Three-Dimensional Computerized Breast Phantom

Based on Empirical Data

by

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Date: December 7, 2010

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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
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ABSTRACT

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Abstract

Breast imaging has improved the early detection of breast cancer thereby decreasing the mortality rate; however, thousands of women are wrongly diagnosed each year. Improving the sensitivity and specificity of breast cancer imaging is an important area of research and development. One of the major hurdles in imaging research arises from the difficulty in accruing human subject data because of cost, time, or patient risk considerations. Consequently, computerized phantoms are an important research tool that can help in developing new imaging techniques and devices. They can simulate a potentially unlimited amount of patient anatomies and provide a known truth with which to quantitatively evaluate, compare, and improve new imaging technologies in a cost-effective and efficient method. It is essential for computerized phantoms to be anatomically realistic and produce realistic imaging data such that results from studies utilizing the phantoms are indicative of what would occur in human subjects.

The purpose of this dissertation is to develop a three-dimensional computer generated breast phantom that is based on empirical data that can be used in breast imaging research. Currently available breast phantoms are either voxelized phantoms with fixed anatomy or flexible mathematical phantoms based on geometric primitives such as spheres and cylinders. In this work, we present the method to generate a suite of hybrid breast phantoms that combine the realism of a voxelized phantom with the flexibility to easily model anatomical variations by incorporating a mathematical basis.

The first step in phantom generation was to acquire and process the imaging data. We received dedicated breast computed tomography imaging data of pendant

uncompressed breasts of human subjects from our collaborators at UC Davis. We implemented pre- and post-reconstruction algorithms to reduce the noise and scatter inherent in the images from the low-dose acquisition of the data and the cone-beam geometry of the CT system, respectively. Following image processing, we developed a custom volumetric segmentation algorithm to differentiate the breast tissues and maintain the high-resolution detail available in the imaging data. Derived from real human data, this step produced an anatomically realistic basis for the breast phantom.

Following segmentation, a subdivision surface model of the breast tissue was generated. This step introduced flexibility to the empirically based phantom by using a mathematical description for the breast tissue surfaces as subdivision surface models can be altered using affine or other transformations. This phantom can be used for imaging studies using an uncompressed geometry or it can be used to generate a finite element mesh of the breast to be used for a compression model.

Simulated compression of the breast phantom was achieved by applying finite element methods that can realistically deform the phantom. The material properties of the different types of breast tissue were incorporated into this model. Also, a comprehensive analysis of the different parameters that can affect breast phantom compression was performed. After simulated compression, the calculated deformations can be applied to the subdivision surface model to be used for studies on modalities with a compressed breast imaging geometry.

Simulated images can be generated directly from the subdivision surface model of the breast phantom with existing image simulation tools. We implemented an analytical

projection algorithm that realistically models the x-ray imaging process and includes effects from quantum noise. Images were generated that exemplify the effect of different mechanical parameter assignments to the breast phantom tissue.

To further expand our database of imaging phantoms, we implemented deformation and morphing techniques to generate new and unique datasets from the limited number of original human subject datasets. In order to illustrate the full capabilities of the phantom, we generated simulated mammograms from several finite element compressed breast phantoms and are in the process of performing a user study to validate their level of realism. While early results from the phantom are promising, there are many future improvements to be made and futures studies to be conducted.

The presented work engenders a substantial advancement in tools for breast imaging research. We have successfully developed a suite of hybrid breast imaging phantoms that combine realistic anatomy with the flexibility of a mathematical approach. These phantoms can be used effectively for imaging research to develop and improve new imaging techniques and devices for breast cancer detection and prevention.

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List of Abbreviations

2D	Two Dimensional
3D	Three Dimensional
4D	Four Dimensional
AOR	Area Overlap Ratio
bCT	Breast Computed Tomography
CC	Cranial-Caudal
CT	Computed Tomography
DBT	Digital Breast Tomosynthesis
FE	Finite Element
FEM	Finite Element Method
ML	Medial-Lateral
MLO	Medial-Lateral-Oblique
MRI	Magnetic Resonance Imaging
NLM	National Library of Medicine
NURBS	Nonuniform Rational B-Splines
PEM	Positron Emission Mammography
PMT	Photomultiplier Tube
RAM	Random-Access Memory
ROI	Region of Interest
XCAT	Extended Cardiac-Torso

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1. Introduction

Computer phantoms are becoming an essential tool for use in medical imaging research. This necessity is because of the difficulty in obtaining real human data due to subject recruitment issues related to time and cost, as well as radiation dose considerations. Simulations can be used to study the imaging system design, acquisition protocols, reconstruction algorithms, and to evaluate image processing techniques. Computerized phantoms are advantageous because they can be modified in terms of size and tissue distribution, provide a “known truth” to aid in evaluating imaging devices and techniques, and do not require any additional material costs or production time other than software processing. This project will combine a flexible and realistic computerized breast phantom with accurate models of the imaging process. The goal of this project is to create a breast phantom that can realistically simulate breast imaging data that is virtually indistinguishable from actual human breast data.

1.1 Clinical Significance

Breast cancer is a significant health problem worldwide, and in the United States it affects one in eight women. The American Cancer Society reports that in 2010, an estimated 207,090 women will be diagnosed with invasive breast cancer, and 39,840 are expected to die from this disease; only lung cancer accounts for more cancer deaths in women[1]. With improvements in early detection and advances in treatment options, the mortality rate has decreased by 2.1% annually since 1990[1].

In breast cancer, the tumor is initially localized to the breast duct or lobule and does not penetrate the duct walls to surrounding tissue. This is typically labeled as Ductal

Carcinoma In Situ and is known as cancer ‘Stage 0’. Women who find their cancer at this stage typically have a 5-year relative survival of 98%. As the cancer metastasizes, the survival rates drops to 27% for distant-stage disease[1]. This underscores the need for early detection to enable the diagnosis and effective treatment of breast cancer before it has a chance to spread[2]. Tremendous efforts have been made to improve detection technologies to permit the cancer to be detected at smaller sizes and earlier stages.

1.2 Breast Imaging Technologies

The basis of mammography stems from the work done in 1913 by A. Salomon who was the first to discover the radiological differentiation between cancerous and non-cancerous tumors, as well the identification of a non-palpable tumor on a radiograph of an excised breast[3, 4]. However, the adoption of mammography was limited until R. Egan developed a reproducible mammographic technique in 1960 and the first dedicated mammography systems with molybdenum targets and compression were available in 1969[3, 4]. Dramatic improvements have been made since the first system was introduced, including reduced dose and superior image quality. Currently, screening mammography is widely accepted as the most important and effective tool for the early detection of breast cancer and has cut the risk of dying from breast cancer by up to 35%[5].

1.2.1 X-ray imaging

1.2.1.1 Digital Mammography

Digital mammography systems are gaining acceptance and have recently been shown to increase the detection accuracy in women who were traditionally difficult to

image - pre or perimenopausal women younger than 50 who have heterogeneously dense breasts[6-8]. This result is primarily due to the radiologist's ability to adjust the images and increase the contrast in the dense areas of the breast to enhance the visibility of subtle masses or microcalcifications. The increased visibility of lesions in dense breasts is important because breast density has been linked to a four times increase in the risk of developing cancer[9].

Despite this improvement, the limitations of mammography have been widely publicized. Reports have shown that on average 30% of cancers are not detected by screening mammography[6]. The low sensitivity is primarily because the image represents the superposition of a three-dimensional object onto a two-dimensional plane, which may reduce lesion visibility because of overlying normal anatomy. Obscured anatomy may also falsely be suspected to be cancer, and may require the patient to undergo uncomfortable biopsies or additional imaging studies. On average, 11% of screening mammograms are read as abnormal and breast cancer is found in only 3% of the abnormal mammograms[2]. This means that for each mammogram, a patient has a 10.7% chance of a false positive result, which causes superfluous additional tests or treatments and unnecessary psychological stress[2]. These limitations have led to the development of other diagnostic imaging techniques that may serve as an adjunct to, or possible replacement of, x-ray mammography such as digital breast tomosynthesis, dedicated breast computed tomography, breast ultrasound, breast MRI, nuclear medicine breast imaging methods, and other emerging breast imaging technologies[10-12].

1.2.1.2 Digital Breast Tomosynthesis

Recent developments in digital detector technology allow for post-acquisition image processing, and have enabled tomographic breast imaging techniques such as digital breast tomosynthesis (DBT) and dedicated breast computed tomography (bCT) to be clinically feasible. Originally pioneered by Ziedses des Plantes in 1932, tomosynthesis is a three-dimensional x-ray imaging technique that acquires a series of projection images over a limited angle, and allows for the reconstruction of an arbitrary set of planes parallel to the detector[13]. The conspicuity of in-plane structures is improved by removing the visual clutter associated with overlying anatomy. The current implementation of DBT is very similar to existing full field digital mammography systems with one modification: the x-ray source moves in a prescribed arc and acquires a fixed number of projection images[14]. The individual projections are very low dose so that the composite dose is less than or equivalent to dual-view mammography. The tomosynthesis images are then reconstructed with one of many different algorithms; including iterative techniques such as maximum-likelihood expectation maximization, and those based on back projection (i.e. conventional shift-and-add). In addition, various deblurring algorithms have been used, including filtered back-projection and matrix-inversion tomosynthesis[15, 16]. In general, tomosynthesis images have high resolution in the x-y plane parallel to the detector and lower resolution in the z, or depth, direction[17]. In-plane objects have improved visibility over out-of-plane objects with a better visualization of the lesion border[14]. The technique is currently undergoing a pivotal clinical trial for FDA approval and there are several studies that show improved detectability of masses and lower recall rates over traditional mammography[17-22].

Unfortunately, DBT is fundamentally constrained by its limited angle acquisition that results in reconstruction artifacts, and the non-isotropic resolution of the image sets has been shown to obscure the visualization of suspicious microcalcifications[19, 20, 23].

1.2.1.3 Dedicated Breast Computed Tomography

Dedicated breast computed tomography (bCT) imaging systems are in development to provide a more complete tomographic approach with near isotropic resolution[24-49]. Earlier breast CT studies involved using conventional CT scanner technology, in which the images were acquired transversely and x-rays had to penetrate the thoracic cavity. This technique led to substantial radiation dose to non-breast structures, and suffered from cardiac and respiratory motion that reduced image quality[35]. More contemporary breast CT involves devices that image only the breast. These dedicated breast CT imaging devices use a geometry that accommodates a breast in a pendant and uncompressed position while the patient lies prone on a specially designed acquisition bed. An x-ray tube mounted on a rotating gantry acquires a series of low dose projections in a full 360° rotation around the breast, with a dose equivalent to dual-view mammography. Benefits of dedicated bCT include 3D breast images with near isotropic resolution that can help to better delineate the extent of disease, reduced motion artifacts, reduced exposure to non-breast anatomy, and high contrast resolution[42].

1.2.2 Non-Ionizing Breast Imaging Technologies

All x-ray imaging modalities expose the patient to ionizing radiation. Non-ionizing breast imaging modalities such as ultrasound and MRI are important additional tools in clinical use and in research.

1.2.2.1 Ultrasound

Breast ultrasound is a modality that has shown promise in improving the specificity of cancer detection. Non-ionizing, high-frequency sound waves, generated by an ultrasound transducer, pass through the uncompressed breast. The sound waves travel into the tissue, and are reflected by internal structures and tissue interfaces in the body, creating echoes. The reflected waves that reach the transducer are used to create images. The echo signals are indicative of the elasticity of the various tissues in the beam path. The depth of an echo-producing structure is determined from the time between the pulse emission and echo return to the transducer[50]. Breast ultrasound is currently used to evaluate breast abnormalities that are found with screening or diagnostic mammography and also to guide the mammographer during fine needle aspiration biopsies. With excellent soft-tissue contrast-resolution, breast ultrasound is useful for differentiating between a benign fluid-filled cyst and a dense mass, a lymph node and a suspicious lesion, and benign and malignant masses[51]. These specific benefits reduce unnecessary biopsies and save the patient from additional exams and discomfort. Ultrasound is a typical follow-up tool when a screening mammogram is suspicious or inconclusive, as often occurs in women with dense breasts[51]. There are many practical considerations that make ultrasound attractive; it is non-invasive, non-ionizing, widely available, and low cost compared with other modalities such as MRI[51]. However, it is not recommended for screening because of spatial resolution limitations, unreliable detection of microcalcifications, higher rate of false-positives, operator skill dependency, and the lack of standardized exam techniques[22, 51, 52].

1.2.2.2 Breast Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is another non-ionizing imaging modality that is used in breast imaging. It uses the magnetic moment of protons in the body to produce images without ionization. During the breast MRI exam, the patient lies prone and the breasts fit into a hole in the table that is surrounded by a breast coil that sends and detects radio wave signals from the breast. The table is then moved into the MRI magnet to perform the scan. The application of a radiofrequency pulse causes the axes of the protons to momentarily go out of alignment. The rate and magnitude of the energy release that occurs as the proton's return to alignment generate a radio signal that is unique to the tissue and is received by the coil. A magnetic field gradient is used to slightly vary the strength of the magnetic field as a function of position thereby varying the proton's resonant frequency and determining the position of each signal by their magnetic moment. Each different tissue type has different local magnetic properties, which create images that are highly sensitive to anatomic variations[50]. A paramagnetic gadolinium-based contrast agent is injected intravenously to provide reliable detection of cancers and other lesions. Contrast-enhanced breast MRI provides a tool with very high sensitivity and can detect invasive breast cancers, even in very dense or fibrous breasts because they can show increased or abnormal blood flow in the breast that is not visible on a mammogram. Many groups have reported studies evaluating breast MRI and it has been shown to have an overall sensitivity ranging from 71-100% versus 16-40% for mammography[53-55]. Screening breast MRI is recommended for women with a 20-25% or greater lifetime risk of breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease[53].

However, the increased sensitivity also makes breast MRI more likely to show false positives than mammography, with specificity rates varying from 80-99% versus mammography's 93-99%[53-55]. The rate of false positives and the prohibitive cost, ten times the cost of a mammogram, make screening MRIs less than ideal for most patients, but useful for women at high-risk. MRI is time-consuming, may require intravenous contrast administration to increase lesion-background contrast, and be problematic for claustrophobic patients[22, 56].

1.2.3 Nuclear Medicine Imaging

While the modalities mentioned previously use tissue-specific properties to create images illustrating anatomic location, nuclear medicine imaging exploits the metabolic characteristics of the tissue to form images demonstrating functional information. Nuclear medicine procedures are very useful to determine the malignancy of a tumor. Since most cancerous tumors are very fast growing, they have a greater density of blood vessels to supply the necessary oxygen and nutrients to the cancer. A radioactive tracer that is injected into the blood stream is designed to be taken up preferentially by highly metabolic areas of the body and give off radiation that is detected by the nuclear medicine imaging system. Nuclear imaging studies form images typically using isotropically emitted gamma rays or annihilation photons from the radioactive decay of the radionuclide. The benefit of functional imaging is that the sensitivity of the technique is less affected by breast density, implants, or architectural distortion after surgery or radiation than other techniques. Unlike radiography, the attenuation of x- or gamma rays is not useful in nuclear medicine, other than for attenuation correction, since the images are formed by measuring the photon flux density[50].

1.2.3.1 Scintimammography and Breast Specific Gamma Imaging

Scintimammography is a nuclear medicine procedure where a radioactive tracer is injected into the circulatory system. The radioactive tracer is preferentially taken up by the increased metabolism of the breast tumor and emits gamma radiation as it decays. The gamma rays are then detected on special gamma cameras that use collimation to determine the direction of the detected photons. The lead walls of the collimator absorb most of the photons that come from directions not aligned with the collimator holes. The photons that pass through the collimator are absorbed into a sodium iodide crystal that then emits visible or ultraviolet light. These light photons are converted into an electrical signal and amplified by the photomultiplier tube (PMT). These signals are further amplified by the preamplifiers. The amplitude of the pulse produced by the PMT is proportional to the amount of light it received from gamma ray interaction in the crystal. The signals are formed into digital images and a cancerous breast will show a bright spot at the lesion site. Scintimammography performed with a general-purpose gamma camera is limited by its inability to reliably image cancers smaller than 1 cm because of its intrinsic resolution. The sensitivity of scintimammography for cancers less than 1 cm is 35%-65%[57, 58].

Breast specific gamma imaging (BSGI) with ^{99m}Tc -Sestamibi is a recently developed technique that uses a high-resolution, small-field-of-view breast-specific gamma camera (Dilon 6800; Dilon Technologies, Newport News, VA). The patient sits with her breast minimally compressed between two plates and four images are acquired in approximately 30-40 minutes. In a recent study, the smallest invasive cancer and the smallest DCIS, both detected by using BSGI, were 1 mm[58]. Overall, the sensitivity of

BSGI for sub-centimeter lesions was 88.9%. These studies show that the sensitivity of BSGI is as good as MRI and potentially has higher specificity[57, 58].

1.2.3.2 Positron Emission Mammography

During a positron emission mammography (PEM) scan, the patient is injected with the glucose containing radiopharmaceutical ^{18}F -fluorodeoxyglucose (^{18}F -FDG) an hour before being imaged with the system. This waiting period allows the radioactive tracer to become concentrated in the breast cancer to allow for sufficient lesion-to-background contrast. Positrons are emitted by the decay of fluorine 18 and eventually will collide with an electron, resulting in the annihilation of both particles and the creation of two gamma-ray photons that are emitted in almost exactly opposite directions. When a photon pair is detected by two detectors on the scanner within a certain amount of time, the straight line between these two detectors is used to compute the location of the annihilation event and form the image. In a standard 10 minute acquisition, the images can be acquired in analogous views to mammography, which allows for co-registration and comparison. A recently FDA approved device that has been developed (Naviscan PET systems, Inc., San Diego, CA) has two moving detector heads, mounted on compression paddles, which perform volumetric acquisition of an immobilized breast[59]. PEM has the capability to differentiate metabolically active cancerous tumors from benign and has shown that it has a sensitivity of 91% and a specificity of 93% with a minimum detected tumor size of 1.5-2 mm[60]. The combination of conventional imaging with PEM resulted in a 95% positive predictive value, highlighting the advantages of combining anatomic with metabolic characterization in cancer detection.

This technique is currently FDA approved for pre-surgical planning, staging of breast cancer, suspicious recurrence, and neoadjuvant chemotherapy response.

1.2.4 Multimodality Imaging

Each of the modalities exploits different physical properties of normal and malignant tissue in order to accentuate their contrast as well as different data-acquisition strategies for image formation. Multi-modality imaging is an important avenue of research because the complexity of diagnosing breast disease is augmented by the wide variety of breast tissue. The fusion of data from two or more modalities may be more successful than a single technique alone and increase diagnostic accuracy. A few examples of ongoing multi-modality breast imaging research are: ultrasound with x-ray imaging or MRI, tomosynthesis and optical imaging, SPECT with CT, and PET with CT[24, 61-65].

1.3 Imaging Phantoms

It is essential for the advancement of these systems to have a tool that can be used for technique testing and evaluation because it is difficult to collect multiple images of the same patient for comparative analysis. Imaging phantoms are often employed to optimize imaging parameters, improve image quality by providing a “known truth” to evaluate new reconstruction algorithms, and aid in the development of novel imaging techniques and systems. Physical phantoms are typically made out of materials that simulate breast tissue but cannot adequately represent a comprehensive patient population with a variety of breast sizes, shapes, compositions, and parenchymal detail. The materials may also be very expensive, which makes it difficult to generate patient-

specific phantoms. Recently, Fujisaki *et al.* presented a novel physical breast phantom that has adjustable glandular fraction depending on the amount of plasticizer added during the phantom creation[66]. Although this is an interesting tool that may be used to improve mammography performance and dosimetry, the requirement for the production of individually varying physical phantoms is time consuming and costly.

Computerized phantoms are an important and increasingly useful tool in medical imaging research because of the difficulty in obtaining real human data. Simulations with computerized phantoms can be used to study many aspects of the imaging system design and image processing techniques. The flexibility provided by computerized phantoms is advantageous because they can be modified in terms of size and tissue distribution to generate any number of anatomical variations present in a patient population. The anatomy and physiology is user-defined so they provide a known truth from which to evaluate imaging devices and techniques without additional material costs and production time other than software processing.

1.3.1 4D-XCAT Phantom

An example of a computerized phantom that is used for imaging research is the four dimensional (4D) extended Cardiac-Torso (XCAT) phantom illustrated in Figure 1-1. The XCAT phantom was developed by Segars *et al.* to provide a realistic and flexible anatomical and physiological model of the human body for use in imaging research[67-71]. The XCAT phantom combines a voxelized approach with a mathematical approach to offer a phantom with realistic and detailed organs that remain flexible to allow for anatomical variation and organ deformation. The XCAT anatomy

was based on the Visible Male and Female CT datasets from the National Library of Medicine (NLM). The structures of the XCAT phantom are defined using a combination of non-uniform rational B-splines and subdivision surfaces, which can accurately model complex 3D anatomical surfaces. The anatomical detail of the XCAT phantom, shown in Figure 1-1, was recently enhanced and extended to include more than 9000 detailed structures from head to toe with the purpose of making the phantom applicable to high-resolution imaging modalities such as MRI and x-ray CT. When combined with accurate models of the imaging process (e.g. SPECT, PET, MRI, ultrasound, and CT) the 4D XCAT is capable of simulating realistic imaging data close to that of actual human subjects. The XCAT phantom has gained widespread use in medical imaging research for evaluating and improving instrumentation, data acquisition, and image processing and reconstruction methods. Despite the advancements made to provide a complete anatomical model, the female anatomy of the XCAT phantom only uses a simple outer surface to model the breast and does not include any detailed structures. As a result, the XCAT phantom is currently limited in its application to breast imaging research.

