cycles/mm). Regions of interest with better visualization are indicated.
The enhanced, quantitative 3D SPECT-CT mammotomography now has the ability to easily autocontour any sized patient breast, and the SPECT subsystem has repeatedly shown high potential to allow detection of sub-centimeter breast cancers, a critical target for effective functional breast imaging. Ultimately, the system still faces the difficult transition from an investigative prototype to a commercial, clinically viable imaging system (as depicted in Figure 7.4), which will be driven by the adoption rate of physicians and the medical imaging community. Larger scale clinical trials are needed to clinically confirm the specificity and sensitivity of 3D SPECT-CT imaging. Many potential SPECT-CT clinical applications remain to
be explored including the use of the system for staging and determination of extent of disease
and monitoring of therapeutic response. The author strongly believes that SPECT-CT imaging
will be a beneficial clinical imaging tool, especially to high-risk women in the earlier detection
and diagnosis of primary breast cancer.
Appendix A

Duke IRB Protocol Pro00000774

A retrospective study of breast volumes, shapes, and sizes using existing anonymized bilateral MRI breast data

Description of the Protocol

1. Purpose: The purpose of this study is to conduct a retrospective study of uncompressed breast volumes, shapes, and sizes using existing bilateral Magnetic Resonance Imaging (MRI) breast data at Duke. Our lab has developed a novel system for uncompressed fully three-dimensional (3D) molecular single photon emission computed tomography (SPECT) breast imaging. The compact camera and positioning hardware allow for 3D imaging anywhere about the pendant breast, providing a complete volume of image information in contrast to a single 2D, flat image. While novel 3D camera paths (orbits) have already been implemented with the system, the setup for these orbits is time consuming and not quickly adaptable to different breast shapes and sizes, and therefore is impractical for clinical imaging. The first step to automating the system is to better understand the variability in pendant, uncompressed breast shapes and sizes. A study of existing clinical MRI breast data will allow us to create surface renderings of the prone uncompressed breast and analyze how to adapt existing orbits for varying breast shapes. Additionally, having some information about the patient (weight, age, ethnicity) may prove useful in characterizing
certain breast shape and volume features, as well as in organizing the database of anonymized images.

2. **Background & Significance:** 3D Nuclear Medicine molecular breast imaging is a promising powerful complementary imaging technique to mammography because of its ability to provide functional information about metabolic processes that can distinguish malignant and benign tissue. Our SPECT system allows for unique 3D imaging trajectories, as opposed to simple circular orbits, with the advantage of using camera tilt to image lesions close to the chest wall as well as for axillary imaging. Currently these orbits are manually calculated. To closely contour a non-uniform uncompressed breast requires first manually moving the camera to many positions around the breast, taking measurements, and interpolating the points around the breast. A small sample of clinical, pendant MRI images of uncompressed breasts (Fig. 1) illustrate a variety of breast shapes and sizes, and reinforce the need to automate the radial (radius-of-rotation, ROR) positioning component of the orbit.

The overall objective of this project is to begin fully automating and optimizing the performance of the current prototype system for enhanced clinical testing. Clinical MRI images, which are also acquired with patient lying prone, are readily available and provide a complete 3D uncompressed breast volume, useful for modeling SPECT acquisition orbits. The MRI breast coil is finite in size so large breasts may have limited compression, but this should only further benefit the study as devices for breast immobilization which may have
limited compression are also under investigation and development in our lab. The existing basis set of orbits will be modified to account for challenges imposed by non-uniform breast shapes. Based on the results of the study, feedback sensors will also be implemented on the camera to maintain a close proximity to the breast while avoiding contact. The result will be a highly flexible 3-D system capable of dynamically contouring breasts.

3. Design & Procedures: The Duke Advance Imaging Laboratories (Dept. Radiology) currently has over 100 volumetric breast magnetic resonance imaging data sets collected as part of another protocol (Duke University IRB # 4245). All samples are pre-existing. The images have already been removed from the clinical PACS system and de-identified prior to burning onto CD-ROMs. Patients will not be consented as the images were already collected under Duke IRB-4245. Dr. Joseph Lo of the Duke Advanced Imaging Labs will provide copies of this de-identified data with the approval of Dr. Victoria Seewaldt, PI of IRB #4245. I will not seek the identity of the participants in this study. The data will then we used to analyze pendant uncompressed breast volumes, shapes, and sizes (Fig. 1) in an effort to model ideal or “typical” orbits that may be used with patients when they would come for a SPECT scan. Duke Medical Center Breast Imaging Fellows will provide training on identifying the key landmarks of a prone breast exam. Using available OsiriX imaging software, we will read in the data and extract the pendant breast sizes: nipple-chest wall distance, superior-inferior distance, medial-lateral distance, and skin thickness. This information is useful for attenuation estimation in SPECT, and computer modeling purposes. A 3-D surface rendering of the external breast shape will also be obtained in order to visualize challenges of contouring the breasts and to classify the data according to size and
shape. Fundamental metrics such as the mean and standard deviation of distance measurements will be tabulated and the varying spectrum of pendant breast surfaces can then be classified based on a variety of features (e.g. size, volume, shape). These breast shapes can then be used as the digital “phantoms” when utilizing computer models for system development and orbit optimization purposes. Metrics obtained from the image dataset may also be used in conference presentations and publications, but will not contain PHI besides those mentioned above (age at scan, pt. weight, breast cancer status or ethnicity).

4. Risk/benefit assessment:

**Risks:** This retrospective study represents minimal risk to the patients as the images have already been de-identified prior to being provided to the PI.

**Benefits:** This study will greatly benefit the lab by providing realistic digital clinical models, thereby allowing us to optimize our imaging orbits without using live patient volunteers. In the long run, it will potentially benefit volunteers and ultimately patients coming for dedicated breast SPECT scans.

5. Subject identification, recruitment, and compensation: Scans were already acquired during patients’ regular visits to Duke Radiology, and represent a random sampling of high risk female breast cancer patients at the Duke University Medical Center. I will not seek to retrospectively identify or consent the participants whose image data and samples were acquired under Duke IRB 4245 and will be used in this study.

6. Subject competency: Not applicable as this is a retrospective study.

7. Costs to the subject: There are no costs to the subject involved in this study.
8. **Data analysis & monitoring**: Images will be analyzed as outlined in Section 3, and stored in a database for future reference.

9. **Data storage & confidentiality**: Confidentiality will be maintained throughout this study. Data files stored at the Multi-Modality Imaging Lab will contain no private patient information. The computers are configured such that security is greater than in routinely shipped installations. Periodically, the computers are remotely scanned to determine network vulnerability or intrusion. Physical and computerized access is limited to the Duke Multi-Modality Imaging Laboratory.
Appendix B

Modifications to the Motion Controller Source Code (DLL)

Relevant modifications to the Phmgantry.dll source code:

```c
// Software Hard limits of ROR (degrees)
#define MAXROR -1300
#define MINROR -30

// Crossover point for breast breaking sensor barrier (Volts)
#define SENSORBREAK 1.67 // 1/3 of 5V DC signal

double GetROR()
{
    int ret;
    double ROR;
    char iBuf[20];
    DWORD dwRead;
    dwRead=0;
    char *p;
    SendCMD("4PA?");
    ret=ReadFile(hComm,iBuf,20,&dwRead,NULL);
    ROR = strtod(iBuf, &p);
    return ROR;
}

double GetVoltage(int channel)
{
    int ret;
    double Voltage;
    char iBuf[20];
    DWORD dwRead;
    dwRead=0;
    char *p;
    CString Command;
    Command.Format(_T("%dRA"), channel);
    SendCMD(Command);
    ret=ReadFile(hComm,iBuf,20,&dwRead,NULL);
    Voltage = strtod(iBuf, &p);
    return Voltage;
}

int ReadSensors(double* v)
{
    int ret, n;
    int j = 0;
    char iBuf[125];
    DWORD dwRead;
    dwRead=0;
    char field[32];
```
SendCMD("RA");
ret=ReadFile(hComm,iBuf,125,&dwRead,NULL);

char *p;
const char *ptr = iBuf;
// Parse string to floating point values
while (*ptr != '\0' & j <= 7) {
    int items_read = sscanf(ptr, "%31[^,]%n", field, &n);
v[j]=strtod(field,&p); // convert sensor voltage to floating point double and
store it in the array
field[0]=\0';
    if (items_read == 1){
        ptr += n; /* advance the pointer by the number of characters read */
        ++j; // advance sensor array pointer
    }
    if ( *ptr != ',' ) {
        break; /* didn't find an expected delimiter so done */
    }
    ++ptr; /* skip the delimiter */
}
return 0;
}