Figure 1-1: Whole-body anatomies of the male (left) and female (right) XCAT phantom. Different levels of detail are shown building up to the whole model for each, shown with transparency. The circulatory system, organs and glands, skeleton, and muscles are shown for both male and female. Figure used with permission by Segars *et al.*

1.3.2 Breast Phantoms

Many emerging and established modalities would benefit from having an accurate and validated model of the breast to allow imaging procedures to be optimized under clinically relevant conditions. The effects of acquisition parameters (e.g. number of angular spacing of projections in tomosynthesis), physical processes (e.g. scatter, beam hardening, heel effect, etc.), and sources of variability (e.g. patient anatomy, dose, and positioning) can all be evaluated and studied in tandem or independently using patient-quality simulated data. A realistic computerized breast phantom would also provide the necessary framework with which to quantitatively compare the effectiveness of different imaging methods in tasks that model clinical practice such as lesion detection. Collaborating or multidisciplinary groups can share the same virtual phantom without having to transport a physical phantom around and impartial comparison can be

performed using the same phantom to evaluate claims from competing groups for publication or regulatory approval.

1.3.2.1 Breast Anatomy

In order for studies performed using a breast phantom to have merit, it is essential that the breast phantom accurately and realistically depict the highly variable human breast anatomy. The normal breast primarily consists of three tissues: fat (subcutaneous, retromammary, and intraglandular), glandular (connective and fibrous tissues, Cooper's ligaments, ducts, and lobules), and skin, which provides the primary support for the breast. Fibrous and connective tissue is found interspersed throughout the breast, providing shape and structure. Cooper's ligaments are criss-crossing and overlapping bits of fibrous tissue that course between deep and superficial layers of the breast, incompletely compartmentalizing the structures of the breast. They form around and support the variable ductal network of the breast, attaching to the skin with superficial extensions. Fat both surrounds and is interspersed throughout the breast by varying amounts. The normal breast is illustrated in Figure 1-2[72]. Although not illustrated in the figure, the vascular, lymphatic, and nervous systems of the breast also play important roles in breast imaging; for example: contrast agents and radionuclides are injected into the vascular network, axillary or intramammary lymph nodes are a primary location for breast cancer staging, and pain and discomfort caused by compression are an impetus for non-compressed imaging geometries. Therefore, all of these structures should be represented in the breast phantom in order to generate realistic simulated imaging data.

Figure 1-2: Illustration of the anatomy of the breast. (Reprinted with consent from Medela AG for educational purposes).

1.3.2.2 Mathematically Based Breast Phantoms

There have been several computerized 3D breast phantoms created; the majority were based either on the voxelization of real subject data or mathematical models based on geometric primitives[73-80]. Bakic *et al.* created synthetic x-ray mammograms using a 3D simulated breast tissue model that consisted of two ellipsoidal regions of predominantly glandular and predominantly adipose tissue. The adipose tissue was organized into round compartments, formed by fibrous Cooper's ligaments. The glandular region also contained smaller adipose circular compartments. In addition, the breast ductal network was modeled by using a randomly branching tree. Bakic *et al.* simulated compression on the phantom by deforming individual regions on breast tissue

slices that were positioned normal to the compression plates. These slices were then stacked together again to form the total compressed breast model. Mammogram generation was simulated using an x-ray propagation model and assumed a monoenergetic x-ray spectrum with parallel beam geometry and no scatter. Although qualitatively the synthetic mammograms appeared to lack vasculature and fine tissue structures, statistical comparisons of three texture descriptors were computed to be similar to those of clinical mammograms[73-75].

Bliznakova *et al.* used 3D geometric primitives to create a comprehensive breast phantom that included the breast external shape, ductal system, 3D mammographic texture, abnormalities, Cooper's ligaments, pectoral muscle, lymphatic system, lymph nodes, blood vessels, and skin. The geometric primitives are transformed to voxel values in the final breast matrix. Simulated monoenergetic fan beam projections of the compressed phantom were used to generate mammographic images of several breast models of different size, shape, and composition and then compared to real mammograms in order to evaluate how realistic the simulations appeared. Quantitative and qualitative evaluation studies were performed with selected ROI's of the simulated images and results showed a good correlation between synthetically generated and real radiographs[76, 80, 81]. While the quantitative analysis on ROIs was promising, the Bliznakova phantom remains a simplistic representation of complex human breast composition and does not appear realistic.

Zhou *et al.* created a 3D breast phantom that included models of ductal structures, fibrous connective tissue, Cooper's ligaments, pectoralis muscle, lesions, and structural noise. Low dose tomosynthesis projections of the uncompressed breast phantom were

simulated and reconstructed using three different algorithms to evaluate the detectability of simulated masses under low-contrast situations with three different reconstruction methods[79].

Shorey presented a 3D voxelized breast phantom that models a half-ellipsoidal breast surrounded by a skin layer, a branching ductal network, a layer of subcutaneous adipose tissue, an inner volume with randomized adipose and glandular tissue components, masses, and microcalcifications[77]. The phantom could be generated at different breast densities and sizes with different realizations of the anatomy. Although offering a complex and detailed simulated anatomy, realism could be improved by modeling real human data.

While all of these phantoms provide detailed internal structures, they are still generated from simple geometric primitives and cannot mimic the complexity of human breast anatomy.

1.3.2.3 Voxelized Breast Phantoms

Hoeschen *et al.* created a voxelized breast phantom, consisting of segmented skin, adipose, and breast tissue; from high resolution CT data of compressed breast specimens taken from cadavers for the purpose of mammographic dose calculations[78]. The Hoeschen phantom appears to be more realistic than mathematically based phantoms, but the phantom's size and composition cannot be modified.

O'Connor *et al.* are creating an ensemble of voxelized breast phantoms that are generated by acquiring CT data of mastectomy specimens placed into holders that shape the excised specimen into an uncompressed or compressed position[82-84]. While the simulated images are realistic, the O'Connor's voxelized phantoms have a fixed anatomy

and position after they have been generated and lack the flexibility of mathematical phantoms. In addition, they are placed in holders that can only simulate breast shape and do not maintain their original anatomical fidelity.

1.3.2.4 Hybrid Breast Phantom

Recent advances have been made towards a hybrid breast phantom. Kellner *et al.* employed segmented bCT data of human subjects to develop a simulated compression algorithm using finite element methods[85, 86]. A study using the segmentation and compression model was used to evaluate an algorithm to measure the volumetric breast density from digital mammograms. They compared the calculated density value of simulated mammograms to the actual value derived from the segmented CT dataset[87]. While this model combines a realistic anatomy with the ability to simulate mammographic compression, it does not have the flexibility of a mathematically based phantom since it remains a model with fixed anatomy.

1.3.3 Dissertation Objectives

Although there are a wide variety of available computerized breast imaging phantoms that have recently been developed, there are limitations to each of them. Mathematical breast phantoms are flexible and can model varying compositions of breasts, but they are too simplistic in their representation of breast tissue and the resultant images do not appear realistic. Voxelized breast phantoms offer a more realistic approach, however they are modeled after a single breast and do not offer the flexibility needed to needed to represent the variability present in the patient population. There is

clearly a need for a realistic and flexible computerized breast phantom to be used for breast imaging research that is able to simulate the variability in human anatomy.

The goal of this work is to create a detailed 3D computerized breast phantom, based on empirical data obtained from dedicated bCT of human subjects and produced using subdivision surfaces to model the complex topological structures of the breast. The breast phantom will be incorporated into the 4D XCAT phantom developed by Segars *et al.* in order to make it applicable to breast imaging research. This will be developed in a similar way as the Kellner model; however there will be distinct advantages that XCAT breast phantom will possess, including the ability to simulate the variability of breast anatomy in the patient population.

This project presents research with a detailed breast phantom that is based on real human data and includes a number of unique properties not currently offered by other phantoms. The specific aims of this project are to (1) generate high resolution bCT data with the scatter and noise removed; (2) segment the denoised and scatter corrected bCT data; (3) create the breast phantom from the segmented data; (4) use finite element techniques to realistically simulate mammographic compression of the phantom; (5) implement a realistic image simulation method to generate images; and (6) generate a suite of breast phantoms from a limited amount of available bCT data by applying deformation and morphing techniques. To the best of our knowledge, this will be the first hybrid breast phantom that combines the realism of high-resolution voxelized data, the flexibility of a mathematical phantom, and the ability to generate unique and distinct datasets. This project has the potential to contribute significantly to breast imaging research for the advancements of cancer detection techniques and technologies.

1.3.3.1 Chapter Summary

A short description of this dissertation's chapters is provided here. Chapter 2 "Imaging Data Preparation" provides the methodology to prepare the imaging data for phantom creation, thereby providing the realistic anatomical basis for the phantom. It provides an overview of how to remove the noise and scatter from dedicated breast CT data by implementing existing pre and post reconstruction techniques. It also includes a short summary of existing segmentation algorithms and follows with a detailed description of the volumetric segmentation algorithm developed specifically for the denoised and scatter corrected bCT data. The work presented in this chapter has been published in the journal Medical Physics[88]. Chapter 3 "Breast Phantom Creation" demonstrates how to introduce the flexibility of a mathematical approach to the XCAT breast phantom from the segmented data by generating a subdivision surface model of the breast tissues that can be altered using affine or other transformations. It also describes how to prepare the phantom for finite element compression by generating a solid mesh of tetrahedral elements. Chapter 4 "Simulated Compression" describes the finite element methods employed to simulate compression of the XCAT breast phantom. The chapter provides an overview of existing FE models of the breast. It describes a slightly modified segmentation algorithm to generate the phantom's anatomical basis than what was described in Chapter 2. The chapter includes an analysis of the parameter choices investigated for the finite element model. Chapter 5 "

Simulated Radiographic Images” explains how to generate realistic imaging data from the subdivision surface model. It covers how to generate images of the compressed phantom by translating the tetrahedral breast model into subdivision surfaces. The chapter includes simulated images generated using the phantom. The work described in Chapters 3, and 4 have been submitted to the journal Medical Physics. Chapter 6 “Generation of a Suite of XCAT Breast Phantoms” presents an algorithm to deform and morph the segmented bCT data in order to generate new and unique breast phantoms. It includes generated images of the new phantoms in order to illustrate the effect of the algorithm. The work described in this chapter will be submitted for publication in the journal of Medical Physics. Chapter 7 “Future Directions and Concluding Remarks” discusses future directions for this work ends with some concluding remarks.

2. Imaging Data Preparation

2.1 Introduction

Any volumetric imaging data may be used to generate the anatomical basis for the phantom. For our particular application, we chose dedicated breast CT data due to its high resolution detail. Depending on the data selected for the phantom, different image processing techniques need to be applied to it so as to facilitate segmentation of the data. Once a dataset is segmented, flexible surface models can be created for each breast tissue.

2.2 Dedicated Breast CT Data

Dedicated breast CT (bCT) is currently an investigational tool that may eventually have applications in breast cancer screening, diagnostic evaluation, or therapeutic applications. There are several groups currently researching dedicated bCT at the University of California (UC) at Davis[33-39, 48], Duke University[24-32], University of Rochester[43-47], University of Massachusetts Medical School[89-91], and University of Texas M.D. Anderson Cancer Center[40, 41]. The majority of our work used the bCT data collected with a prototype dedicated breast CT scanner from the group led by John Boone at UC Davis.

Data from over one-hundred human subjects has been collected to date. The subject lies in the prone position on a scanning table with the pendant breast hanging through an opening in the table without compression. The gantry rotates 360° in the horizontal plane around the breast and acquires 500 cone-beam projection images in 16.6 seconds. Each breast is scanned separately and the mean glandular radiation dose delivered to the breast is constrained to be the same as two-view mammography by

varying the breast CT technique factors such as tube voltage and tube current-time product.

The low-dose acquisition of the breast data and the cone-beam geometry of the CT system result in image degradation due to considerable quantum noise and scatter radiation, respectively. Therefore correction of scatter and noise is a necessary part of this project because the non-uniformity of the background may cause the denser tissue (glandular tissue) values to be lower than the less-dense (adipose tissue) values and vice versa. This presents a problem when the segmentation of bCT data is performed using value-based techniques in order to create the breast model. Algorithms were implemented to reduce noise and correct for scatter in the breast CT images as described below.

2.2.1 Noise Reduction

A denoising algorithm developed by Xia *et al.* [92, 93] was used in order to suppress noise in bCT projection images prior to reconstruction and without loss of spatial resolution. In a bCT projection image, the noise is larger toward the chest wall, and when the dose is reduced, this phenomenon becomes more pronounced. The Xia method removes noise with a spatially adaptive partial diffusion equation technique that takes into account the non-uniform distribution of noise in the projection images. The projection images were processed with 40 iterations of the Xia denoising algorithm instead of the recommended 10 iterations, based on subjective evaluation of the effect of noise suppression on subsequent segmentation. Tomographic images were reconstructed using a custom written Feldkamp filtered back-projection algorithm[92, 93] and generated 255 768×768 coronal images with an in-plane resolution of 250 μm and slice

thickness of 500 μm . The slice thickness was chosen based on having sufficient data for phantom creation. To demonstrate the noise reduction achieved with the denoising algorithm, the projections were processed using different numbers of denoising iterations (0,10,40) before reconstruction. Ten 100×100 regions of interest (ROI's) were chosen across ten slices throughout the reconstructed image volumes and the mean of the standard deviations of these ROI's was measured.

2.2.2 Scatter Correction

A post-reconstruction scatter correction technique was implemented to correct for background non-uniformity in each coronal image[94]. The cupping artifact due to scatter radiation was modeled as a circularly symmetric additive background signal profile in the reconstructed breast images. The artifact lowers the true tissue signal in a non-uniform way with a greater bias towards the breast center. The correction signal was based on a radial sampling technique to obtain an estimate of the adipose tissue signal in the coronal images. The center of each coronal slice was defined and the minimum value of each radius was used to generate an estimate of the adipose tissue signal. Any inconsistencies or trends across the adipose tissue signal were assumed to be from scatter and were manifested in the coronal image as a cupping artifact. A 2nd degree polynomial was fit to each coronal slice's estimate for the adipose tissue signal. The values for the polynomial function were averaged across all slices and used to simulate the cupping artifact in each slice. The 2nd degree polynomial used for correction was $0.13x^2 - 0.64x + 9858$. The simulated cupping artifact was subtracted from the breast volume in order to correct for scatter. Figure 2-1 illustrates the signal that was subtracted from each slice in order to perform post-reconstruction scatter correction to remove the cupping artifact.

Figure 2-1: Signal matrix subtracted from each slice to correct for the cupping artifact due to scatter.

2.2.3 Image Processing Results

Figure 2-2 illustrates the denoising algorithm's effect on the original images. It clearly removes a significant amount of noise and provides for clearer visualization of the glandular tissue in the denoised data. Table 2-1 shows that the average standard deviation of ten 100×100 ROI's decreases as the number of denoising iterations increases, which demonstrates the noise reduction due to implementing the denoising technique.

Figure 2-2: (A) is the original reconstructed CT data. (B) is the data with 10 denoising iterations, as optimal for image review. (C) is the data with 40 denoising iterations to perform maximum noise reduction for segmentation purposes only.

Table 2-1: Comparison of standard deviations for different levels of denoising

Original Data (0 iterations)	Denoised Data (10 Iterations)	Denoised Data (40 Iterations)
0.119±0.013	0.07±0.011	0.057±0.011

2.3 Image Segmentation

After the datasets were prepared by performing noise and scatter correction, the next step was the automated classification of the bCT data into the various breast tissues that were used to define the appropriate physical characteristics of each voxel during simulated compression (Chapter 4) and image generation (Chapter 0). This was made difficult by image non-uniformity and noise as covered in the previous section. Although ameliorated by the denoising and scatter correction steps, these issues may result in segmentation errors if they caused denser tissue (i.e. glandular tissue) to appear less dense (i.e. adipose tissue) and vice versa. There was no exact demarcation between adipose, glandular, and skin tissues based on the voxel values as illustrated in the histograms shown in Figure 2-3. This made the segmentation of the breast data difficult and we could not use a simple histogram classifier alone.

Figure 2-3: (a) Histogram of full breast data. (b) Histogram of a single coronal slice.

2.3.1 Overview of Segmentation Algorithms

There are numerous strategies to perform segmentation of varying degrees of complexity and we describe a few methods herein. The first method is K-means clustering. This is an iterative method that first assigns each pixel in the image to a single cluster by calculating its minimum “distance” (defined by variance, value, location, etc) to one of K previously defined cluster centers. The cluster center is recomputed by averaging all pixels currently in the cluster and the clustering process is repeated with the new cluster centers. The second group are histogram methods, which define groups by using the peaks and valleys of the histogram and setting thresholds for differentiation. The third encompasses region growing methods. These methods typically use a “seed” as an input that marks the starting point for each object to be segmented. The regions are grown around the seed by calculating the similarity of each neighbouring pixel with the current region, in order to decide whether or not to assign it to the region. The fourth method uses morphological operations, which are a set of image processing techniques

derived from set theory and based on shape. The input signals are compared to a structuring element B of an arbitrary shape with the final aim to transform the signal into a simpler one by removing irrelevant information. The most basic building blocks for many morphological operators are dilation and erosion. Dilation is obtained by reflecting B about its origin and then shifting this reflection by x. The dilation of A by B is the set of all x displacements such that A and the reflection of B overlap by at least one nonzero element. The value assigned, is the maximum value of all the overlapping pixels. The erosion of A by B is the set of all x displacements such that A and B overlap completely. The value assigned is the minimum value of all the overlapping pixels.

$$\text{Dilation: } A \oplus B = \{x \mid [(\hat{B})_x \cap A] \subseteq A\} \quad (2-1)$$

$$\text{Erosion: } A \ominus B = \{x \mid (B)_x \subseteq A\} \quad (2-2)$$

2.3.1.1 Breast Specific Segmentation Algorithms

There are segmentation methods that have been developed for processing different breast imaging modalities, and a few examples are given here. Li *et al.* developed a method to segment breast tissue from background as well as glandular tissue from adipose tissue in breast MRI images[95]. For the glandular segmentation method, they used a spatially adaptive threshold value that was implemented with a sliding window. Yuan *et al.* developed a lesion segmentation method for digital mammograms using a geometric active contour model that minimized an energy function along the evolving lesion contour. A radial gradient index was first applied to set the initial segmentation, and a dynamic stopping criterion was implemented to terminate the contour evolution when it reaches the lesion boundary[96]. The authors used the area overlap ratio (AOR) between a manually segmented lesion and a computer segmented

lesion to quantitatively evaluate performance. Defining an AOR threshold of 0.4, they found that their method correctly segmented 85% of the images they tested. Ikedo *et al.* presented a tool to automatically detect masses in whole breast ultrasound images[97]. The authors used the Canny edge detector, and the edges were classified as either near-vertical or near horizontal. The near-vertical edges were chosen as potential mass candidates and then segmented with the watershed algorithm. Mass candidate regions were detected using the segmented regions and previously defined low density regions.

Lesion segmentation methods such as those by Yuan and Ikedo may not apply to whole breast segmentation because of the breasts' varying glandular tissue distribution.

2.3.1.2 Dedicated bCT Image Segmentation

There have recently been segmentation schemes developed specifically for dedicated bCT data. Nelson *et al.* used the dedicated bCT data from UC Davis that we are using, to develop an automated classification method for each slice of the volume[85]. The images were reconstructed using a modified Feldkamp cone-beam algorithm. Variations in CT number due to cone-beam artifacts across the field of view and through the volume required normalization between slices by aligning the pixel histograms for each slice. They used a five-point median filter in order to reduce the noise in each slice prior to computing the slice histogram. Next, they used a two compartment Gaussian fit of the histogram to separate between fat and skin/glandular tissue. By assuming that skin was exterior and glandular tissue was interior, they differentiated between skin and glandular tissues based on their geographic location. They used region growing to define both the skin and fatty tissue and then classified everything else within the breast as glandular tissue. They automatically compared these

tissue classifications with the original histogram and re-assigned incorrectly classified voxels to complete the procedure. Overall, their results demonstrated a successful classification of breast tissues. Their process was validated by adding increasing amounts of Gaussian noise to segmented slices and then re-segmenting them. The results of the segmentation agreed with the original reference segmented slices to within 1% using a voxel-to-voxel comparison. However, this validation was not a true measure of segmentation accuracy because they simply added noise to a segmented slice and re-segmented it. There were no scatter artifacts or fine-detail dense structures added that the segmentation may have misclassified. Radiologists were asked to grade the quality of the segmentation, and they found that 97.7% of the classification was judged to be very good or better. However, they used only a subset of their segmented slices for this analysis in view of time constraints. Their results may change if they used the entire volume of data or if they quantitatively compared what a radiologist would actually draw to the segmented data. The main challenges to the algorithm's performance were due to the non-uniformity from the cone-beam geometry and image noise from the low dose acquisition, which ultimately limited the breast tissue contrast.

Packard and Boone also created an automated segmentation scheme for the same set of bCT data from UC Davis[98]. They used a histogram-based 2-means clustering algorithm to first segment the breast from the background, and then second, to estimate a threshold to segment the glandular from the adipose/skin tissues by estimating the percent glandularity. A seven-point 3D median filter was applied to the CT volume, and the histogram-based 2-means clustering algorithm was repeated in order to recalculate a new percent glandularity. This iterative process made the histogram appear more bimodal,

until the percent glandularity converged. In order to eliminate low frequency variations they applied a 2D parabolic correction to flatten the adipose tissue in each slice after the median filtering. In addition, an adaptive median smoothing algorithm was used to smooth the adipose tissue while preserving the thin glandular fibers. Finally, the skin was segmented by raster scanning each slice for the air/tissue boundary and using the threshold between glandular and adipose tissues to define the skin border. The segmentation technique was tested on the bCT datasets and subjectively showed good performance with little to no noticeable degradation of glandular tissue. Two 3D mathematical phantoms were used to quantitatively determine the accuracy of the segmentation. It was found to measure the percent glandularity in the phantom to within 0.03%. However, the authors found that their method was only able to preserve small microcalcification sized spheres greater than 0.8 mm and small fibers with diameters greater than 1.2 mm.

At the 2008 SPIE Medical Imaging Conference, O'Connor *et al.* presented a method to develop a breast model from segmented reconstructed images of mastectomy specimens. These specimens were placed in a special holder and imaged with a prototype bench-top cone beam bCT imaging system[82-84]. The group used a commercially available segmentation tool in the Mimics software (Materialise NV, Leuven, Belgium). In addition to value thresholding, the tool also included morphologic operations, region growing, and Boolean operations on single or multi-slices. The final segmentations were visually evaluated to have good agreement with the actual specimen reconstruction. Since the software was essentially a “black-box”, the author’s have investigated creating their own segmentation algorithm so that they can control and refine

the parameters for segmentation. However, they have not detailed their methods except to mention using prior knowledge of the slice histogram to differentiate tissues.

2.3.2 Segmentation Algorithm for the XCAT Breast Phantom

Although promising, the segmentation methods mentioned above did not perfectly segment the breast data based on our visual inspection. The majority of them operated on 2D slice data and did not incorporate information from neighboring slices, which may improve segmentation results. We initially approached the segmentation of bCT data by using a manual segmentation tool developed by Segars *et al.* to segment CT data. A screenshot of the segmentation tool is shown in Figure 2-4. This proved to be not only inefficient but also inexact because of the high variability and complexity of breast tissue.

Figure 2-4: Screenshot of the manual segmentation tool.

Therefore we focused on generating an automated segmentation algorithm that could accurately differentiate the tissues on bCT data and incorporate 3D information. All segmentation steps were performed using MATLAB R2007a (The MathWorks, Inc.,

Natick, MA). Only three user interactions in the segmentation routine were required. The first was to define the first and last coronal slice in the bCT data. This ensured that artifacts near the chest wall would not hinder the segmentation and that memory usage could be minimized by disregarding the extra coronal slices that did not contain any breast data. The second was to define parameters that adjust the scatter correction matrix to optimally work for the breast undergoing segmentation. The third was to tune the threshold between the breast volume and air to each breast. The methods described in this chapter were developed and described for a single breast dataset; but the techniques have been implemented successfully to segment several additional bCT datasets.

2.3.2.1 Breast Masking

After the user defined parameters were entered, the first step in segmentation was to define a binary mask for both the breast volume and the skin. This mask was used to target the segmentation to the breast volume and not the background. This mask also served to classify the adipose tissue by default, since the algorithm assumed that everything within the breast volume that was not classified as glandular tissue or skin would be classified as adipose tissue. Several steps were used to define the mask including thresholding, filtering, and morphological operations. The breast volume mask can be defined using a threshold between the background and breast tissue. However, as previously mentioned, the threshold needed to be tuned to each breast volume since the noise reduction and scatter correction image processing steps may have changed the values of the data.

The order of binary masking performed was not critical to the overall performance of the phantom. In the experimental method described, the skin mask was

defined first since the skin mask required a non-masked image to create and masking of the entire breast volume was done directly after the mask definition.

2.3.2.1.1 Breast Skin Mask Definition

To define a mask for the skin, the local standard deviation of each coronal slice was determined using the Matlab '*stdfilt*' function. The '*stdfilt*' function requires a structuring element, which was defined as a ball of height and radius of 6 voxels. The output of '*stdfilt*' was normalized and thresholded using 0.1 as the cut off. To define a mask for the skin, the result was morphologically dilated to ensure full skin coverage with the skin mask. The dilation structuring element used was a disk of radius 6. The values used to define the morphological structuring elements were determined by trial and error for a single example breast.

2.3.2.1.2 Breast Mask Definition

The breast volume mask can be defined with a threshold between the background and breast tissue. However, the threshold needed to be tuned to each breast volume since the different image processing steps may have changed the values of the data. To define a mask for the breast volume undergoing segmentation, all voxels that were less than 8000 in value were set equal to zero. The remaining breast was morphologically opened using a disk structuring element with a radius of 20. This ensured that all voxels within the breast volume would be maintained even if some were below 8000 in value. A threshold was found using the Matlab '*graythresh*' function and the mask for the breast was defined with this value. The mask was applied to the breast such that all values not defined with the mask were set to zero.

2.3.2.2 Iterative Histogram Classification

After the mask was applied to the breast data, all that remained was the breast tissue. A histogram classifier was used to differentiate between adipose and other types of tissues due to differences in their voxel values. Based on a method developed by Packard and Boone[98], an initial segmentation of the breast tissues was done by iteratively evaluating the histograms of each coronal slice. The histogram for each coronal slice of the scatter corrected breast was found. The left and right edges were used to define the center of the histogram. The mean of the left and right side of the histogram were found and used as the left and right bounds to re-define the center. This process was repeated until there was little to no change in the center value between iterations. The signal containing the center values of each slice was smoothed with a 7-point moving average filter. A 2nd degree polynomial was fit to the data and the first 60 values were replaced with the moving average filter output. This maintained the larger values near the chest wall and minimized large swings in the signal. The smoothed signal was used to define the threshold point for each slice such that all values above the smoothed center value were classified as glandular and skin, and all values below were considered to be adipose tissue and were classified as zero. This process left each coronal slice of the segmented volume containing an initial segmentation of only glandular and skin tissue.

Figure 2-5 shows the signal that contained the threshold during iterative histogram classification for each coronal slice. Both the originally determined threshold level and the applied smoothed level values are shown.

Figure 2-5: Signal of threshold points used for iterative histogram classification.

2.3.2.3 Breast Skin Definition and Removal

After the initial histogram segmentation, the skin mask was applied. The histogram classifier does not differentiate between skin and glandular tissue, therefore the pre-defined mask was used for skin definition. All non-adipose tissue specified by the histogram classifier, that lay within the skin mask was classified as skin. The segmented skin was saved and removed from the segmented breast and all following steps were performed only on the remaining classified glandular tissue. In addition, single pixel islands that were likely to be residual mis-segmented adipose tissue were removed by using Matlab's *'bwmorph' 'clean'* function. All remaining steps were performed on glandular tissue only.

2.3.2.4 Pre-defined Morphological Functions

A binary volume of the glandular tissue was created, and in each coronal slice the Matlab *'bwareaopen'* function was used to remove any groups of pixels in the slice that

contained fewer than five pixels. Then a series of Matlab '*bwmorph*' operations were performed to fill-in, or bridge, missing pixel connections.

2.3.2.5 Ellipsoidal Connection Algorithm

There remained several small groups of less than 50 pixels that visually appeared to be disconnected from nearby groups of pixels. The size was chosen based on the current dataset after visually inspecting islands that were known to be connected based on the bCT data and disregarding islands that were too large. However, some islands were disjointed sections that appeared as linear objects and appeared to be connected to islands in the current slice and some were circular and appeared to continue through to the next slice. Therefore, it was necessary to differentiate between circular islands and linear islands. In order to define and link the appropriate sections together, the ellipsoidal shape of the islands was evaluated using the Matlab '*regionprops*' '*eccentricity*' function. The island was classified as closer to a line and possibly connected in the current plane if it had greater than 85% eccentricity and close to a circle and connected to the next plane if it was less. This differentiation was made assuming that any glandular fibers going between planes would appear rounder than glandular fibers staying within the plane. If an island was found to have greater than 85% eccentricity and an area of less than 50 pixels, then it was considered a candidate for linking to another nearby island. If another group of pixels were within 20 pixels away and along the angular orientation of the candidate island, then the line connecting them was labeled as glandular tissue. This was done by using Matlab '*imclose*' function with a line structuring element of length 20 pixels at the designated angular orientation.

2.3.2.6 Targeted Region Growing

After the previous step identified probable islands (small and linear ellipses) that were supposed to be joined, there were still certain areas that should be joined and were not identified as small linear ellipses. The targeted region growing algorithm was used to join these regions. It defined the distance between islands and searched for short ladder patterns, and then classified the ladder as part of the glandular tissue. This step joined together separated islands that were located close enough to indicate that they should be connected. In order to address missing connections for regions that were larger than 50 pixels and not linear in shape, it was necessary to extend these regions under specific conditions such that the original shape and size of each region was essentially preserved by growing only under certain conditions. It was assumed that regions that should be joined would be relatively close together and there would be a specific short path between them. To find distances between regions, the Matlab '*bwdist*' function was used to define a distance-map for each binary coronal slice of classified glandular tissue. Ladder-like patterns in the distance-map were searched for at 10 degree angular increments from -85° to 85° , such as:

$$[1 \ 2 \ 3 \ 2 \ 1], \begin{bmatrix} 1 \\ 2 \\ 3 \\ 2 \\ 1 \end{bmatrix}, \text{ and } \begin{bmatrix} 1 & 0 & 0 & 0 & 0 \\ 0 & 2 & 0 & 0 & 0 \\ 0 & 0 & 3 & 0 & 0 \\ 0 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 1 \end{bmatrix}, \text{ for example. If the pattern was found, it was classified as}$$

glandular tissue. The maximum ladder distance was 5 pixels for the coronal slices.

2.3.2.7 Volumetric Processing

Up to this point, all of the segmentation had been performed only in coronal planes. There may remain some discontinuities between slices due to the 2D processing.

Therefore, in order to join the glandular tissue volumetrically and smooth away the discontinuities, segmentation was performed in all directions: axial, coronal and sagittal.

In order to remove discontinuities between the coronal slices, the ‘Pre-defined Morphological Functions’, ‘Ellipsoidal Connection Algorithm’, and ‘Targeted Region Growing’ were performed on the axial and sagittal slices as well. The Matlab ‘*bwmorph*’ function was used on the classified coronal slices to fill in any small holes prior to processing in the axial and sagittal directions. The values used for the different functions during volumetric processing were that the candidate region area for the ‘Ellipsoidal Connection Algorithm’ was 30 with eccentricity of 0.85, and the maximum ladder distance used for the ‘Targeted Region Growing’ algorithm was 3.

2.3.2.8 Density Differentiation

Although the breast is composed primarily of the three segmented tissue types, there is often a compositional marbling effect, where glandular and adipose tissues are interspersed in varying degrees. This marbling effect was visible in the reconstructed data where some glandular regions appeared less dense and had a pixel value between that of adipose and glandular tissue. The segmentation algorithm takes into account the varying levels of adipose content in the glandular tissue by dividing the segmented glandular tissue into three regions based on voxel value. The algorithm results in the breast segmented into five components: adipose, skin, and three varying levels of glandular tissue.

After the ‘Volumetric Processing’ step, the glandular tissue had been classified as well as the skin. All voxels located within the pre-defined mask for the breast that were not skin or glandular tissue voxels, were classified as adipose tissue. The histogram of

the glandular tissue breast voxels was determined and divided into 4 segments. Because the glandular tissue density visually appeared to consist primarily of less dense tissue, the density differentiation was skewed towards the lower half. The first two segments were accordingly classified as primarily adipose tissue with a low percentage (25%) of glandular tissue. The 3rd segment was classified as 75% glandular tissue and the 4th segment was classified as 100% glandular tissue. This differentiation incorporated the marbling property of the different breast tissues. Three glandular levels were chosen because this provided a balance between simplicity and realism for the resulting segmented data; fewer levels would not provide a model with enough realism and higher levels were unnecessary because it complicated the final model and did not increase the realism of the final image.

2.3.2.9 Segmentation Algorithm Results

Figure 2-6 is the binary data used during segmentation and illustrates the effect of using pre-defined morphological operations along with the ellipsoidal connection algorithm and targeted region growing to classify the glandular data. Although subtle, there was improvement with the ellipsoidal connection algorithm and targeted region growing. These methods added noticeably to the high resolution detail of resulting images simulated with the phantom without perturbing the overall shape and structure of the breast tissue.

Figure 2-6: (A) The initial binary slice after histogram classification. (B) The slice after the ellipsoidal connection algorithm. (C) The slice after targeted region growing. Arrows show regions added with the algorithm.

Figure 2-7 illustrates the output of classification from the ‘Volumetric Processing’ step of the described algorithm. Performing the segmentation steps volumetrically fills in holes between neighboring slices and further improves the classification performance.

Figure 2-8 shows the final segmented slice. The density differentiation is shown, which more closely represents the real data than using a single value to describe the glandular tissue.

Figure 2-7: (A) Noise and scatter corrected bCT slice (B) Result from iterative histogram classification. (C) Result from coronal processing. (D) Result from sagittal processing. (E) Result from axial processing.

Figure 2-8: Final segmented slice showing five different tissue density classifications. From darkest to lightest: adipose, glandular1, glandular2, glandular3, skin.

Table 2-2 summarizes the methods we used to create the breast phantom.

Table 2-2: Methodology to create breast phantom

2.4 Conclusion

As previously mentioned, in order for studies using the phantom to have merit, it is essential that the XCAT breast phantom accurately depict human breast anatomy. This chapter described methods used to generate a realistic anatomical basis for the phantom by using processed bCT data and a volumetric segmentation algorithm. The utilization of a pre-reconstruction denoising algorithm combined with a post-reconstruction scatter correction method help to smooth the high-resolution imaging data and prepare it for the segmentation step. Although not quantitatively validated, the volumetric segmentation algorithm was able to differentiate the breast tissues and subjectively appears to closely mimic the original imaging data, thereby providing an anatomical basis for the XCAT breast phantom that is very similar to real human anatomy.

3. Breast Phantom Creation

3.1 Introduction

Segmentation creates a voxelized phantom specific to each subject's breast anatomy. In order to incorporate the flexibility of a mathematical approach to the XCAT breast phantom, a surface mesh model of the data was generated. The surface mesh model can be altered using affine or other transformations and can be used to directly generate uncompressed imaging data using available simulation tools. Alternatively, it can be translated into a finite element mesh for simulated deformation into a compressed state to simulate compressed geometry modalities.

3.2 Surface Model Generation

In order to be incorporated into the flexible and realistic XCAT phantom, a subdivision surface model of the breast needed to be generated. We defined each structure in the breast using subdivision surfaces[99]. Unlike the NURBS surfaces that define the XCAT phantom, subdivision surfaces have the ability to model complicated branching structures (e.g. the glandular tissue) with a single surface. NURBS surfaces would require defining a surface for each branch meaning the structure would be composed of many tiny NURBS surfaces. Subdivision surfaces are, therefore, much better for modelling the complicated structures of the breast. They represent a surface by specifying a polygon mesh model and recursively subdividing each polygonal face into smaller faces that can better approximate a smooth surface

Figure 3-1: (A) Surface rendering of the skin. (B) Illustration of the inner structures.

After the breast has been segmented a polygon mesh model of each classified tissue was created using the Matlab '*isosurface*' function, which is similar to the Marching Cubes algorithm. The Marching Cubes algorithm is a computer graphics technique that renders isosurfaces in volumetric data. By creating triangle models of constant density surfaces, this allows for the visualization of complex models[100]. The algorithm uses a divide-and-conquer approach to locate the desired surface in a cube created from eight pixels; four each from two adjacent slices. The algorithm determines how the surface intersects the cube by determining if each of the cube vertices is interior or exterior to the surface of the object. Based on the combination of the vertex locations (Figure 3-2), the edge of the surface that intersects the cube is known from a pre-calculated table. Where the surface intersects the cube edge can then be interpolated. By determining which edges of the cube are intersected by the isosurface, triangular patterns are generated that divide the cube between regions inside the isosurface and regions outside. Connecting these patches from all cubes on the surface boundary will give the initial mesh surface representation.

Figure 3-2: Vertices numbering of cube and a description showing how the edge crossing index is chosen.

The Matlab '*isosurface*' function was used to generate initial polygon mesh objects for the skin tissue, three levels of glandular tissue, and adipose tissue. For illustration, the polygon mesh of each of the three main tissue types was input to the Rhinoceros NURBS modeling software[101] and a surface was fit to it. Figure 3-1 shows an example surface rendering from the mesh model of the segmented bCT data. The polygon mesh created for each structure using Matlab, serves as the initial mesh of a subdivision surface for incorporation into the XCAT phantom. If necessary, the mesh can be iteratively subdivided and smoothed to create a smoother surface. The surface definition of breast tissue provides the mathematical basis that gives the XCAT phantom flexibility as the surface models can be altered easily using different types of transformations. The generated breast phantom defined by subdivision surface models, can be incorporated into the XCAT phantom and make it applicable to breast imaging studies, that require a non-compressed geometry.

3.3 Finite Element Mesh Model Generation

In order to simulate realistic compression of the XCAT breast phantom, finite element methods were implemented. This will be described in detail in the Chapter 4 “Simulated Compression”. In preparation of the simulated compression, several steps were required to generate a finite element breast model.

The segmented breast volume was resized with bilinear interpolation to achieve isotropic 500 μm resolution. An isosurface that encapsulated completely the resized segmented breast volume was generated using Matlab to generate a breast shell structure. The shell was imported into Hypermesh (Hypermesh 10, Altair Engineering, Inc., Troy, MI)[102] and a ‘*shrinkwrap*’, illustrated in Figure 3-3-A, was applied to achieve a spatial low-pass filter on the outer shell of the 3D breast volume in order to facilitate automatic meshing with 4-noded, solid tetrahedral elements. Mesh-generation penalties were imposed for elements with high aspect ratios (>25) or extreme element angles ($<5^\circ$) to avoid numerical artifacts due to malformed elements undergoing finite deformations.

Material properties for the skin, glandular and adipose components of the breast were assigned based on the segmented data. The following criteria were used to assign material properties to elements that were ambiguously located in the segmented image: (1) elements that had vertices in multiple materials were defined based on the location of their centroid, (2) if the centroid was outside of the defined breast volume or close to air (within 500 μm in the coronal plane or 1 mm in the anterior direction), it was assigned skin material properties using the assumption that all elements adjacent to air were skin, ensuring a continuous layer of skin around the breast. Figure 3-3-B illustrates a slice from the tetrahedral mesh with the materials assigned.

Figure 3-3: (A) Illustration of the shrinkwrap generated for the breast shell. (B) Illustration of the finite element mesh with the breast tissues assigned: Fat (red), Glandular (blue), Skin (green).

3.4 Conclusion

In this chapter we have described how to generate the XCAT breast phantom from segmented volumetric imaging data. The generated breast phantom, defined by subdivision surfaces, can be incorporated into the XCAT phantom and make it applicable to breast imaging studies that require a non-compressed geometry. The chapter also detailed how to prepare the phantom for finite element compression by creating a solid mesh of tetrahedral elements. The created breast phantom has the anatomical basis of real human data combined with the flexibility of a subdivision surface model and finite element definition. The next chapter describes how to use the finite element model to realistically simulate mammographic compression.

4. Simulated Compression

4.1 Introduction

The breast is compressed during mammography and this is essential to produce high quality images. Breast compression optimizes image quality by reducing the breast thickness and therefore increases the visibility of small lesions. Compression also minimizes patient movement that would cause blurring effects in the resulting mammograms. Finally, x-rays pass through less breast thickness, resulting in reduced radiation dose. Many breast imaging modalities employ compression including: mammography, digital breast tomosynthesis, and nuclear medicine techniques. In order to make the breast phantom applicable for research in these modalities, it was necessary to create a compression model component for the phantom.

4.1.1 Simplistic Compression Algorithm

Initially we implemented a simple model to simulate compression using the nodes defined by the subdivision surface model. The breast was compressed in one dimension (x) and extended in the other dimensions (y and z) simulating compression between stiff plates [103]. The breast phantom was assumed to be incompressible, meaning its volume did not change, and isotropic, meaning its material properties were the same throughout and invariant with respect to direction. The subdivision surface node locations were determined to be inside or outside the final compressed thickness of the breast. Each x-value of the vertices located outside was multiplied by the compression ratio to give the new x-values for the compressed vertices location. Each vertex with an x-value originally located between the simulated compression paddles remained unchanged. If the breast

volume was assumed to be a cone with a circular base, the volume (V) was assumed to be a factor of the radius (r) and height (h) where (α) was a multiplicative factor:

$$\text{Breast volume:} \quad V = \alpha r^2 h = \alpha r_x r_y h_z \quad (4-1)$$

The assumption made was that if the x-value was changed by a factor (*compression_ratio*), the other two dimensions will change by the inverted square root of that factor to maintain the same volume; such that the y-value and z-value are multiplied by:

$$\text{Factor to maintain volume:} \quad \frac{1}{\sqrt{\text{compression_ratio}}} \quad (4-2)$$

The compression is illustrated in Figure 4-1.