bool MotionDone(int mode)
{
    // Checks to see if the motors are still moving
    // Mode 1 = check ROR only
    // Mode 2 = check Azimuth and Polar only
    int ret, statusROR, statusPOLAR, statusAZIMUTH;
    bool Done = false;
    char iBuf[3];
    DWORD dwRead;
dwRead=0;
    if(mode==2) { // check all axes
        SendCMD("2MD?");
        ret=ReadFile(hComm,iBuf,1,&dwRead,NULL);
        statusPOLAR = atoi(iBuf);
        SendCMD("1MD?");
        ret=ReadFile(hComm,iBuf,1,&dwRead,NULL);
        statusAZIMUTH = atoi(iBuf);
        if(statusPOLAR==1 && statusAZIMUTH==1) Done=true;
    }
    else { // only check ROR
        SendCMD("4MD?");
        ret=ReadFile(hComm,iBuf,1,&dwRead,NULL);
        statusROR = atoi(iBuf);
        if(statusROR==1) Done=true;
    }
    return Done;
}

int ReadEuler(int index)
{
    char thetatemp[20], phitemp[20], rortemp[20];
    double r, s1, s2, e1, e2, e3, d, f, rdeg, test, test2, currROR, RORcm;
    FILE *infile_ptr;
CString Data, Volts;
long byteoffset;
int counter, h, del, RORLimit, debugchoice;
test = 0.0;
test2 = 0.0;
del = 0;
RORLimit = 0;
double voltages[8]={5.0, 5.0, 5.0, 5.0, 5.0, 5.0, 5.0, 5.0}; // 5V
CString RORpos;

// Read in Orbit File on first projection
if(index==0)
{
    // Create Output ROR file for autocontouring based on timestamp at beginning of scan
    struct tm* tm;
time_t now;
    now = time(0); // get current time
tm = localtime(&now);
sprintf(RORfilename, "d:\LumaGEM\ROR\ROR_%02d%02d%02d%02d%02d%04d.txt", tm->tm_hour, tm->tm_min, tm->tm_sec,tm->tm_mon+1,tm->tm_mday, tm->tm_year+1900);

    // read in orbit file
   (infile_ptr = fopen("d:\LumaGEM\orbit.txt", "r");
    counter=0;
    byteoffset=0;
    while(!feof(infile_ptr))
    {
        r=0.0; s1=0.0; s2=0.0; e1=0.0; e2=0.0; e3=0.0; d=0.0; f=0.0;
        fseek(infile_ptr, byteoffset, SEEK_SET);

        fscanf(infile_ptr,'%7lf %7lf %7lf %7lf %7lf %7lf %7lf %7lf', &r, &s1, &s2, &e1, &e2, &e3, &d, &f);
        byteoffset=0; byteoffset = ftell(infile_ptr);

        // ROR conversion equation (from [cm] to [degrees]):
        rdeg = f*pow(r,8) + 0.0058753f*pow(r,7) - 0.098951f*pow(r,6) + 0.85935f*pow(r,5) - 4.0686f*pow(r,4) + 10.4225f*pow(r,3) - 23.0693f*pow(r,2) + 200.0849f*r - 1053.4719f;

        _gcvt(rdeg,12,rortemp);
        _gcvt(e1,12,thetatemp);
        _gcvt(e2,12,phitemp);

        for (h=0; h<20; h++)
        {
            ror[counter][h]=rortemp[h];
            theta[counter][h]=thetatemp[h];
            phi[counter][h]=phitemp[h];
        }
        counter++;
    }
}
fclose(infile_ptr);
// For Manual ROR Contouring from orbit.txt file:
if (scanmode == 6) {
    Data=CString("1pa")+thetatemp+CString(";2pa")+phitemp+CString(";4pa")+rortemp;
    SendCMD(Data);
    while(!MotionDone(2)); // Make sure gantry is done moving
} else {

    // Autocontouring with IR sensors
    currROR = GetROR();
    Data=CString("1pa")+thetatemp+CString(";2pa")+phitemp;
    SendCMD(Data); // Send Rotation and Polar tilt commands
    do { // keep monitoring ROR while in motion (polar or ROR)
        // Step 1: Make sure breast is not too close to camera
        ReadSensors(voltages);
            SendCMD("4PR10");
            currROR = currROR + 10; // Move ROR back
            Sleep(1000); // pause 100 msec until movement is finished
            ReadSensors(voltages); // Check to see if beam is still blocked
            RORLimit = 1; // we had to back the camera away so we don't want to move it back in at all
        }

        // Step 2: Make sure breast is within 1 cm of camera
        ReadSensors(voltages);
            SendCMD("4PR-10");
            currROR = currROR - 10;
            Sleep(1000); // Added 1000 msec delay to avoid overlap in commands to the motion controller
            ReadSensors(voltages);
            RORLimit = 2; // We moved in so don't back the camera out this projection
        }
    } // end inward movement
    // SendCMD("4ST"); // Stop ROR
    while(!MotionDone(2)); // Checks to see if polar and azimuth motion are complete
} // End Autocontouring ROR Sensors

while(!MotionDone(1)); // Wait for ROR to finish
r = GetROR();