Figure 4-1: Illustration of breast compression geometry.

A projection was simulated of the uncompressed and compressed phantom to evaluate the compression algorithm's effect on the image. The projection was simulated using an analytical noise-free simulator described in section 5.2.1. There was increased

contrast and visibility of the internal breast structures in the compressed image over the uncompressed.

Figure 4-2: (A) Projection of uncompressed breast. (B): Projection of compressed breast.

While this method was able to simulate compression of the breast phantom, this was not a realistic approach. It did not take into account the different material properties of the breast tissue or realistically deform the model. Additionally, there were visible artifacts in the simulated x-ray images from the surface modeling of the skin as seen in Figure 5-2. Therefore, we investigated finite element methods in order to realistically simulate mammographic compression.

4.1.2 Overview of Finite Element Breast Models

Although there are multiple ways to create a mechanical model of the breast, we focused primarily on finite element techniques. Deformable biomechanical breast models

employing finite element methods have been explored to predict breast compression, calculate potential deformations during biopsy procedures, and predict cosmetic surgical outcomes[104-108]. Finite element analysis is commonly used to determine the stresses and displacements in mechanical objects and systems. The object is represented by a geometric model consisting of multiple, linked, simplified representations of discrete elements defined by a mesh network. The mesh nodes are all assigned the material and structural properties that define how the structure will react to certain loading conditions. The compression simulations are typically based upon a deformation model that includes realistic tissue elasticity properties such as the Young's linear elasticity modulus (E) that relates strain (ε), as a measure of deformation, and stress (σ), the force applied to the surface area of the deformed object. The material's Poisson's ratio (ν) is a measure of the tendency of a material to contract in two dimensions in reaction to being stretched in the 3rd dimension. It is calculated using the ratio of the transverse strain to the axial strain. Another important factor is the deformation gradient tensor F that is based on the reference (undeformed) (X) and deformed (x) position of the node.

$$\text{Young's elasticity modulus:} \quad E = \frac{\sigma}{\varepsilon} \quad (4-3)$$

$$\text{Poisson's ratio:} \quad \nu = -\frac{\varepsilon_{trans}}{\varepsilon_{axial}} \quad (4-4)$$

$$\text{Deformation gradient:} \quad F = \frac{\partial x}{\partial X} \quad (4-5)$$

Biomechanical breast models using finite element analysis vary mainly with respect to the mesh generation, the boundary conditions employed, the assumed tissue properties, and the equation solution strategies. They are commonly criticized as being too simplistic or inaccurate in their modeling of the tissue mechanical properties. A few examples of finite element models of the breast are described below.

Azar *et al.* created a method for tracking the position of a tumor during compression in a clinical breast biopsy[109]. After classifying breast tissues from MRI data into fat, parenchyma, or cancerous tissues, the authors set initial and boundary conditions defining the compression plate locations and compression distance. Each tissue was considered isotropic, homogeneous, incompressible, and had non-linear elastic properties. Therefore, the mechanical behavior of each breast tissue was defined using a single elastic modulus. In an iterative process to calculate deformation, the strain component was recalculated based on the materials experimentally determined stress-strain curve. This curve was approximated by an exponential function, to model the material's non-linear behavior. The algorithm was validated by comparing images from simulated breast model compression with actual patient images. The authors found that it was possible to create a deformable model of the breast based on finite elements with non-linear material properties capable of modeling the deformation of the breast during compression.

Samani *et al.* used a 3D finite element model to predict breast tissue deformation based on the biomechanical parameters of the breast tissue[110]. The adipose and glandular tissues were modeled as incompressible and hyperelastic materials and the skin was modeled using membrane elements with linear elastic properties. Hyperelastic

materials are able to experience large elastic strain that is recoverable and generally have very small compressibility. The authors used a polynomial function to account for the nonlinearity of breast tissue properties. The governing equations for the model are based on a finite deformation formulation in conjunction with the hyperelastic material.

Bakic *et al.* incorporated a mammographic compression model in the 3D breast tissue phantom they developed[73]. The compression simulation they used was based upon a deformation model that included realistic tissue elasticity properties such as the Young's linear elasticity modulus. The two regions of different tissue types were made up of geometrical elements that were assigned separate linear Young's moduli. A slice of the breast model was replaced by its rectangular approximation. It was then modeled as a composite 2D elastic beam that was positioned between two compression plates. A force was applied to the compression plates that then deformed the composite beam. The deformed slices were then stacked together to form the 3D compressed breast model.

Chung *et al.* developed a patient-specific 3D finite element representation of the breast from MRI data[104, 105]. The model provided physical constraints on the image registration process in order to improve the tracking of tumors from the compressed configuration to other configurations required for further examination or surgery. The simulated compression methods were evaluated by comparing predictive simulation with physical measurements. They compared simulation results to tracked points on a silicon gel model that was compressed with boundary conditions and included gravity loading. The authors noted that better predictions were achieved in the simulations that incorporated the effects of gravity. The experiment showed that modeling the soft-tissue

mechanics of the breast can assist the tracking of tumors from the compressed state during mammography to other configurations needed for further examination[105].

Zhang *et al.* presented a method that uses a 3D model to facilitate two-view (CC – MLO) registration by predicting breast deformation from compression[111]. The authors created a 3D biomechanical finite element breast model with segmented breast MRI data. The model was capable of simulating both compression and decompression. The authors solved motion equations with two types of boundary conditions for displacement and force. They modeled the different breast tissues as isotropic, linear, and homogenous; but assigned a uniform Young's modulus and Poisson's ratio to the entire model. A stepwise incremental approach was used to simulate the compression plate motion. This enabled the modeling of large breast deformations through a series of static equilibrium calculations. Experiments using real patient data demonstrated that a mammographic feature can be successfully registered from one view to another.

Del Palomar *et al.* created a finite element model to predict real deformations from surgery[108]. The authors used CT data of the patient lying in a prone position to generate a virtual deformable breast model. This model could be altered based on gravity and tissue composition, to emulate the breast of the patient in a standing position. The structural complexity of the breast was simplified by only assigning an average value of mechanical properties to the glandular and adipose tissue in the volume. The results of the deformed model were registered with a surface model of the patient's breasts while standing, which was reconstructed from multiple photographs. The effect of the gravity force was evaluated, and surface displacements were compared with manually identified

point landmarks. The authors found that their simple model could be used for pre-surgical estimation of deformations for a normal breast depending on the patient's posture[108].

Kellner *et al.* simulated the mechanical compression of breast tissue on a model based on the same bCT data we are using[86]. Skin, glandular, and adipose tissues were assigned separate Young's modulus and a uniform Poisson's ratio. Progressively greater macroscopic compressive strains were applied until a convergence criterion was met.

Tanner *et al.* provided a review of biomechanical breast models to address their accuracy and evaluate the influence from their choice of mechanical breast properties[107, 112-114]. They used six linear and three non-linear elastic material models, with and without skin, and compared these to hyperelastic models. It was found that the best results were achieved for accurate boundary conditions, appropriate Poisson's ratios, and models where glandular tissue was less than four times stiffer than adipose tissue.

The level of accuracy of a biomechanical simulation is largely dependent on how physically realistic and detailed the substructures of the object are represented in the model. Several of the aforementioned patient-specific biomechanical breast models have been developed to simulate compression and are able to predict the compressed location of registration markers to less than 5mm[73, 86, 104, 106, 107, 110, 113, 115-120]. Most of these models have been optimized to yield results in a clinically-relevant timeframe (<30 minutes) but tend to utilize relatively coarse meshes (node spacing on the order of centimeters) to decrease computational time at the expense of spatial resolution.

Although successful for their clinical end points, the patient-specific models detailed above were not intended to provide high spatial resolution or be used as a tool

for evaluating imaging techniques and devices. For an imaging phantom, a detailed representation of the breast anatomy is necessary to optimize and develop new technologies and imaging processing techniques. Our method, described herein, realistically simulates 3D compression using finite element methods of a high-resolution breast phantom that will ultimately be used for imaging research purposes. In addition to generating high-resolution images, a suitable breast phantom should also have the ability to simulate changes in the breast over time due to age and hormonal variations as well as accommodate user-defined mechanical properties to encompass the wide variability in breast composition (e.g., breast glandular density) that exists among female subjects; therefore, the effect of changing these parameters was analyzed in this study.

4.2 XCAT Breast Phantom Compression Simulation

In this section, we describe a finite element (FE) model to simulate realistic compression of the 3D breast phantom. The XCAT Breast Phantom Finite Element Background section will review the mechanical models used to simulate compression of the breast tissues. The following Methods and Finite Element Analysis section describes the updated segmentation algorithm used to delineate the different materials of the breast (skin, adipose and glandular tissues) from CT images and the incorporation of those different material definitions into a three-dimensional FE model to simulate breast compression. The Simulated Compression Results section shows a parametric analysis of the breast model properties that affect the compression of the breast, including the relative stiffness of the different tissue types, skin friction, mesh density, element type, breast density, and material/mass density. Finally, the Discussion of Finite Element Compression section explores the impact that the model parameters have on the

simulated 3D breast deformation, future efforts to improve the accuracy of the model, as well as limitations of the current implementation of breast compression described in this work.

4.2.1 XCAT Breast Phantom Finite Element Background

Breast compression simulation methods have typically used finite element techniques because of their ability to solve for the large (finite strain) deformation of complex 3D structures. Mammographic compression plates induce a large-body strain, which can be greater than 50%, on the breast in the direction of compression. During simulation, FE methods evaluate the strain and displacement induced in the other dimensions in response to a prescribed uniaxial compression. For linear, isotropic, elastic materials under such uniaxial compression, strain energy and stress are related by Hooke's law such that[121]:

$$\sigma_{ij} = \frac{E_Y}{1+\nu} \left(\epsilon_{ij} + \frac{\nu}{1-2\nu} \delta_{ij} \epsilon_{kk} \right) \quad (4-6)$$

where σ_{ij} is the stress tensor, E_Y is the material's Young's modulus, ν is the Poisson's ratio, ϵ_{ij} is the strain tensor, δ_{ij} is the Kronecker delta, and ϵ_{kk} is the first scalar invariant of strain. Strain is related to displacement, u , as a symmetric tensor using the following equation:

$$\epsilon_{ij} = \frac{1}{2} \left(\frac{\partial u_i}{\partial x_j} + \frac{\partial u_j}{\partial x_i} \right) \quad (4-7)$$

Because a dynamic solution was obtained through the use of an explicit FE solver, mass effects were included in this model as described by:

$$\rho_o \frac{\partial^2 u_i}{\partial t^2} = \rho_o B_i + \frac{\partial \sigma_{ij}}{\partial x_j} \quad (4-8)$$

where ρ_o is the materials mass density and gravity was neglected in this analysis such that $B_i = 0$. For the models described herein, a prescribed, uniaxial displacement (strain) was applied to the breast through a contact problem with rigid plates, and the resultant 3D stress/strain data were solved for throughout the volume of the simulated breast.

4.2.2 Methods and Finite Element Analysis

4.2.2.1 Segmented Data Generation

The image acquisition and image processing techniques were detailed in Chapter 2. A slightly modified segmentation method was used for this section of work; the changes are summarized herein. The denoised and scatter-corrected datasets were segmented into three components: adipose, glandular, and skin tissues using a semi-automated segmentation algorithm developed specifically for these dedicated breast CT datasets[88]. The first coronal slice was defined for each dataset by visual inspection as the location where the denoised data appeared to be fully within the breast volume and without substantial scatter artifacts. The last coronal slice was defined for each dataset by finding the last slice that appeared to have breast data. All pixels before the first slice and after the last slice were assigned to zero. A breast-to-air threshold was defined by a using a certain percentage, ranging from 25% - 55% of the maximum value in each breast slice. Each breast was masked such that all air pixels were set to zero. An initial segmentation on the breast tissue was performed using an iterative histogram classification technique that separated glandular and skin tissue from adipose. For each slice, the left and right bounds of the histogram were used to calculate the mid-point of the breast values. Next the average of each half of the histogram was used to redefine the bounds and iteratively

recalculate the mid-point until it converged to a single value. A 2nd order polynomial fit to the calculated mid-points across all of the slices was used to make a smoothly varying segmentation threshold. The threshold was applied and all values below the slice specific threshold were assigned to zero.

Next, the breast mask and segmented glandular and skin data was used to determine the skin thickness. For each coronal slice, the mask was eroded by a single pixel and then the eroded mask was subtracted from the breast mask to get a single-pixel-thick mask. The sum of the segmented breast values located within the thin mask was found. This process was repeated until the mask hit the skin-fat barrier which was determined as the point when the sum of the values dropped by greater than 40%. An average thickness of the skin was determined from all of the slices and used to define the skin for the breast. Typical breast skin ranges from 1 to 3 mm in thickness[122]; the determined skin thickness for the different datasets ranged from 1.5 to 2.5 mm.

The segmented breast values located within the skin were removed and subsequent operations were performed solely on the segmented glandular tissue. A series of morphological operations were performed in the coronal, sagittal, and axial planes using the MATLAB R2007a (The MathWorks, Inc., Natick, MA) '*bwmorph*' '*bridge*' and '*diag*' operations to fill small holes between segmented glandular areas. This was repeated three times and then '*bwmorph*' '*close*' and '*majority*' operations as well as the '*bwareaopen*' function were used in the coronal slices to remove isolated islands of glandular tissue that were smaller than 2 mm in diameter. This step was important for the mesh generation since glandular segments smaller than 2 mm in diameter do not need to be defined by the generated mesh. As described in the phantom creation

methodology[88], the segmented glandular tissue was further classified into three different types of glandular tissue. This information was used for the simulated image projection but was not used for the described compression analysis. The previously defined skin mask was added to the segmented glandular image to complete the segmented breast volume shown in Figure 4-7. In order to categorize the 17 breast datasets considered in this study, the breasts' glandular density percentage was calculated as the ratio of the total number of voxels assigned to glandular tissue to the total number of voxels in the breast volume. The breast densities were calculated for all of the datasets and resulted in an average density of $25 \pm 16\%$ {Table 4-2}. Parametric FEM analysis was performed on the 28% dense breast and two additional subjects were selected in different density ranges for analysis on the effect of glandular density on simulated compression {Figure 4-7}.

4.2.2.2 Mesh Generation and Boundary Condition Assignment

The finite element mesh was generated as detailed in the preceding chapter. In summary (1) an isosurface of the breast shell was created with Matlab. (2) the shell was low-pass filtered in Hypermesh[102] in order to generate a smooth surface, (3) the smooth shell was used to generate a solid mesh of 4-noded tetrahedral elements, and (4) the materials were assigned to the elements according to the elements centroid location in the segmented data.

Mesh refinement was studied using average element edge lengths of 1.5 mm, 2.5 mm, 3.75 mm, 5 mm, and 1 cm to ensure that element density was not a first-order determinant of the deformation data. Figure 4-3 shows how the higher mesh density (*e.g.* lower element edge lengths) exponentially increases the number of elements and Figure

4-4 demonstrates how the breast can be represented with the varying mesh densities. An average element edge length of 2.5 mm was chosen for most simulations presented herein to achieve mesh-independent results while minimizing computational overhead. Using an average element edge length of 2.5 mm, the total number of elements across the different breasts ranged from 131,026 to 718,928.

Figure 4-3: Demonstrates how the element count exponentially increases as the edge length decreases.

Figure 4-4: Graphical representation of different mesh densities generated using different average element edge lengths: (A)= 1.5mm, (B)= 2.5mm, (C)= 3.75mm, (D)= 5mm, and (E)= 10mm. The axis shows the orientation of the breast and planes used throughout this work. Notice how the qualitative curvatures of the breast are poorly represented with the more coarse meshes.

The meshes were defined as continuous solid elements without contact interfaces between the different materials. All elements located near or on the first coronal slice were assumed to be attached to the chest wall, with restricted motion in the anterior-posterior direction but permitted degrees of freedom in the superior-inferior and medial-lateral directions.

4.2.2.3 Finite Element Analysis

In order to realistically predict 3D tissue deformation due to compression, the equations of state (Equation 4-8) were solved using LS-DYNA (Livermore Software Technology Corp., Livermore, CA)[123], an explicit, time-domain solver. While we were only interested in the steady-state compression of the breast for these studies, we utilized an explicit solver to reduce the RAM requirements for these simulations

compared to using an implicit method. These models were run on Intel Xeon 5140 processors operating at 2.33 GHz in an SMP parallel environment over 4 CPU cores using <1GB of RAM; typical runtimes ranged from 3-4 hours.

Typically, the 4-noded tetrahedral elements utilized for these models are not ideal for modeling incompressible soft tissues. To investigate if it was necessary to capture 2nd order behavior, the type of elements used to define the mesh was investigated to compare how 4-noded tetrahedral elements differed from simulations using 10-noded tetrahedral elements and 1-point tetrahedral elements. Although breast tissue is typically defined as a hyperelastic material, a linear elastic definition has been shown to sufficiently approximate its behavior[73, 86, 107, 116]. Therefore, the breast materials (skin, glandular and adipose) were modeled as linear, elastic, isotropic solids. Unfortunately, there are difficulties measuring the stress-strain relationship of breast tissues accurately because the mechanical properties are dependent on the *in situ* environment of the tissue and the mechanical measurement technique (i.e., static vs. dynamic). Consequently, there are a wide range of values for the elastic modulus of different breast tissues used in current biomechanical models[73, 86, 104, 106, 107, 110, 113, 115-120, 124]: adipose tissue ranges from 0.5 to 25 kPa, glandular tissue from 0.08 to 272 kPa, and skin from 0.088 to 3 MPa. For our analysis, changing the separate tissues' Young's moduli relative to one another was parametrically studied to determine the impact on the simulated tissue compression (Table 4-1). In addition to varying the stiffness of the tissue, the impact of friction between the compression plates and the skin was parametrically evaluated since factors such as the subject's age, skin moisture and sample location can affect this mechanical response. Coefficients of kinetic friction (μ) ranging from 0 to 1.0 were

studied in these simulations[87, 125]. All material properties used for analysis are shown in Table 4-1.

Table 4-1: Mechanical properties investigated

		FAT	GLANDULAR	SKIN
Mass Density[126, 127] (g·cm ⁻³)		0.928	1.035	1.1
Poisson's ratio		0.49		
Coefficient of Friction (skin-plates) (μ)		0, 0.1, 0.46, 1.0		
YOUNG'S MODULUS (kPa)	Scenario 1	1	1	1
	Scenario 2	1	5	1
	Scenario 3	1	10	1
	Scenario 4	1	1	10
	Scenario 5	1	1	88
	Scenario 6	1	2.5	10
	Scenario 7	1	5	10
	Scenario 8	1	10	88
	Scenario 9	10	50	100

The compression was modeled using two rigid plates that were infinite in the axial plane at predefined sagittal locations set with one located superior and the other inferior to the breast without initial contact. In order to simulate typical compression levels of mammography, the plates were moved at a constant velocity of 6.25 mm/s to achieve a 5 cm compression thickness in 10 seconds; this compression was held 50 additional seconds in order for inertial transients to be damped and achieve a steady-state compression.

Figure 4-5 shows a representative breast (28% dense) pre and post-compression. The initial chest wall diameter was 12.8 cm and 5 cm in thickness post-compression (61% strain).

Figure 4-5: The 28% dense breast model. (A) pre-compression; (B) post-compression, (C) off axis view to get a 3D view of the compression.

Since a purely elastic material without material viscosity was modeled, oscillations from the dynamic compression resonate through the material unless numerically damped to achieve the steady state response. A critical damping coefficient (D_{cr}) was calculated by first solving the un-damped model to find the resonant frequency ω_r of the system.

$$D_{cr} = 2\omega_r \quad (4-9)[128]$$

The power spectrum of the displacement signal in the direction of plate movement, of a surface node that did not contact the compression plates and was located near the nipple, was used to determine the resonant frequency. The average damping coefficient for all the different breast models was calculated to be 0.686 ± 0.08 ; $D_{cr} = 0.686$ rad/s was used for all models presented herein. Figure 4-6 shows the effect that the imposed critical damping had on the displacement of the analyzed node near the nipple; note the convergence to the steady-state behavior occurs much earlier after cessation of the plate compression (10s).

For analysis, the compressed nodal information generated for the finite element tetrahedral mesh was linearly interpolated in three dimensions to provide a new location for each uncompressed image voxel. The relative overall displacement between

compressed breasts was calculated in traditional imaging planes and evaluated as a function of the different mechanical parameters in the model to determine their impact on the simulated deformation of the breast phantoms.

Figure 4-6: Damping coefficient effect. The undamped solution was used to calculate the resonant frequency that was suppressed in order to attain a critically damped solution; note the convergence to the steady-state behavior occurs much earlier in time after cessation of the plate compression (10 s).

4.3 Simulated Compression Results

4.3.1 Categorization of Segmented Breast Models

The breasts were categorized into three groups based on glandular density, shown in Table 4-2. A 28% dense breast was used for parametric analysis of different mechanical properties. The effect of breast density on simulated compression was evaluated using two additional breasts from the other density categories, which are shown in Figure 4-7.

4.3.2 Finite Element Results

Several different analyses were run to demonstrate the difference between using different mesh densities as well as different breast tissues with varying mechanical properties. The majority of analyses were performed on a 28% dense breast; however, comparisons were also done with a 14% dense and 40% dense breast to show the effect of modulus choice on breasts with different glandular densities. Figure 4-9 through Figure 4-14 show boxplots representing the distribution of overall displacements of all the nodes in the breast model to provide a graphical representation of the relative global breast distortion between different material parameters. In these box plots, the solid black line is the mean, the solid red line is the median, the box is the interquartile range, and the boxplots whiskers range from 2.7σ above and below the mean of the displacement data as shown in Figure 4-8. All displacements in the boxplots are measured in millimeters. Figure 4-9 demonstrates how the final compressed locations of each voxel in the original breast data changed as a function of average overall displacement between the different models, from the 2.5 mm mesh breast to the other mesh densities. Figure 4-10 shows the overall displacement changes when changing different mechanical properties of the model: using real mass density values as defined in Table 4-1 for each material versus a uniform mass density of $1 \text{ g}\cdot\text{cm}^{-3}$ for all materials. Figure 4-11 demonstrates how the overall displacement changes when changing the type of the element used to define the mesh (10-noded and 1-point tetrahedral elements) versus the 4-noded tetrahedral element. Figure 4-12 shows how including a coefficient of friction between the skin and the compression plates changes the overall displacement. Figure 4-13 shows how changing the ratio of Young's modulus for the different breast tissues affects the final overall

displacement of the breast compared to a mesh where all the tissues have the same modulus. Figure 4-14 illustrates how breast density changes the overall displacement between breasts using different modulus ratios.

Table 4-2: Breast CT data categorized by glandular density and size

%Density	0-15%	15-30%	30%+
Number of datasets	7	4	6
Average volume (cm ³)	890	732	467

Figure 4-7: Columns show breasts in different density categories from left to right: 14% dense, 28% dense, 40% dense: Scatter corrected breast data is in the top row, and segmented data is in the bottom row.

Figure 4-8: Legend for the boxplots shown in Figure 4-9 through Figure 4-14.

A mesh-refinement study was performed to evaluate the impact of element density on the final deformations simulated by the breast phantom. Figure 4-15 shows an axial slice through the representative breast (28% dense, $E[\text{fat:glandular:skin}] = 1:5:10$ kPa, $\nu = 0.49$, $p_{\text{real}} = \text{Table 4-1}$, and $\mu = 0.46$) at full compression using the 5 different element sizes ranging from 1.5 – 10 mm; the different colors represent the different materials. Note how the distribution of the materials converges for the finer meshes, with greater structural detail being preserved.

Figure 4-16 shows the displacement profiles in the same axial slice using three different combinations of modulus values for fat:glandular:skin tissue (1:1:1, 1:5:10, 1:10:88 kPa with $\nu = 0.49$, $p_{\text{real}} = \text{Table 4-1}$, and $\mu = 0.46$). In order to demonstrate the spatial distribution throughout the breast of the effect of different mechanical properties, a sagittal and axial slice through the center of the breast is shown in Figure 4-17, Figure 4-18, and Figure 4-19. For Figure 4-17 – Figure 4-19 the two top rows show the interpolated nodal displacement of the two datasets under analysis (in the plane and direction of interest) and the bottom row shows the difference between the two datasets to highlight where they differ the most.

Figure 4-9: Effect of changing mesh density on final displacement. (28% dense, 4-noded tetrahedral elements, $E(\text{fat:glandular:skin}) = 1:5:10$ kPa, $\nu = 0.49$, $\rho = \text{real}$, and $\mu=0.46$).

Figure 4-10: Average displacement between using the real density for each material and uniform density values.

Figure 4-11: Average displacement from the 4-noded tetrahedron mesh when 10-noded and 1 point tetrahedrons are used to define the mesh (note the very small displacement scale)

Figure 4-12: Average displacement between a coefficient of friction $\mu=0.1$ and 0.46 versus no friction. (28% dense, 4-noded tetrahedral elements, $E(\text{fat:glandular:skin}) = 1:5:10$ kPa for all but the mass density comparison, which used $E(\text{fat:glandular:skin}) = 1:1:1$ kPa).

Figure 4-13: Effect of changing moduli on final displacement from a model with uniform moduli. (28% dense, 4-noded tetrahedral elements, $\nu = 0.49$, $\rho = \text{real}$, and $\mu=0.46$).

Figure 4-14: Effect due to breast density. How displacement changes using different moduli ratios from the uniform model in breasts of different densities. (28% dense, 4-noded tetrahedral elements, $\nu = 0.49$, $\rho = \text{real}$, and $\mu=0.46$).

Figure 4-15: Effect of mesh density on tissue distribution under compression. Using a breast that is: 28% dense, 4-noded tetrahedral elements, $E(\text{fat:glandular:skin}) = 1:5:10$ kPa, $\nu = 0.49$, $\rho = \text{real}$, and $\mu=0.46$. Fat is red, glandular is blue, and skin is green. (A) 1.5mm, (B) 2.5mm, (C) 3.75mm, (D) 5mm, (E) 10mm.

Figure 4-16: An axial slice through the same breast at full compression showing different tissue locations on the left and total displacement values on the right. Moduli ratios from top to bottom: 1:1:1, 1:5:10, 1:10:88 kPa (28% dense, 4-noded tetrahedral elements, $\nu = 0.49$, $\rho = \text{real}$, and $\mu=0.46$). A zoom view of the boxed section is shown in the middle to illustrate the different breast morphology using different moduli ratios. The colormap for the displacement images range from 15 – 35 mm. Notice how the overall shape of the breast and the tissue deformation deep in the breast varies depending on the relative stiffness ratio between the different tissue types.

Figure 4-17: Difference using real mass density values: top is the total displacement with uniform density values, middle is total displacement with real density values as defined in Table 4-1, and bottom is the total difference between the models. Note the small scale of the difference image compared to the original models.

Figure 4-18: difference due to friction: top without friction; middle with friction; and bottom is the difference between the models. It is clearly demonstrated that the change due to adding friction between the skin and the compression plates is concentrated primarily on the edges of the breast.

Figure 4-19: change in moduli: above is uniform 1:1:1, middle is 1:10:88, and bottom is total change between displacements. The figure shows that the difference between models using varying moduli ratios is distributed throughout the breast.

4.3.3 Discussion of Finite Element Compression

A breast phantom for imaging research purposes ideally should have high spatial resolution information about the breast tissue and also have a realistic estimation of the redistribution of breast tissues under compression. This would allow the researcher to define assumptions and a level of complexity for a specific project. Our investigation into the effect of mesh density and different material properties in a breast phantom show that slight alterations in the models properties can change the final distribution of the tissue under compression. Although this may not be significant for the purposes of tumor tracking for biopsy or post surgical outcomes that require a model within a relatively short time frame, this could potentially be of interest for the development of new imaging tools and techniques for breast cancer research.

4.3.3.1 Relative Displacement Analysis

A higher mesh density with smaller elements was necessary to capture small structures and maintain the mechanical integrity of the model. Figure 4-9 shows that changing the mesh density can alter the overall average deformation, and demonstrates that lower density meshes can result in larger differences from the 2.5 mm mesh. The differences in tissue distributions shown in Figure 4-15 can affect the overall deformation of the breast that occurs due to the stiffness of different breast materials. The overall effect of mesh density on the average total displacement from the 2.5 mm element edge length mesh was less than 5 mm for meshes utilizing edge lengths smaller than 5 mm; however, subtle movements of small glandular structures may not be captured with coarser meshes {Figure 4-9}. Although the overall shape of the glandular tissue was captured, small and/or thin glandular regions are missing. In addition, structures smaller

than 2 mm in diameter in the coronal plane were removed in the segmentation step and would not be represented in the generated mesh, hence a 1.5 mm edge length mesh may not be necessary for the current FE model. However, future iterations of the breast phantom may include additional models for the suspensory Cooper's ligaments, which will further affect the distribution of tissue through the compressed breast. The addition of smaller structures in the breast will require even further mesh refinement, which will subsequently increase runtime. The 1.5 mm elements took over seven times longer to run than the 2.5 mm elements used for the results in this manuscript. Smaller elements would impose even greater memory penalties if formulated in an implicit solver, requiring computers with great degrees of parallelization and RAM to run in practical amounts of time.

An average displacement of 0.4 mm indicates that utilizing real values for the density of the tissues did not greatly affect the overall displacement from using uniform values for the different tissues {Figure 4-10}. However, in contrast with modulus ratios, the density values for the breast tissues are well studied and can be defined without questioning their actual value, therefore the real density level should be included. Altering the type of the element used in the model to 10-noded tetrahedral elements and 1-point tetrahedral element did not greatly alter the overall relative displacement from the 4-noded tetrahedral element with the average overall displacement between models of $<25 \mu\text{m}$ {Figure 4-11}. This was most likely because the 2.5 mm element edge length mesh was refined enough that the 2nd order behavior captured by a 10-noded tetrahedral was unnecessary for this analysis.

Modeling the friction of the skin against the compression plates had the most effect on the skin's deformation. Figure 4-18 demonstrates that using a non-zero coefficient of friction mostly affects deformation in the edges of the breast, but not as much in the center. Medial-lateral displacement in a sagittal plane centered in the breast, and superior-inferior displacement in an axial plane centered in the breast, change greatly with or without friction. This was most likely because simulated friction restricts the breast from sliding across the compression plates while no friction allows the skin to slide, affecting the breast tissue near the edges, but not the deformation nearer the middle of the breast. Increasing the coefficient of friction to 1.0 did not have as substantial an impact as simply including a coefficient of friction of 0.1, which indicates that some model of friction is necessary but the precise value has a secondary effect. Computationally, sliding contact interfaces can increase run times over 25%; therefore, depending on the area of interest, this may not be a viable parameter to include. Studies have investigated the effect of modeling the breast with a different material definition of skin. However, the skin is 1-3 mm thick and a coarse mesh on the order of centimeters will not be able to characterize or model skin effectively. We can define a thin skin that realistically encapsulates the breast fully and remains <3 mm thick. Figure 4-13 shows that with increasing skin modulus, the overall displacement increases, which demonstrates that skin does affect breast deformation. This demonstrates the need for a high density mesh with a skin definition that is able to describe the skin with realistic mesh elements.

Analyzing Figure 4-13 shows that the absolute values of the moduli has less effect on the relative deformation than changing the ratio of the moduli, since the 1:5:10 ratio

was similarly displaced (<0.5 mm) as the 10:50:100 ratio. In addition, it demonstrates that each change of the modulus has an effect on the overall deformation from a breast with uniform modulus; the larger the ratio change, the larger the change in the nodal displacement. Figure 4-19 shows that the overall deformation differences with higher modulus ratios are dispersed throughout the breast, which shifts the tissues around in a non-uniform manner. This effect is further demonstrated in Figure 4-16, which shows how changing the modulus alters the deformation of different tissues and the shape of the overall breast under compression. The magnified region shows how some tissues come into plane differently with different moduli, and the displacement image shows how the tissues move differently with varying the defined modulus ratios. The effect of changing modulus ratios was further compounded when the breast density was altered. Figure 4-14 illustrates that changing the ratios of Young's modulus had the greatest overall effect on the least dense breast where the more compliant adipose tissue was more dependent on the smaller volume percentage of stiffer glandular tissue that can concentrate the stress from the plate compression. The greatest differences in the simulated deformations occurred in the medial-lateral direction, orthogonal to the compression direction, which was where the breast redistributes across the compression plates to maintain the incompressibility constraint according to Equation 4-6.

The effect of using a high-resolution realistic FEM compression algorithm is shown in Figure 5-5. The shape and overall morphology of the phantom was very different in the simulated projection generated using the FEM compression algorithm from the original simplistic compression algorithm. The glandular tissue realistically reaches more towards the edges of the breast and produces a more realistic projection

than the previous compression algorithm. Figure 5-5 also demonstrates how different mechanical parameters (i.e. varying the modulus ratios of the different tissues) can also affect the distribution of the tissue in the resulting projection.

4.3.3.2 Simulated Compression Limitations and Future Directions

Both linear and hyperelastic material models have been used in the past to model breast compression. However, hyperelastic materials introduce even more degrees of freedom in the parametric analysis that would further complicate the first-order material dependencies that we studied with this model and increase the computational overhead. The results presented under the assumptions of purely elastic materials can be treated as a foundation on which the higher-order effects such as hyperelasticity can be added. In addition, another group has demonstrated that the breast exhibits anisotropic deformation and can be modeled using transverse isotropic materials[114]; tissue anisotropy can also be added to these models in the future, though information about tissue orientation, etc. must be provided from the segmented image data.

The interleaved tissues within the modeled breasts were connected to one another without the ability to slide past one another. While this was a good approximation for most of the breast where fibrous interconnects tether tissues to one another, encapsulated masses and structures may be more accurately modeled with slip boundary conditions. Initial investigation into generating a high-resolution compression model with compartmentalized tissues was attempted; however, automatic mesh generation of these complex 3D entities yielded malformed elements that prevented analysis. More highly-refined segmented entities with smoother transitions between different material types may facilitate such an effort.

Other groups have used registration markers and the outline of the breast in a real mammogram to evaluate the accuracy of the simulated compression[104, 106, 107, 110, 115-120]. However, since we are using the simulated compression as part of a breast phantom package, it was superfluous to evaluate the accuracy of the simulated compression. Although unnecessary for the purpose of the phantom, it would be interesting to quantitatively evaluate the realism of simulated compression in the future.

Changing the level of material incompressibility also changes the ultimate deformation of the breast. However, because we chose to use an explicit solver and an elastic material with large deformation, the elements moved into a numerically unstable state as a Poisson's ratio of 0.5 was approached from 0.45 to 0.49999. For analysis, the models were run using $\nu=0.49$, to approximate a level of incompressibility that did not produce artifacts in the overall deformation and did not make the materials unrealistically compressible. If an alternate FE tool or Poisson's ratio is used for compression analysis, the results should be verified that they do not contain artifacts from numerically unstable elements.

The 4-noded tetrahedral elements utilized for these models are not ideal for modeling incompressible soft tissues; however, our mesh was refined enough that we didn't need the 2nd order behavior captured by higher-order (10-noded) tetrahedral elements, which may also have prohibitively long runtimes and greater memory requirements. More ideal hexahedral elements would require extreme manual intervention during the mesh generation process that would be dependent on each image that was segmented, and would, therefore, not be amenable to a generalized breast phantom model. Numerical artifacts associated with the 4-noded tetrahedral elements

were minimized with the prescribed mesh generation penalties, though true accuracy in the compression can only be evaluated in a study with pre- and post-compression image comparison that was not available for these studies.

The compression plates were modeled as infinite rigid walls in the axial plane. Although this was not realistic as the plates normally contact and terminate at the chest wall, we assumed that the breast data we had available contained limited chest wall information and would be fully compressed during mammogram acquisition. Thus, the breast data under compression was attached to an imaginary chest wall and allowed to fully compress. In the future, we can model a generic chest wall and pectoral muscle to attach the breast to, and then use a compression plate definition that is finite in the axial plane and contacts and terminates at the chest wall.

We did not account for the initial position of the breast during mammography, where the breast is rested on the inferior compression plate while the superior plate is moved down. In addition, we did not remove the effects of gravity on the breast during image acquisition of the pendant breast. In an elastic simulation, such as those presented, the effects of gravity on the breast would be superimposed on the compressed solutions, though this approach would not be appropriate when utilizing hyperelastic material definitions where the initial strain-state of the tissues is important.

The compression algorithm generated in this work utilized proprietary mesh generation and FEM solvers that require specific parameters. Although the methods can be translated to other tools, the compression may entail some slight modifications to the procedure used herein. A demonstration of the compression algorithm translated to non-proprietary tools is given in the Chapter Appendix.

4.4 Finite Element Compression Conclusion

We have developed a 3D, finite element breast phantom model that can yield high spatial resolution breast deformations under uniaxial compression for imaging research purposes. Skin, adipose and glandular tissue were successfully segmented from breast CT images and mapped onto a 3D tetrahedral finite element mesh. This breast phantom model allows for user-defined mechanical properties of the breast tissue and the analysis demonstrates potential differences due to the chosen assignment. Varying the relative Young's modulus of the constituent tissues of the breast can have a significant impact of the 3D deformation of the breast, especially in less dense breasts. The presence of skin and its assigned modulus can affect the overall deformation. In addition, incorporating friction between the skin and the compression plates affects deformations near the edges of the breast, but not as much in the center. Future iterations of this model will incorporate connectivity with adjacent chest wall tissues, include smaller and more refined structures such as Cooper's ligaments, and be extended to more complicated material models. This work demonstrates the effect of several parameters on tissue compression. It can be a basis for researchers choosing material properties and mechanical parameters in breast phantoms or in simulation studies for other applications such as tumor tracking or predicting surgical outcomes.

4.5 Chapter Appendix

4.5.1 Using Open-Source FEM Software

In order to demonstrate that the breast phantom can be used by researchers without access to proprietary mesh generation tools and FEM solvers such as Hypermesh and LS-DYNA, open-source FEM software was used to simulate compression on the

phantom. The segmented breast data was used to generate an STL file of the breast surface using a function called ‘SURF2STL’, available from the MATLAB Central website[129]. The STL file was input into LS-PrePost (Livermore Software Technology Corp., Livermore, CA)[130] to generate a 4-noded tetrahedral mesh with elements of edge length ~5 mm. Materials were assigned to the mesh elements in the same way as described for the LS-DYNA method. The model was run using FEBio (Musculoskeletal Research Laboratories, University of Utah, Salt Lake City, UT)[131] with slightly different material definitions in order for the model to run to completion: Neo-Hookean materials, no coefficient of friction, restricted movement in the coronal and axial directions at the chest wall, and a slower compression (30 seconds to 5 cm compression thickness). In addition, it was necessary to define contact surfaces between the skin and the rigid wall compression plates. We selected the surface elements located superior or inferior of the axial mid-plane of the breast to contact their respective rigid walls. Figure 4-20 illustrates the breast phantom pre and post compression using FEBio. This small foray into open-source FEM packages demonstrates that it is possible to use the phantom with alternative tools. Therefore, if a research group is more familiar with another FEM package, they can still use the breast phantom for their studies with compressed simulation.

Figure 4-20: images from FEBio simulation. (A) uncompressed phantom; (B) compressed phantom.

5. Simulated Radiographic Images

5.1 Introduction

The objective of all imaging phantoms is to generate realistic images that accurately model the imaging process. The realism of the phantom can be validated if generated images of the phantom appear similar to, or ideally indistinguishable from, real human subject data. If the phantom created from this work provides a realistic simulation of breast anatomy and imaging texture, this is a compelling reason to use this phantom over other methods. Therefore, simulated image generation is a necessary component to evaluate the phantom's clinical utility.

Once the phantom is defined, it can be combined with existing simulation packages to generate imaging data for any modality. The simulation packages can be applied to the voxelized phantom or to the subdivision surface model. For our purposes, in order to demonstrate all aspects of the XCAT breast phantom, we simulated mammograms using a previously developed projection algorithm that accurately models the x-ray imaging process, including quantum noise, and can generate realistic high-resolution imaging data directly from the surface mesh model[132].

5.2 Simulated Image Generation Background

There are multiple x-ray simulation algorithms available that vary in complexity. The modeling process typically consists of a description of the imaging geometry and material characteristics of the model. Kellner *et al.* simply integrated the intensity distribution along the z-axis of their compressed voxelized breast phantom created from segmented CT data in order to generate projection images[86]. Bliznakova *et al.*

generated mammograms of their geometric 3D voxelized breast phantom by simulating monochromatic beams emerging from a point source at a given distance from the object plane[76]. Photon transport was calculated as the transmitted intensity reaching the detector, based on the exponential attenuation of monoenergetic beams. Scatter and detector response simulations were possible but were not included. Bakic *et al.* used an image generation model for their breast phantom that included the attenuation by breast tissue, conversion of the x-ray energy into film density, and a model of mammographic film digitization[73]. The authors assumed a monoenergetic x-ray spectrum, parallel beam geometry, and no scatter. The model incorporated parameters of the imaging system and compression factors into their calculations. Gong *et al.* used the Bakic breast phantom and developed a realistic computer simulation to model x-ray path through the phantom, as well as the signal and noise propagation through a flat-panel imager. They used polyenergetic x-ray spectra for mammogram simulations and manually determined the intensity of x-ray spectra based on total mean glandular dose for a breast CT acquisition[90].