// ROR conversion equation (from [degrees] to [cm]):
// Note: Used 8-degree polyfit in matlab to generate coefficients based on ruler measurements

// For Manual ROR Contouring from orbit.txt file:
if (scanmode == 6) {
    Data=CString("1pa")+thetatemp+CString(";2pa")+phitemp+CString(";4pa")+rortemp;
    SendCMD(Data);
    while(!MotionDone(2)); // Make sure gantry is done moving
} else {

    // Autocontouring with IR sensors
    currROR = GetROR();
    Data=CString("1pa")+thetatemp+CString(";2pa")+phitemp;
    SendCMD(Data); // Send Rotation and Polar tilt commands
    do { // keep monitoring ROR while in motion (polar or ROR)
        // Step 1: Make sure breast is not too close to camera
        ReadSensors(voltages);
            SendCMD("4PR10");
            currROR = currROR + 10; // Move ROR back
            Sleep(1000); // pause 100 msec until movement is finished
            ReadSensors(voltages); // Check to see if beam is still blocked
            RORLimit = 1; // we had to back the camera away so we don't want to move it back in at all
        }

        // Step 2: Make sure breast is within 1 cm of camera
        ReadSensors(voltages);
            SendCMD("4PR-10");
            currROR = currROR - 10;
            Sleep(1000); // Added 1000 msec delay to avoid overlap in commands to the motion controller
            ReadSensors(voltages);
            RORLimit = 2; // We moved in so don't back the camera out this projection
        }
    } // end inward movement
    // SendCMD("4ST"); // Stop ROR
    while(!MotionDone(2)); // Checks to see if polar and azimuth motion are complete
} // End Autocontouring ROR Sensors

while(!MotionDone(1)); // Wait for ROR to finish
r = GetROR();

// ROR conversion equation (from [degrees] to [cm]):
// Note: Used 8-degree polyfit in matlab to generate coefficients based on ruler measurements

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\[ RORcm = -8.8156 \times 10^{-23}r^8 - 3.7796 \times 10^{-19}r^7 - 6.4041 \times 10^{-16}r^6 - 5.3346 \times 10^{-13}r^5 - 2.0890 \times 10^{-10}r^4 - 1.1581 \times 10^{-08}r^3 + 2.5135 \times 10^{-05}r^2 + 0.0198r + 9.4252; \]

AutocontourROR = fopen( RORfilename, "a+" );
fprintf( AutocontourROR, "%i \t %3.2f\n", index, RORcm);
fclose( AutocontourROR );

return 1;
}

int ResetMotor()
/* Make sure all motors are on; reset velocities for each. */
{
SendCMD("1mo; 2mo; 4mo; 1va8; 2va2"); // (1va40 for SPECT only) 1va8 for hybrid
scanmode = MessageBox(NULL, (LPCSTR)"Manual ROR Contouring? (Press no for
Autocontouring mode)", "Select ROR Scan Mode", MB_YESNO);
SendCMD("AM2"); // Initialize Analog Read Mode (0-10V)
return 0;
}

float ReadROR()
/* Make sure Radius of Rotation Motor is enabled. Returns ROR position */
{
CString Data;
Data = CString("4mo");
SendCMD(Data);
float initialROR = 0;
initialROR = GetROR();
return initialROR;
Bibliography


Biography

Place of Birth: Salt Lake City, Utah
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EDUCATION

Duke University, Durham, NC
Ph.D. in Biomedical Engineering October 2010
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IEEE Conferences in Medical Imaging
(Conferences in Puerto Rico, San Diego, Hawaii, Germany)

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Department of Defense
“Automation and Preclinical Evaluation of a Dedicated Emission Mammotomography System for Fully 3-D Molecular Breast Imaging”

Student Travel Award, 2008
Workshop on the Nuclear Radiology of Breast Cancer, Dresden, Germany

Student Scholarship Award 2009
Apple Worldwide Developers Conference, San Francisco, CA
PEER-REVIEWED PUBLICATIONS


CONFERENCE PROCEEDINGS AND PRESENTATIONS


ABSTRACTS AND ADDITIONAL PRESENTATIONS


SJ Cutler, CN Brzymialkiewicz, P Madhav, MP Tornai. “A new approach to 3D molecular breast imaging with dedicated emission mammotomography.” Presented at the Duke University Comprehensive Cancer Center Annual Meeting, Durham, NC, 10 Apr. 2006, 105-106.