The Monte Carlo method is a way to predict x-ray spectra from different combinations of target/filter using various tube voltages and different anode angles to simulate radiation transport through an object, incorporating incoherent and coherent scattering, and photoelectric absorption. There are multiple software packages that have been used to simulate x-ray imaging and dosimetry of the breast. Saunders *et al.* used the Penelope Monte Carlo code[133] to model a breast tomosynthesis acquisition of a 3D geometric voxelized breast phantom[77]. The model included contrast degradation from scatter, realistic beams, detector effects, and acquisition geometry. The authors used

previously published data for the elemental composition of the phantom materials to derive their attenuation properties with Penelope. The MASTOS simulation package developed by Spyrou *et al.* uses Monte Carlo methods to simulate the photon transport phenomena through properly designed software phantoms[134]. This package takes into account the geometry and operational characteristics of the mammography unit including: anode material and angle, focal spot size and shape, and the spatial and spectral distribution of x-rays.

The majority of breast phantoms in the literature are validated by subjectively evaluating the images, measuring deformation from compression, or quantitatively performing texture analysis on the images. A couple of groups that incorporated quantitative image analysis are described here. Bakic *et al.* compared texture properties computed in synthetic and clinical images using two statistical comparisons in order to validate their breast model: texture energy and fractal analysis[74]. The authors suggested that agreement between distributions of mean texture features indicated that synthetic images sufficiently simulated clinical images. Bliznakova *et al.* used subjective evaluation, as well as fractal dimensions and histogram analysis, to demonstrate the quality of their synthetic mammograms[76].

5.2.1 Voxelized Phantom Approach

Initially in our project, an analytical noise free simulator was used to model the image simulation in a very simplistic approach. The mesh model of the non-FEM compressed breast was voxelized prior to simulated image generation. In order to increase computational efficiency, the coronal plane resolution was lowered from 400 μm to 800 μm . During voxelization, the linear attenuation coefficient of the voxel was

assigned based on tabulated values for different tissues at certain peak tube voltages. Skin, glandular, and muscle were assigned the same attenuation coefficient. For the mammography generation, the attenuation coefficients were set to obtain contrast similar to real patient mammograms. For the tomosynthesis projection generation, the attenuation coefficients for the tissues were defined for a monoenergetic beam (21 keV) that was based on spectrum data for Mo/Mo with 28 kVp[135]. The breast was placed 15 mm from the detector surface and the x-ray source was placed 65 cm from the detector. Twenty-five projections were acquired over 45° in an arc above the breast in a geometry that was modeled after the prototype Siemens Mammomat Novation system (Figure 5-1)

Figure 5-1: Imaging geometry for projection image acquisition of compressed breast.

The transmitted intensity reaching the detector was calculated by a line integral that summed up the spatially dependent linear attenuation coefficients ($\mu(x,y,z)$) along the ray connecting the detector element to the source, which had an intensity of I_o .

Ray tracing algorithm:
$$I = I_o * \exp\left(-\int_{\mu} \mu(x,y,z)dl\right) \quad (5-1)$$

The final mammogram was corrected with a sigmoidal output transform (see Figure 5-3) for optimal image viewing. The tomosynthesis dataset was reconstructed using Siemens' proprietary filtered back projection algorithm[136]. The resulting simulated images have approximately the same appearance and similar texture as the real human subject data; however, they do not contain as much high frequency information. This was most likely due to the fact that the originally used denoised reconstructions were not done at the same high resolution as the original bCT data and the simulated image generation implementing the voxelized approach used an even further reduced resolution because of computational time considerations. In the simulated tomosynthesis images, there are artifacts (wavy lines) that are due to inadequate sub-sampling of the surface model of the skin. Sample images from the voxelized approach of simulating mammogram and tomosynthesis slice images are shown in Figure 5-2.

Figure 5-2: (A) is a simulated mammogram using the voxelized approach. (B) is a tomosynthesis slice using the voxelized approach.

The initial image simulation procedure had several issues resulting from simulating images of voxelized data. The voxelization of a high-resolution model was computationally intensive and required a significant amount of computer storage. Alternatively, if the voxel size was too large, there may have been projection errors that resulted in reconstruction artifacts. Following studies implemented an image simulation algorithm directly on the mesh surface model, which reduced computational time and allowed for a more exact solution without voxelization errors.

5.3 XCAT Breast Phantom Image Simulation

In order to generate images from the XCAT breast phantom, x-ray projection images were simulated directly from the surface mesh model using a technique developed by Segars *et al.*[132]. The algorithm calculates the line integrals directly from the surface definition. It can simulate mono or polychromatic sources by sampling a provided energy spectrum. Quantum noise is modeled by adding statistical uncertainty directly to the line integrals and then scaling the projection according to the simulated projection parameters and geometry. Additionally, Poisson noise is simulated in the spectral energy bins and the effects of beam hardening are included. The resulting projection data has realistic noise levels and statistics[132].

As presented previously[103], the geometry of the simulated imaging system was equivalent to that of the Seimens Mammomat Novation System illustrated in Figure 5-1. Attenuation coefficients for adipose, glandular, and skin were derived from International Commission on Radiation Units and Measurements (ICRU) tissue data[127]. The three different levels of glandular tissue were assigned attenuation coefficients between adipose and muscle in order to account for their relative amount of marbling. The densest

glandular tissue was assigned the elemental composition of muscle for our purposes since glandular tissue was not available in the database used. A custom polyenergetic spectra was used to simulate a 50 μm Rhodium filter with a Tungsten target[137]. Images were simulated with 1000x1000 pixels at 250 μm resolution.

After a simulated projection was generated, a sigmoidal correction function was applied in order to simulate the appearance of a screen-film mammogram, similar to what is currently applied to digitally acquired mammograms. Figure 5-3 shows the characteristic curve that was used on simulated projection images in order to simulate a screen-film mammogram appearance.

Figure 5-3: Characteristic curve used on simulated projection image in order to simulate mammogram.

5.3.1 Simulated Images from Simplistic Compression

After developing the image processing and segmentation methodology to generate a breast phantom with a realistic anatomical basis, we generated images of the breast phantom. It was processed with the simplistic compression method, which did not realistically compress the breast model or take into account the varying mechanical properties of the tissue. However, the image simulation step was necessary to evaluate the level of anatomical detail available in the breast phantom resulting from the image processing and segmentation steps. The subdivision surface model of the non-FEM compressed phantom was used directly to simulate a medial-lateral (ML) projection¹.

Figure 5-4 shows two simulated ML mammograms of the breast phantom. Figure 5-4-A shows a mammogram of the non-FEM compressed phantom using defined attenuation coefficients ranging from adipose to muscle for the differentiated glandular tissue. Figure 5-4-B shows a mammogram of the phantom with artificially enhanced attenuation coefficients to illustrate the high resolution detail. The simulated mammograms subjectively demonstrate the realism of the phantom and the level of detail in the tissue structures appears similar to actual mammograms.

¹ When we received the bCT data, we were unsure of the breast geometry. We mistakenly simulated ML views instead of the traditional cranial-caudal views. That is why the analysis in this section was performed on the ML images.

Figure 5-4: Simulated images generated directly from the mesh surface model of the non-FEM compressed phantom. (A) is the ML mammogram with defined attenuation coefficients that are described with 3 levels of fibroglandular tissue ranging from adipose to muscle. (B) is the ML mammogram with enhanced attenuation coefficients to demonstrate high-resolution detail of the phantom.

A quantitative validation of the non-FEM compressed breast phantom simulated images was performed using the fractal dimension (FD) calculated from ROI's of the simulated mammograms (Figure 5-4.A & B) and compared to typical FD values obtained from real mammograms[73, 138, 139]. Ten different 150x150 ROI's located near the nipple were used for the FD measurement. The FD was estimated using the circular average power spectrum method[140, 141] that has been used successfully in prior mammography applications[142]. Initially, the two-dimensional power spectrum of the image was obtained using zero-padding and a radial Hamming window to ensure better estimation of the power spectrum[143, 144]. The 2D power spectrum was then transformed into one dimension by linear averaging the spectrum as a function of the radial distance from zero frequency. The Fourier power spectrum was plotted on a log-log scale as a function of the frequency and linear regression was applied to estimate the

slope of the fitted line. The slope was then transformed into a FD measure as described by Tourassi *et al.*[142].

The average results from the simulation are shown in Table 5-1 as compared to a study from Bakic *et al.* performed on actual mammograms[73]. The simulated results compare quantitatively to published findings. They also compare similarly to other studies by Caldwell *et al.*[138] and Byng *et al.*[139] that have found the FD to be within the range of 2.25 to 2.6.

Table 5-1: Comparison of the FD distributions calculated from simulations to published results observed from actual mammograms.

Fractal Dimension -the mean and standard deviation are displayed.	Hamming Window	Published Results[73]
Simulated Mammogram (Figure 5-4.A)	2.18 ± 0.016	2.36 ± 0.10
Simulated Mammogram (Figure 5-4.B)	2.23 ± 0.007	

5.3.2 Simulated Images from Finite Element Compression

While the calculated FD of images generated using the non-FEM compressed breast phantom were similar to other studies, this was not a realistic compression method. Therefore, as detailed in the preceding chapter, a realistic compression algorithm was developed using finite element techniques. In order to simulate images from the FEM compressed breast phantom, the projection code required a subdivision surface definition. Therefore Matlab's '*isosurface*' function was used to generate triangular surfaces from the segmented breast data of the uncompressed breast for each of the different materials (fat, three density levels of glandular tissue, and skin). In order to apply the compression to the segmented imaging data, the new compressed location for each node in the

triangular surface definition of the original uncompressed breast was given by 3D linear interpolation of the new locations of the FE mesh model. However, due to the spatial low-pass filtering effect of the '*shrinkwrap*' function used during mesh generation, not all of the triangulated surface nodes from the segmented data could be defined with the interpolation from the tetrahedral mesh. The new location for undefined nodes was determined by linearly interpolating in 3D between the two nearest defined nodes. This method provided a compressed subdivision surface model of the breast.

A cranial-caudal projection and a medial-lateral projection were generated using the projection code. To demonstrate the effect of varying the mechanical properties of the different breast tissues, projections of two modulus ratios (1:5:10 and 1:10:88) are illustrated in Figure 5-5. For comparison to the realistic FEM compression, ML and CC projections of the breast phantom that were processed with the non-FE simplistic compression method described previously[88], which did not take into consideration varying mechanical properties, are also shown.

Figure 5-5: Simulated Image Projection of the 28% dense phantom (using 4-noded tetrahedral elements, $\nu = 0.49$, $\rho = \text{real}$, and $\mu = 0.46$). (A) is an ML projection with moduli ratio = 1:5:10; (B) is a CC projection with moduli ratio = 1:5:10; (C) is an ML projection with moduli ratio = 1:10:88; (D) is a CC projection with moduli ratio = 1:10:88; (E) is an ML projection using a simplistic compression algorithm; (F) is a CC projection using a simplistic compression algorithm. Note how the projection of the breast is different using different moduli ratios. Additionally, the new realistic FEM compression method distributes the tissue differently than the old simplistic compression, which did not take into account the varying mechanical properties of the different breast tissue.

5.4 Conclusion

Two image generation simulation methods were implemented. One method used a voxelized phantom and the other simulated images directly from the mesh surface model of the phantom. The voxelized generation method was time consuming and memory intensive. It also did not include a realistic model for quantum noise or scatter. We decided to use a more flexible and efficient image generation code previously developed to generate images directly from the surface mesh model. This image generation tool incorporates realistic models for quantum noise and the algorithm can be modified to include scatter in the future. The images generated using the FEM compressed phantom illustrate a difference in shape and overall morphology from the original simplistic non-FEM compression algorithm. The images also demonstrate how adjusting the material properties of the breast can also affect the distribution of the tissue in the resulting projection.

Combining three necessary components of a computerized breast phantom – a realistic anatomical base from the image processing and segmentation step, a realistic deformation of the phantom modeled using finite element techniques, and an analytical projection algorithm that realistically simulates clinical image generation – produces an realistic and flexible XCAT breast phantom package that can be used to develop and improve breast imaging techniques and devices. An additional component of the phantom package was to incorporate the ability to deform or morph the breast phantom and generate new and unique datasets. This will be covered in the following chapter.

6. Generation of a Suite of XCAT Breast Phantoms

6.1 Introduction

The ultimate goal of developing hybrid breast phantoms that combine empirical data with flexible computer graphics techniques, is for them to be used in breast imaging research because of their ability to produce realistic data and simulate the variability of human anatomy. The computerized breast phantoms generated from our project are unique in that they are a hybrid of the two phantom generation techniques. They are based on dedicated breast CT datasets (dedicated bCT) of human subjects, thus encompassing the variability and complexity of real human anatomy, and by using computer-graphics techniques they also have the flexibility intrinsic in a mathematical phantom [88]. However, to date, these phantoms have been based on single subjects and one of the goals of this effort is to generate multiple phantoms from the limited set of dedicated bCT data that we have access to.

Image morphing is a technique to construct new images by gradually transitioning between two sets of images by applying geometric transformations that generate distorted datasets. There are numerous morphing techniques developed for the computer graphics field and the medical imaging field that can be used to deform images including: mesh warping, field morphing, multi-dimensional spline deformation, energy minimization, free-form deformations, etc[145-152]. The deformation can be applied to the image data, or to finite element or surface meshes generated from the image data.

The concept of producing new datasets by deforming and morphing CT data is not new. There have been efforts to generate supplementary datasets for clinicians to analyze during training. Deformation and morphing of real images allows for the

simulation of a diversity of disease states to complement the available data for study [153, 154]. In addition, deformation and morphing techniques are already used for medical image registration to perform temporal change assessments and for multimodality registration[148, 155, 156]. However, to our knowledge this is the first application of deformation and morphing applied to dedicated bCT datasets of different human subjects.

A basic deformation and morphing method employing mesh warping on the bCT image data is described. Mesh warping is a method that uses two images: a base image I_B and a target image I_T . Both images have a mesh associated with them, referred to as M_B and M_T respectively. M_B specifies the coordinates of the control points used in I_B and M_T specifies their corresponding positions in I_T . M_B and M_T are used to generate a spatial transformation that maps all points on I_B onto I_T . Several different M_T meshes can be generated that change the deformation of M_B , which result in several unique realizations of a deformed and morphed I_B . Although some deformation and morphing can be minor, we demonstrated previously in Chapter 4 “Simulated Compression” that changing the structure of the phantom slightly can greatly affect the mechanical response of the breast during simulated compression and the resulting appearance of the simulated images. Therefore, a basic deformation technique can make a large impact in generating new and unique datasets.

This work presents a methodology that can be used to generate of a variety of computerized breast phantoms that are based on empirical data from a limited number of human subjects. This suite of flexible breast phantoms can be used for imaging research to provide a known truth while concurrently producing realistic simulated imaging data.

6.2 Deformation and Morphing Methods

The acquisition and segmentation of the dedicated bCT datasets has been described previously in Chapter 2[88, 157]. The segmented datasets of two different human subjects were used as the base and target for deformation and morphing to generate new morphed data. The segmented datasets consisted of 300 384x384 coronal slices with 500 μm isotropic resolution and contained 3 different tissue types: fat, glandular, and skin. Multiple image deformation and morphing strategies were implemented: glandular translation, breast rotation, glandular tissue rotation, glandular displacement, glandular erosion, morphing between breast shapes, and morphing between glandular structures. The level and complexity of the morph was user defined and automatically executed using MATLAB R2007a (The MathWorks, Inc., Natick, MA) to perform all deformation and morphing functions.

6.2.1 Initial Shape Transformation

The shape of the morphed breast data was changed by rotating the target breast or making the shell of the target breast wider or narrower. A mask of the target breast was generated to encompass the breast data. Erosion and dilation of coronal slices of the target breast mask using a disk structuring element with a radius of 2 was done to shrink or grow the diameter of the morphed breast data. The '*imrotate*' function was used on the coronal slices of the target mask to rotate the shell of the morphed breast by a user defined angle. The shape-transformed data was the new target data for transformative mesh generation.

6.2.2 Transformative Mesh Generation

The original breasts differed in their overall size, shape, and location; thus it was necessary to generate a transformative mesh to map between the base dataset and the target dataset in order to produce the morphed data. The transformation in the sagittal (chest-to-nipple) direction was determined through a mapping of the coronal slice number of the base breast data to the target breast data in which every slice in the base data was mapped to a slice in the target data. If the target data's chest-to-nipple distance was greater than the base breast data, there would be target slices that would not have any base slice mapped to it; these intermediary slices were interpolated to be a linear combination of the nearest defined slices, which are described in the mapping step below. In the case where the target chest-to nipple distance was less than the base breast data, there would be multiple coronal slices in the base data that map to a single slice in the target data. For simplicity, we chose a single slice from the base, the slice furthest from the chest wall, to be mapped to the target slice. The sagittal direction mapping of the base to target was determined from the arrays shown below:

$$Base\ Slices = [FirstSlice_{Base}:1: LastSlice_{Base}]$$

$$Target\ Slices =$$

$$[FirstSlice_{Target}:(LastSlice_{Target}-FirstSlice_{Target})/(LastSlice_{Base}-FirstSlice_{Base}):LastSlice_{Target}]$$

The transformation in the coronal plane was determined using a radial mesh that was generated for both the base and the target data. The center of each coronal slice was determined by using the half-way point between the outer bounds of the coronal breast slice. The breast diameter through the center and across a coronal slice of the base breast was divided into 50 uniform segments. This was repeated for each breast diameter at 0.5 degree increments for 180 degrees to fully cover the breast data and form the mesh of

radial control points. The corresponding angular diameters of the target breast were also divided into 50 segments to form a target mesh. Different strategies to morph the base breast data were implemented by changing the spacing of the control points in the target mesh and are described below and illustrated in Figure 6-1.

6.2.3 Direct Translation of Coronal Data

If the uniformly spaced control points on each angular diameter of the base data slice are mapped directly to the uniformly spaced control points on each corresponding angular diameter of the target data slice, this was called a direct translation of the coronal data. This method was used to shift the breast tissue to fit into the shell of the target breast, without changing the overarching structure of the tissue. This method essentially places the breast tissue from the base data into the shell of the target data.

6.2.4 Shape Morphing

In order to generate phantoms of intermediary slices and shapes beyond the simple initial shape transformation described above, the shape of the morphed breast can be based on a combination of the base and target datasets. The user can define at what intermediary stage between the base and target data to set the shape of the morphed breast. This was done by comparing the length of each angular diameter from the base data with the length of the corresponding angular diameter of the target data. A user defined fraction 'f' was used to define how long the new length of the morphed angular diameter would be between the two datasets. For example, if $f = 0.5$, and the angular diameter of the base was 100 units long and the angular diameter of the target was 140 units long, the new length of the morphed angular diameter would be 120 units long.

6.2.5 Glandular Data Translation

For each angular diameter in the target data, if the user wanted to translate the tissue of the base breast towards the edges of the target breast, the control points of the target mesh could be defined closer together near the edges of the breast and farther apart in the center. If the user wanted to contract the data to be closer to the center of the breast, the target control points could be spread out more on the edges and more closely spaced near the center. The spacing of the control points on each angular diameter of the target data was low-pass filtered with a moving average filter to smooth any sharp transitions from the translation parameters. The target control points are mapped to the uniformly spaced mesh control points on the corresponding angular diameter of the base data.

6.2.6 Non-uniform Skewing of the Coronal Data

The level of how much to translate the breast data in each coronal slice could be specified in a way that would non-uniformly skew the tissue so that it was not an overall translation, but a smoothly varying targeted change that was distributed throughout the different angular diameters. A normal probability distribution function was defined with a user specified angle as the mean of the distribution and a user specified standard deviation that was used to spread the change over the adjacent angular diameters. The spacing of the target control points on each angular diameter of the target data was low-pass filtered to smooth any sharp transitions from the skewing parameters. The skewed grid control points on each angular diameter in the target data are mapped to the uniformly spaced grid control points on the corresponding angular diameter of the base data.

6.2.7 Rotation of Glandular Data

The glandular data could also be rotated by a user defined angle separately from the overall rotation of the breast described in the initial shape transformation step described above. The translation and non-uniform skewing map the base control points on one angular diameter to the control points on the corresponding angular diameter of the target. In order to rotate the glandular data in the coronal slice, we map the base control points on one angular diameter to the control points on a non-corresponding angular diameter that was offset from the base by a user defined angle.

6.2.8 Mapping

For each coronal slice in the base data, a uniform radial mesh of control points was generated and mapped to a radial mesh of control points on the target data. The translation from the base to the target mesh was extrapolated across the target breast data in the coronal slice corresponding to the coronal slice in the base data using '*griddata*' with the linear interpolation option specified. Mapping provided the new 3D coordinate location in the morphed data for each breast voxel in the base data.

6.2.9 Tissue Deformation

During tissue deformation, the mapping specified through the prior step was used to place the segmented value of the voxel from the base data into its new location in the morphed dataset. In the cases where the chest to nipple distance of the target was larger than the base, resulting in coronal slices without a direct mapping from the base, the translation maps of the two defined coronal slices on either side (sagittally) are linearly interpolated to generate a translation for the undefined slice.

There may not be a one-to-one mapping of the base data voxels to the morphed data, therefore steps are taken to generate non-sparse structures. A mask of the base data was morphed and used to create a mask of the morphed data that was used to define both the fat and the skin. The coronal slice of the morphed data mask was morphologically closed with a disk structuring element of radius 10. It was also then closed in the sagittal and transverse planes using a disk structuring element of radius 3. To remove any extraneous spots or holes, the '*bwmorph*' '*majority*' function was used over all the anatomical planes as well.

The altered glandular data undergoes a similar set of steps to generate non-sparse glandular structures; however, the '*bwmorph*' '*fill*' operation was used first and then followed by a morphological closing using a disk structuring element with a radius of 1. These steps allow the altered glandular tissue to maintain small structures and holes in the glandular tissue, instead of generating a large contiguous block.

6.2.10 Combining the Glandular Tissue of the Base and Target Data

To generate morphed breasts with glandular tissue that resulted from a combination of the base and target data, a distance transform was applied to the glandular tissue of the newly generated morphed data and the target data's glandular tissue. The '*bwdist*' function was used to separate the glandular tissue in terms of its Euclidean distance from other tissues. For example, a value of 1 would be immediately adjacent to fat or skin in any direction, and a value of 10 would be 10 voxels away from fat or skin in any direction. The maximum distance ($d_{\max}$) of the glandular tissue for the coronal slices in both the morphed data and the target data was used to determine the threshold for each dataset by a user defined fraction (f) of $d_{\max}$. The threshold for each dataset was applied

in each coronal slice such that for one dataset, glandular voxels with distance values that were 1 to $f \cdot d_{\max_1}$ were used, and in the other dataset, voxels with distance values $f \cdot d_{\max_2}$ to $d_{\max_2}$ were used. In order to ensure that there were no extraneous spots or holes, the new combinatorial glandular tissue was morphologically closed in all anatomical planes with a disk structuring element of radius 1. This technique allowed for a combination of the smaller glandular structures from one dataset with the larger structures from the other dataset.

6.2.11 Erosion of Glandular Tissue

Following the completion of morphing the glandular data in any of the ways previously described, the user could also make the glandular tissue thinner. In order to maintain the small vessels that traverse the breast in sagittal and transverse planes, both of these planes were the target for erosion by a disk structuring element of radius 1. The coronal planes were next morphologically closed with the same disk structuring element.

6.2.12 Sagittal Extension of the Glandular Tissue

In some cases, the different morphing methods may not have produced glandular tissue that reaches the nipple. However, knowing that anatomically there is a ductal network that branches off from the nipple, we developed a simple method to extend the glandular tissue to the furthest coronal slice from the chest wall, which was assumed to be the nipple. The glandular data in the last coronal slice that contained glandular data was morphologically dilated using a disk structuring element of radius 1 to allow the glandular tissue to slowly grow towards the nipple. Every other coronal slice was dilated and the in-between slices were simply a copy of preceding slice.

6.3 Skin and Fat Assignment

In order to generate a layer of skin that was 2 mm thick, coronal slices of the mask of the morphed breast were eroded by a disk structuring element of radius 4. The eroded mask was then assigned to the fat region and the 2 mm thick eroded layer surrounding the fat was assigned to skin.

6.4 Glandular Density Assignment

Only the morphed glandular tissue that overlapped with the fat region was used to define the glandular tissue of the complete morphed data. This ensured that any morphing functions that extended the glandular tissue beyond the bounds of the breast skin would be corrected by only allowing the glandular tissue that lay within the skin to be assigned.

The morphed dataset was extrapolated out to 300 768×768 coronal images with an in-plane resolution of 250 μm and slice thickness of 500 μm , in order to be used for tissue assignment after compression. The glandular data of the large morphed dataset was divided into three different densities[88]. However, since there was no original bCT data to base the density groupings on, the distance transform (using ‘*bwdist*’) was applied to rank the glandular tissue according to Euclidean distance from other tissue. The distances were sorted in ascending order and the lowest half was assigned to the lowest density level, half to three-quarters of the maximum distance was assigned to the middle density level, and the highest quarter of distances was assigned to the highest density level. This technique was chosen because this trend was observed in the segmented human data.

6.5 Simulated FE Compression and Image Generation

Methods previously described in Chapter 3 “Breast Phantom Creation” were used to generate a tetrahedral mesh from the morphed 500 μm isotropic resolution data with 2.5 mm elements. Compression of the morphed breast was simulated using finite element methods as described in Chapter 4 “Simulated Compression”. The modulus ratio (Fat:Glandular:Skin) chosen for the tissues was set to 1:10:88, the poisson’s ratio was set to 0.49, a coefficient of friction of 0.46 was used for the skin, and the breasts were all compressed to 5 cm thickness. The compressed tetrahedral model was then assigned tissue values according to the large morphed dataset that contained fat, three density levels of glandular tissue, and skin; and then translated into a subdivision surface model as described in Section 5.3.2. A simulated projection of the compressed morphed breast phantom was generated and a sigmoid correction function was applied in order to generate a simulated mammogram[88, 132].

6.6 Observer Study

To evaluate the realism of images generated using the suite of XCAT breast phantoms, a preliminary subjective observer study was performed with a 10 point scale of assessed realism where 1 was “Fake”, 5 was “Somewhat Real”, and 10 was “Real”. The images were graded in terms of the realism of displayed breast parenchyma and not on the viewing platform. In order to generate images for review, three original breast datasets were used as the base and targets for deformation and morphing to generate 59 new datasets. The original datasets were chosen from three different volumetric density levels: 14%, 28%, and 40%.

Sixty-two simulated CC mammograms were generated from the suite of XCAT breast phantoms for the observer study. Three images were selected that were generated from breast phantoms created directly from the bCT data without deformation or morphing and 59 of the images were a result from different combinations of deformation and morphing of the original datasets. The radiologists viewed all simulated mammograms on a web image viewer (www.Jalburn.com) with the viewing environment limited by standard web resolution and personal computer settings. The radiologists did not have any user controls to adjust contrast, window or levelling. Thus far, three experienced breast radiologists have responded with their rankings.

6.7 Deformation and Morphing Results

In order to demonstrate how the radial grid works to deform the coronal slices, Figure 6-1 shows some examples of a base and target grids that can be used for deformation. Figure 6-2 illustrates what coronal slices from the new segmented datasets look like after implementing a number of deformation and morphing techniques. Figure 6-3 contains mammograms generated using three datasets of original segmented bCT data and 6 new datasets that were morphed or deformed version of the three using methods described in this chapter.

Figure 6-1: This illustrates how the radial grids implement mapping from the base to the target in order to implement deformations. (A) Base breast radial grid; (B) Target breast radial grid (direct translation); (C) Target breast radial grid (glandular data translation-stretch towards edge); (D) Target breast radial grid (glandular data translation-shrink towards center); (E) Target breast radial grid (non-uniform skewing).

Figure 6-2: (A) Coronal slice from the base breast (B) Coronal slice from the target breast; (C-J) Coronal slices from new segmented datasets resulting from deforming and morphing the base and target breasts using different combinations of translation, non-linear skewing, shape changes, rotation of either breast shell or glandular tissue, and morphing between the breasts.

Figure 6-3: Simulated CC mammograms ranging from realism rankings of 6 to 10. (A) 14% dense original breast; (B) 28% dense original breast; (C) 38% dense original breast; (D) deformed/morphed A and B; (E) deformed/morphed A and B; (F) deformed/morphed A and C; (G) deformed/morphed B and C; (H) deformed/morphed A and B; (I) deformed/morphed B and C.

6.8 Observer Study Preliminary Results

The breast radiologists who have reviewed the simulated mammographic images generated from the suite of XCAT breast phantoms provided comments and rankings. The radiologists commented that all of the simulated cases were of “scattered tissue or heterogeneously dense” breasts and none were “fatty replaced or extremely dense”. They also commented that the “images look very good to excellent on the whole”, some looked “really realistic”, and that “almost all cases have appropriate distribution of tissue”. The average rank was 6.85 ± 1.12 with an average 64.5% of the images scoring 7 or above. The lowest ranking images had large areas of homogenous fat that does not typically appear in real images and “needs more texture”.

6.9 Discussion of Morphing and Deformation Tactics and Future Work

The simplistic morphing and deformation techniques implemented in this work demonstrate the ability to generate new and unique imaging phantoms, which can be used for breast imaging research. Although the level of deformation was primarily through simple transformations using rotation, translation, or small alterations in the size and shape of the breast tissue; these small changes affect the morphology of the breast and its mechanical response to finite element compression, which ultimately affects the simulated images generated from the phantom.

There are several options that can change the resulting morphed data including: choice of the base and target datasets, rotation angles, size changes, fraction choices, size and shape of structuring elements, FEM parameter choices, and breast density allocation percentages. The large number of variables allows for a flexible breast phantom that can

generate numerous phantom realizations using a limited number of human subject datasets.

There are some issues that are not addressed in the presented work that will be the subject of future investigations. One of the major issues in deciding on the morphing variables was predicting how realistic the resulting datasets or simulated images would be. We tried to maintain similar tissue distribution as the base and target images for the morphed datasets in order to maintain the level of realism provided by the original data. However, a smooth transition between the glandular tissues of the base and target datasets was not realistically approached because of the complexity of the tissue, most notably the disparate distribution of the glandular tissue between different subjects. Therefore the resulting combination of the dissimilar glandular tissues may have resulted in a morphed dataset that contained structures that would never occur in human subjects.

Currently, a comprehensive qualitative evaluation of the realism of the morphed data was not performed for this effort, since only three breast radiologists provided rankings. This can be addressed in the future by performing a more in depth user study where breast radiologists evaluate the realism of each of the morphed datasets and also evaluate the realism of simulated images generated from the phantoms along with some real mammograms from human subjects.

However, the observer rankings indicate that the methodology to generate a suite of XCAT breast phantoms can produce realistic imaging data. There may still need to be additionally simulated structures to disallow for homogeneous areas of fat, which can be an area of future study.

The breast phantoms should have the ability to generate models with a user-defined volumetric glandular density since this is an active area for research because it is more difficult to detect cancer in dense breasts than in less dense breast. Currently our phantoms do not have the capability to tune the breast density, but this is an area for future improvement. Computational anatomy methods that can handle both the growth and atrophy of tissue can be investigated in the future to generate more realistic transitions between the base and target dataset[158]. Lastly, the suite of phantoms need to be able to simulate different levels of health or disease. This can be explored in the future by developing 3D tumors or microcalcifications that can be added to the phantom.

6.10 Conclusions

We have described a simple methodology to generate a suite of unique breast phantoms from a limited number of dedicated bCT datasets by using a combination of mesh deformation and morphing techniques. To our knowledge, this is the first presentation of deformation and morphing of dedicated bCT data from different subjects to create new morphed datasets. Future efforts will include more complicated morphing techniques to improve on the presented deformation and morphing methods as well as a user study to evaluate the level of realism achieved with a suite of computerized breast phantoms. This new suite of phantoms presented in this work may provide an important tool to optimize, evaluate, and improve new and existing breast imaging techniques and devices.

7. Future Directions and Concluding Remarks

The development of a suite of flexible, three-dimensional, computerized breast imaging phantoms that provide realism, based on human subject data and the flexibility of a mathematical phantom utilizing computer graphics techniques, has been described in this work. However, there are several areas for improvements to the phantoms that could be made in the future.

7.1 Future Directions

One of the major limitations of the currently presented suite of breast phantoms is the lack of a comprehensive user study to provide a subjective evaluation of the realism of the phantoms. Although a quantitative evaluation of the phantom's realism has been demonstrated by measuring the fractal dimensions of a simulated image[88]; quantitative measures may not convince researchers of the high level of realism provided in the phantoms presented herein. Therefore, a comprehensive qualitative study with experienced breast imagers will be performed using a reality ranking of both generated and real images. This study will either provide a validation of the phantom or be an informative study on necessary areas for improvement of the presented breast phantoms. Some known limitations of the phantoms and some potential improvements are detailed below.

The morphology of the breast phantoms is limited by the ability of the segmentation routine to adequately differentiate tissues in the bCT data. However, there are limitations in the segmentation due to the geometry and low-dose acquisition of the imaging data that was used as a basis for the segmentation. For example, microcalcifications and

structures such as Cooper's ligaments may have limited visibility in the bCT data[33, 38]. In addition, researchers may want to have phantoms of varying health and disease states on which to develop and test their techniques. The dedicated bCT datasets that the phantoms are based on were acquired of normal breast with no cancer. Therefore, none of these structures will exist in the phantoms since they would not be in the segmented imaging data. Future plans include developing methods to simulate Cooper's ligaments, microcalcifications, and abnormalities to provide an additional level of realism to the phantom. In addition, other computer generated breast phantoms have added simulated texture to their phantoms as part of their image synthesis[74, 77, 79, 80]. This could be a possible area for improvement since the simulated texture could simulate structures not captured by the segmentation or the supplementary simulated anatomy.

One of the important factors in staging breast cancer is to know if the patient's lymph nodes contain cancer cells. In dual view mammography, cranial-caudal and medial-lateral-oblique views are acquired in order to give radiologists different views of the breasts with different information. The MLO view is especially useful in imaging and diagnosing cancer in the axillary lymph nodes, which could be indicative of invasive breast cancer. The dedicated bCT datasets were acquired of a pendant uncompressed breast and the geometry of the acquisition does not typically allow for imaging of the chest wall or axillary region in its current configuration[33, 38]. We plan to attach the breast to the chest wall of the XCAT phantom. This will allow for imaging of simulated lymph nodes in the axillary region as well as enable the simulation of MLO mammograms. Attaching the breast phantom will require many steps. The XCAT

phantom chest wall and pectoral muscle will have to be grown and stretched to attach to the breast. This attachment will also affect how the simulated compression is performed.

Currently the finite element compression used simulated rigid compression plates parallel to, and infinite in, the transverse plane. A new finite element model for the compression plates will need to be developed. The plates will need to stop at the chest wall and have a smooth edge that will contact the breast at the breast-to-body boundary during simulated compression. Also, because of the attachment of the breast to the chest, a change in the displacement of the tissues near the chest is also expected as currently the breast is allowed to displace infinitely in the coronal direction at the chest wall area, but this movement will be limited by the connecting tissues from the chest.

The finite element model currently employed presents many areas for continued investigation and possible improvement; a few are described here. Currently, the FE model uses tetrahedral elements; however, there are other types of elements that may give better results depending on the choice of the material and the loading conditions. For example, hexahedral elements behave differently than tetrahedral elements when the material is defined to be nearly incompressible. Also, we have defined a contact definition to model the compression, but it could be possible to use point loads as an alternative. In the current model, materials share nodes with adjacent dissimilar materials, but a sliding contact between dissimilar materials may be more representative of how real tissues make contact, and this is another option to investigate in the future. At this time, we have only defined three different types of tissue: fat, glandular, and skin; however the level of tissue heterogeneity can be changed by incorporating the segmented three levels of glandular density into the model and adjusting their defined stiffness ratios and

material densities to be between the defined values for fat and glandular tissue. We have assumed that the initial state of the uncompressed breast is unloaded; however, since the dedicated bCT data was acquired of a pendant breast, it was loaded by gravity. It could be possible to simulate the breast in an unloaded state by removing the gravity loading and then simulating the compression, which may produce different results. Finally, evaluating how well the FE method works requires a metric to measure by. Future studies can investigate the similarity of the actual mammograms acquired of the human subjects that the phantoms were based upon with images simulated using varying FE parameters.

There are additional options that researchers may like to add to the phantom. For example, breast glandular density is an active topic for research since it is more difficult to detect cancer in dense breasts than in less dense breasts. Thus it would be beneficial to be able to specify a level of glandular density in order to generate a suite of imaging datasets that can contain a variety of phantoms with different levels of user defined glandular densities. Computational anatomy methods that can handle both the growth and atrophy of tissue will be investigated in the future to generate smoothly varying transitional states of the glandular tissue[158]. This may help to allow for more realistic transitions of the glandular data than the morphing algorithm currently provides and allow for the creation of datasets with a user defined glandular density.

The breast phantoms presented in this work have demonstrated the ability to generate high-quality x-ray imaging data. However, the utility of the phantoms in other modalities has not yet been fully investigated. Future studies should evaluate the realism

of images generated from the breast phantom with additional modalities such as MRI, ultrasound, SPECT, PET, and other emerging breast imaging technologies.

7.2 Concluding Remarks

This work has produced a suite of breast phantoms that can be combined with the existing XCAT phantom and make it applicable to breast imaging research for the first time. Using dedicated bCT imaging data, we have developed a methodology to produce a realistic anatomical basis for the phantoms by reducing the noise and scatter in the imaging data and utilizing a volumetric segmentation algorithm developed specifically for bCT data. The flexibility of the XCAT breast phantoms was derived from using computer graphics techniques to produce subdivision surface models of the breast tissue that can be altered using affine or other transformations and a finite element technique to realistically simulate compression. Unique datasets can be generated from a limited number of human bCT data by implementing deformation and morphing tactics, which allows for the ability to simulate the variability inherent in the patient population. The breast phantoms can be combined with existing simulated image projection tools to simulate realistic high-resolution imaging data. The methods described, provide the capability to produce very realistic phantoms of a sufficient number of simulated human subjects to enable large scale observer studies of breast imaging modalities.

The presented work is a substantial advancement in tools for breast imaging research with several considerable improvements over currently available phantoms: (1) it is based on actual human subject data, (2) it is able to produce high-quality images with moderately high resolution and excellent realism, and (3) it includes the ability to produce multiple distinct datasets. The suite of XCAT breast phantoms have the realism

and flexibility that computerized phantoms require in order to find widespread usage in breast imaging research and development.

References

- 1 ACS, "American Cancer Society: Key statistics about breast cancer? ," (2010).
- 2 S. W. Fletcher and J. G. Elmore, "Clinical practice: mammographic screening for breast cancer," *N Eng J Med* **348**, 1672-1680 (2003).
- 3 L. Bassett and R. Gold, "The Evolution of Mammography," *American Journal of Roentgenology* **150**, 493-498 (1988).
- 4 A. Haus, "Historical Technical Developments in Mammography," *Technology in Cancer Research & Treatment* **1**, 119-126 (2002).
- 5 L. Humphrey, M. Helfand, B. Chan and S. Woolf, "Breast cancer screening: a summary of evidence for the U.S. Preventative Services Task Force," *Annals of Internal Medicine* **137**, 347-360 (2002).
- 6 E. D. Pisano, C. Gatsonis, E. Hendrick, M. Yaffe, J. K. Baum, S. Acharyya, E. F. Conant, L. L. Fajardo, L. Bassett, C. D'Orsi, R. Jong and M. Rebner, "Diagnostic performance for digital versus film mammography for breast-cancer screening," *The New England Journal of Medicine* **353**, 1773-1783 (2005).
- 7 E. D. Pisano, R. E. Hendrick, M. J. Yaffe, J. K. Baum, S. Acharyya, J. B. Cormack, L. A. Hanna, E. F. Conant, L. L. Fajardo, L. W. Bassett, C. J. D'Orsi, R. A. Jong, M. Rebner, A. N. A. Tosteson, C. A. Gatsonis and D. I. G. For the, "Diagnostic Accuracy of Digital versus Film Mammography: Exploratory Analysis of Selected Population Subgroups in DMIST," *Radiology* **246**, 376-383 (2008).
- 8 E. A. Rafferty, "Digital Mammography: Novel Applications," *Radiologic Clinics of North America* **45**, 831-843 (2007).
- 9 J. Harvey and V. Bovbjerg, "Quantitative Assessment of Mammographic Breast Density: Relationship with Breast Cancer Risk," *Radiology* **230**, 29-41 (2004).
- 10 C. K. Kuhl, S. Schrading, C. C. Leutner, N. Morakkabati-Spitz, E. Wardelmann, R. Fimmers, W. Kuhn and H. H. Schild, "Mammography, Breast Ultrasound, and Magnetic Resonance Imaging for Surveillance of Women at High Familial Risk for Breast Cancer," *J Clin Oncol* **23**, 8469-8476 (2005).
- 11 J. V. Frangioni, "New Technologies for Human Cancer Imaging," *Journal of Clinical Oncology* **26**, 4012-4021 (2008).
- 12 B. J. Tromberg, B. W. Pogue, K. D. Paulsen, A. G. Yodh, D. A. Boas and A. E. Cerussi, "Assessing the future of diffuse optical imaging technologies for breast cancer management," *Medical Physics* **35**, 2443-2451 (2008).

- 13 J. T. Dobbins, III and D. J. Godfrey, "Digital x-ray tomosynthesis: current state of the art and clinical potential," *Physics in Medicine and Biology* **48**, R65-R106 (2003).
- 14 E. A. Rafferty, "Breast Tomosynthesis," *Advances in Digital Radiography: RSNA Categorical Course in Diagnostic Radiology Physics* 219-226 (2003).
- 15 T. Wu, R. H. Moore, E. A. Rafferty and D. B. Kopans, "A comparison of reconstruction algorithms for breast tomosynthesis," *Medical Physics* **31**, 2636-2647 (2004).
- 16 Y. Chen, J. Y. Lo and J. T. Dobbins, III, "Impulse response analysis for several digital tomosynthesis mammography reconstruction algorithms," *SPIE Medical Imaging: Physics of Medical Imaging* **5745**, 541-549 (2005).
- 17 J. M. Park, E. A. Franken, Jr., M. Garg, L. L. Fajardo and L. T. Niklason, "Breast Tomosynthesis: Present Considerations and Future Applications," *Radiographics* **27**, S231-240 (2007).
- 18 L. T. Niklason, B. T. Christian, L. E. Niklason, D. B. Kopans, D. E. Castleberry, B. H. Opsahl-Ong, C. E. Landberg, P. J. Slanetz, A. A. Giardino, R. Moore, D. Albagli, M. C. DeJule, P. F. Fitzgerald, D. F. Fobare, B. W. Giambattista, R. F. Kwasnick, J. Liu, S. J. Lubowski, G. E. Possin, J. F. Richotte, C. Y. Wei and R. F. Wirth, "Digital tomosynthesis in breast imaging," *Radiology* **205**, 399-406 (1997).
- 19 W. F. Good, G. S. Abrams, V. J. Catullo, D. M. Chough, M. A. Ganott, C. M. Hakim and D. Gur, "Digital Breast Tomosynthesis: A Pilot Observer Study," *Am. J. Roentgenol.* **190**, 865-869 (2008).
- 20 S. P. Poplack, T. D. Tosteson, C. A. Kogel and H. M. Nagy, "Digital Breast Tomosynthesis: Initial Experience in 98 Women with Abnormal Digital Screening Mammography," *Am. J. Roentgenol.* **189**, 616-623 (2007).
- 21 D. Gur, "Tomosynthesis: Potential Clinical Role in Breast Imaging," *Am. J. Roentgenol.* **189**, 614-615 (2007).
- 22 W. A. Berg, "Tailored Supplemental Screening for Breast Cancer: What Now and What Next?," *Am. J. Roentgenol.* **192**, 390-399 (2009).
- 23 Y. Chen, J. Y. Lo and J. T. Dobbins, III, "Importance of point-by-point back projection correction for isocentric motion in digital breast tomosynthesis: Relevance to morphology of structures such as microcalcifications," *Medical Physics* **34**, 3885-3892 (2007).
- 24 D. J. Crotty, P. Madhav, R. L. McKinley and M. P. Tornai, "Patient Bed Design for an Integrated SPECT-CT Dedicated Mammotomography System," *Nuclear Science Symposium Conference Record, 2006. IEEE* **6**, 3915-3919 (2006).

- 25 R. L. McKinley, C. N. Brzymialkiewicz, P. Madhav and M. P. Tornai, "Investigation of cone-beam acquisitions implemented using a novel dedicated mammotomography system with unique arbitrary orbit capability," 2005 Proc. SPIE: Phys. of Med. Imag. **5745**, 609-617 (2005).
- 26 R. L. McKinley, E. Samei, C. N. Brzymialkiewicz, M. P. Tornai and C. E. Floyd, "Measurements of an optimized beam for x-ray computed mammotomography," 2004 Proc. SPIE: Phys. of Med. Imag. **5368**, 311-319 (2004).
- 27 R. L. McKinley and M. P. Tornai, "Preliminary investigation of dose for a dedicated mammotomography system," 2006 Proc. SPIE: Phys. of Med. Imag. **6142**, (2006).
- 28 R. L. McKinley, M. P. Tornai, C. N. Brzymialkiewicz, P. Madhav, E. Samei and J. E. Bowsher, "Analysis of a novel offset cone-beam transmission imaging system geometry for accommodating various breast sizes," *Physica Medica* **21**, 48-55 (2006).
- 29 R. L. McKinley, M. P. Tornai, C. N. Brzymialkiewicz, E. Samei and J. E. Bowsher, "Analysis of a novel offset cone-beam computed mammotomography imaging system for attenuation correction of SPECT in a proposed dual modality dedicated breast mammotomography system," *2004 Workshop on the Nuclear Radiology of the Breast (In Press)*, (2004).
- 30 R. L. McKinley, M. P. Tornai, E. Samei and M. L. Bradshaw, "Initial study of quasi-monochromatic beam performance for x-ray computed mammotomography," *IEEE Trans. Nucl. Sci.* **52**, 1243-1250 (2005).
- 31 R. L. McKinley, M. P. Tornai, E. Samei and M. L. Bradshaw, "Simulation study of a quasi-monochromatic beam for x-ray computed mammotomography," *Med. Phys.* **31**, 800-813 (2004).
- 32 M. P. Tornai, R. L. McKinley, C. N. Brzymialkiewicz, P. Madhav, S. J. Cutler, D. J. Crotty, J. E. Bowsher, E. Samei and C. E. Floyd, "Design and development of a fully-3D dedicated x-ray computed mammotomography system," 2005 Proc. SPIE: Phys. of Med. Imag. **5745**, 189-197 (2005).
- 33 J. M. Boone, A. L. Kwan, K. Yang, G. Burkett, K. K. Lindfors and T. R. Nelson, "Computed tomography for imaging the breast," *Journal of Mammary Gland Biology and Neoplasia* **11**, 103-111 (2006).
- 34 J. M. Boone, A. L. C. Kwan, T. R. Nelson, N. Shah, G. Burkett, J. A. Seibert, K. K. Lindfors and G. Ross, "Performance assessment of a pendant-geometry CT scanner for breast cancer detection," 2005 Proc. SPIE: Phys. of Med. Imag. **5745**, 319-323 (2005).
- 35 J. M. Boone, T. R. Nelson, K. K. Lindfors and J. A. Seibert, "Dedicated Breast CT: Radiation Dose and Image Quality Evaluation," *Radiology* **221**, 657-667 (2001).

- 36 A. L. C. Kwan, J. M. Boone and N. Shah, "Evaluation of x-ray scatter properties in a dedicated cone-beam breast CT scanner," *Med. Phys.* **32**, 2967-2975 (2005).
- 37 A. L. C. Kwan, J. M. Boone, K. Yang and S. Huang, "Evaluation of the spatial resolution characteristics of a cone-beam breast CT scanner," *Med Phys* **34**, 275-281 (2007).
- 38 K. K. Lindfors, J. M. Boone, T. R. Nelson, K. Yang, A. L. Kwan and D. F. Miller, "Dedicated Breast CT: Initial Clinical Experience," *Radiology* **246**, 725-733 (2008).
- 39 K. Yang, A. L. Kwan and J. M. Boone, "Computer modeling of the spatial resolution properties of a dedicated breast CT system," *Medical Physics* **34**, 2059-2069 (2007).
- 40 L. Chen, C. C. Shaw, S. Tu, M. C. Altunbas, T. Wang, C. Lai, X. Liu and S. C. Kappadath, "Cone-beam CT breast imaging with a flat panel detector: a simulation study," 2005 Proc. SPIE: Phys. of Med. Imag. **5745**, 943-951 (2005).
- 41 C. Lai, C. C. Shaw, L. Chen, M. C. Altunbas, X. Liu, T. Han, T. Wang, W. T. Yang, G. J. Whitman and S. Tu, "Visibility of microcalcification in cone beam breast CT: Effects of x-ray tube voltage and radiation dose," *Medical Physics* **34**, 2995-3004 (2007).
- 42 W. T. Yang, S. Carkaci, L. Chen, C.-J. Lai, A. Sahin, G. J. Whitman and C. C. Shaw, "Dedicated Cone-Beam Breast CT: Feasibility Study with Surgical Mastectomy Specimens," *Am. J. Roentgenol.* **189**, 1312-1315 (2007).
- 43 B. Chen and R. Ning, "Cone-beam volume CT mammographic imaging: feasibility study," *Med. Phys.* **29**, 755-770 (2002).
- 44 R. Ning, D. Conover, X. Lu, Y. Zhang, Y. Yu, L. Schffhauer and J. Cullinan, "Evaluation of flat panel detector cone beam CT breast imaging with different sizes of breast phantoms," 2005 Proc. SPIE: Phys. of Med. Imag. **5745**, 626-636 (2005).
- 45 R. Ning, X. Tang and D. Conover, "X-ray scatter correction algorithm for cone beam CT imaging," *Med Phys* **31**, 1195-1202 (2004).
- 46 R. Ning, X. Tang and D. L. Conover, "X-ray scatter suppression algorithm for cone beam volume CT," 2002 SPIE Medical Imaging Conference **4682**, 774-781 (2002).
- 47 R. Ning, Y. Yu, D. L. Conover, X. Lu, H. He, Z. Chen, L. Schiffhauer and J. Cullinan, "Preliminary system characterization of flat-panel-detector-based cone-beam CT for breast imaging," 2004 Proc. SPIE: Phys. of Med. Imag. **5368**, 292-303 (2004).
- 48 K. K. Lindfors, J. M. Boone, M. S. Newell and C. J. D'Orsi, "Dedicated Breast Computed Tomography: The Optimal Cross-Sectional Imaging Solution?," *Radiologic Clinics of North America* **48**, 1043-1054 (2010).

- 49 A. M. O'Connell, D. L. Conover and C.-F. Linda Lin, "Cone-Beam Computed Tomography for Breast Imaging," *Journal of Radiology Nursing* **28**, 3-11 (2009).
- 50 J. T. Bushberb, J. A. Seibert, E. A. Leidholdt and J. M. Boone, *The Essential Physics of Medical Imaging*, Lippincott Williams & Wilkins, 2002.
- 51 R. A. Smith, D. Saslow, K. Andrews Sawyer, W. Burke, M. E. Costanza, W. P. Evans, III, R. S. Foster, Jr., E. Hendrick, H. J. Eyre and S. Sener, "American Cancer Society Guidelines for Breast Cancer Screening: Update 2003," *CA Cancer J Clin* **53**, 141-169 (2003).
- 52 W. A. Berg, J. D. Blume, J. B. Cormack, E. B. Mendelson, D. Lehrer, M. Bohm-Velez, E. D. Pisano, R. A. Jong, W. P. Evans, M. J. Morton, M. C. Mahoney, L. Hovanessian Larsen, R. G. Barr, D. M. Farria, H. S. Marques, K. Boparai and A. I. for the, "Combined Screening With Ultrasound and Mammography vs Mammography Alone in Women at Elevated Risk of Breast Cancer," *JAMA* **299**, 2151-2163 (2008).
- 53 D. Saslow, C. Boetes, W. Burke, S. Harms, M. O. Leach, C. D. Lehman, E. A. Morris, E. D. Pisano, M. D. Schnall, S. Sener, R. A. Smith, E. Warner, M. Yaffe, K. S. Andrews and C. A. Russell, "American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography," *CA: A Cancer Journal for Clinicians* **57**, 75-89 (2007).
- 54 C. D. Lehman, C. Gatsonis, C. K. Kuhl, R. E. Hendrick, E. D. Pisano, L. Hanna, S. Peacock, S. F. Smazal, D. D. Maki, T. B. Julian, E. R. DePeri, D. A. Bluemke, M. D. Schnall and A. T. I. G. the, "MRI Evaluation of the Contralateral Breast in Women with Recently Diagnosed Breast Cancer," *N Engl J Med* NEJMoa065447 (2007).
- 55 M. Kriege, C. T. M. Brekelmans, C. Boetes, P. E. Besnard, H. M. Zonderland, I. M. Obdeijn, R. A. Manoliu, T. Kok, H. Peterse, M. M. A. Tilanus-Linthorst, S. H. Muller, S. Meijer, J. C. Oosterwijk, L. V. A. M. Beex, R. A. E. M. Tollenaar, H. J. de Koning, E. J. T. Rutgers, J. G. M. Klijn and G. the Magnetic Resonance Imaging Screening Study, "Efficacy of MRI and Mammography for Breast-Cancer Screening in Women with a Familial or Genetic Predisposition," *N Engl J Med* **351**, 427-437 (2004).
- 56 J. G. Elmore, K. Armstrong, C. D. Lehman and S. W. Fletcher, "Screening for breast cancer," *JAMA* **293**, 1245-1256 (2005).
- 57 R. F. Brem, M. Fishman and J. A. Rapelyea, "Detection of Ductal Carcinoma in Situ with mammography, breast specific gamma imaging, and magnetic resonance imaging: A comparative study," *Academic Radiology* **14**, (2007).
- 58 R. F. Brem, A. C. Floerke, J. A. Rapelyea, C. Teal, T. Kelly and V. Mathur, "Breast-specific gamma imaging as an adjunct imaging modality for the diagnosis of breast cancer," *Radiology* **247**, 651-657 (2008).

- 59 W. A. Berg, I. N. Weinberg, D. Narayanan, M. E. Lobrano, E. Ross, L. Amodei, L. Tafr, L. P. Adler, J. Uddo, W. Stein, III, and E. A. Levine, "High-Resolution Fluorodeoxyglucose Positron Emission Tomography with Compression ("Positron Emission Mammography") is Highly Accurate in Depicting Primary Breast Cancer," *The Breast Journal* **12**, 309-323 (2006).
- 60 K. Schilling, P. Conti, L. Adler and L. Tafr, "The role of positron emission mammography in breast cancer imaging and management," *Applied Radiology* **37**, 26-36 (2008).
- 61 F. Arena, T. DiCicco and A. Anand, "Multi-modality data fusion aids early detection of breast cancer using conventional technology and advanced digital infrared imaging," *Proceedings of the 26th Annual International Conference IEEE EMBS* **26**, (2004).
- 62 S. P. Sinha, M. A. Roubidoux, M. A. Helvie, A. V. Nees, M. M. Goodsitt, G. L. LeCarpentier, J. B. Fowlkes, C. L. Chalek and P. L. Carson, "Multi-modality 3D breast imaging with x-ray tomosynthesis and automated ultrasound," *Proceedings of the 29th Annual International Conference of the IEEE EMBS* (2007).
- 63 P. Madhav, D. J. Crotty, R. L. McKinley and M. P. Tornai, "Initial Development of a Dual-Modality SPECT-CT System for Dedicated Mammotomography," *Nuclear Science Symposium Conference Record*, 2006. IEEE **4**, 2382-2386 (2006).
- 64 W. Yibao, Y. Kai, N. Packard, F. Lin, J. Stickel, T. Vi-Hoa, Q. Jinyi, J. M. Boone, S. R. Cherry and R. D. Badawi, "Characteristics of the PET Component of a Dedicated Breast PET/CT Scanner Prototype," *Nuclear Science Symposium Conference Record*, 2006. IEEE **4**, 2335-2339 (2006).
- 65 Q. Fang, J. Selb, S. A. Carp, G. Boverman, E. L. Miller, D. H. Brooks, R. H. Moore, D. B. Kopans and D. A. Boas, "Combined Optical and X-ray Tomosynthesis Breast Imaging," *Radiology*
- 66 T. Fujisaki, M. Kimura, H. Saitoh, S. Abe and T. Hiraoka, "Production design and evaluation of a novel breast phantom with various breast glandular fractions," *Radiation Medicine* **24**, 647-652 (2006).
- 67 W. P. Segars, "Development and application of the new dynamic NURBS-based cardiac-torso (NCAT) phantom," *Biomedical Engineering Thesis*, pp (2001)
- 68 W. P. Segars, M. Mahesh, T. Beck, E. C. Frey and B. M. W. Tsui, "Validation of the 4D NCAT simulation tools for use in high-resolution x-ray CT research," *SPIE Medical Imaging Conference* **5745**, 828-834 (2005).
- 69 W. P. Segars, B. M. W. Tsui, E. C. Frey and E. K. Fishman, "Extension of the 4D NCAT phantom to dynamic x-ray CT simulation," *IEEE Nuclear Science Symposium* **5**, 3195-3199 (2003).

- 70 W. P. Segars, G. Sturgeon, S. Mendonca, J. Grimes and B. M. W. Tsui, "4D XCAT phantom for multimodality imaging research," *Medical Physics* **37**, 4902-4915 (2010).
- 71 W. P. Segars and B. Tsui, "MCAT to XCAT: The Evolution of 4-D Computerized Phantoms for Imaging Research," *Proceedings of the IEEE* **97**, 1954-1968 (2009).
- 72 Medela AG, *Breast Anatomy Images*, <http://www.medelabreastfeedingus.com/for-professionals/cbe-information/106/breast-anatomy-research>.
- 73 P. Bakic, M. Albert, D. Brzakovic and A. Maidment, "Mammogram synthesis using a 3D simulation. I. Breast tissue model and image acquisition simulation," *Medical Physics* **29**, 2131-2139 (2002).
- 74 P. Bakic, M. Albert, D. Brzakovic and A. Maidment, "Mammogram synthesis using a 3D simulation. II. Evaluation of synthetic mammogram texture," *Medical Physics* **29**, 2140-2151 (2002).
- 75 P. Bakic, M. Albert, D. Brzakovic and A. Maidment, "Mammogram synthesis using a three-dimensional simulation. III. Modeling and evaluation of the breast ductal network," *Med Phys* **30**, 1914-1925 (2003).
- 76 K. Bliznakova, Z. Bliznakov, V. Bravou, Z. Kolitsi and N. Pallikarakis, "A three-dimensional breast software phantom for mammography simulation," *Physics in Medicine and Biology* **48**, 3699-3719 (2003).
- 77 J. Shorey, "Stochastic Simulations for the Detection of Objects in Three Dimensional Volumes: Applications in Medical Imaging and Ocean Acoustics," Department of Electrical and Computer Engineering PhD Thesis, 257 pp (2007)
- 78 C. Hoeschen, U. Fill, M. Zankl, W. Panzer, D. Regulla and W. Dohring, "A High-Resolution Voxel Phantom of the Breast for Dose Calculations in Mammography," *Radiation Protection Dosimetry* **114**, 406-409 (2005).
- 79 L. Zhou, J. Oldan, P. Fisher and G. Gindi, "Low-Contrast Lesion Detection in Tomosynthetic Breast Imaging Using a Realistic Breast Phantom," *SPIE Medical Imaging: Physics of Medical Imaging* **6142**, (2006).
- 80 K. Bliznakova, S. Suryanarayanan, A. Karellas and N. Pallikarakis, "Evaluation of an improved algorithm for producing realistic 3D breast software phantoms: Application for mammography," *Medical Physics* **37**, 5604-5617 (2010).
- 81 C. Zyganitidis, K. Bliznakova and N. Pallikarakis, "A novel simulation algorithm for soft tissue compression," *Medical and Biological Engineering and Computing* **45**, 661-669 (2007).

- 82 J. M. O'Connor, M. Das, C. Didier, M. M. Mah'D and S. J. Glick, "Using mastectomy specimens to develop breast models for breast tomosynthesis and CT breast imaging," *Medical Imaging 2008: Physics of Medical Imaging* **6913**, (2008).
- 83 J. O'Connor, M. Das, C. Didier, M. Mah'D and S. Glick, "Comparison of Two Methods to Develop Breast Models for Simulation of Breast Tomosynthesis and CT," *Digital Mammography*, 417-425 (2008).
- 84 J. O'Connor, M. Das, C. Didier, M. Mah'd and S. Glick, "Development of an Ensemble of Digital Breast Object Models," *Digital Mammography*, 54-61 (2010).
- 85 T. R. Nelson, L. I. Cervino, J. M. Boone and K. K. Lindfors, "Classification of breast computed tomography data," *Medical Physics* **35**, 1078-1086 (2008).
- 86 A. L. Kellner, T. R. Nelson, L. I. Cervino and J. M. Boone, "Simulation of Mechanical Compression of Breast Tissue," *Biomedical Engineering, IEEE Transactions on* **54**, 1885-1891 (2007).
- 87 O. Alonzo-Proulx and et al., "Validation of a method for measuring the volumetric breast density from digital mammograms," *Physics in Medicine and Biology* **55**, 3027 (2010).
- 88 C. M. Li, W. P. Segars, G. D. Tourassi, J. M. Boone and J. T. Dobbins III, "Methodology for generating a 3D computerized breast phantom from empirical data," *Medical Physics* **36**, 3122-3131 (2009).
- 89 S. J. Glick, "Breast CT," *Annual Review of Biomedical Engineering* **9**, 501 (2007).
- 90 X. Gong, S. J. Glick, B. Liu, A. A. Vedula and S. Thacker, "A computer simulation study comparing lesion detection accuracy with digital mammography, breast tomosynthesis, and cone-beam CT breast imaging," *Medical Physics* **33**, 1041-1052 (2006).
- 91 X. Gong, A. A. Vedula, S. Thacker and S. J. Glick, "A comparison of lesion detection accuracy using digital mammography and flat-panel CT breast imaging," *SPIE Medical Imaging: Physics of Medical Imaging* **5745**, 860-869 (2005).
- 92 Q. Xia, "Dedicated computed tomography of the breast: Image processing and its impact on breast mass detectability," *Biomedical Engineering PhD Thesis*, 111 pp (2007)
- 93 J. Xia, J. Lo, K. Yang, C. E. Floyd and J. Boone, "Dedicated breast computed tomography: Volume image denoising via a partial-diffusion equation based technique " *Medical Physics* **35**, 1950-1958 (2008).
- 94 M. C. Altunbas, C. C. Shaw, L. Chen, C. Lai, X. Liu, T. Han and T. Wang, "A post-reconstruction method to correct cupping artifacts in cone beam breast computed tomography," *Medical Physics* **34**, 3109-3118 (2007).

- 95 L. Li, Y. Chu, A. F. Salem and R. A. Clark, "Image segmentation and 3D visualization for MRI mammography," *Medical Imaging 2002: Image Processing* **4684**, (2002).
- 96 Y. Yuan, M. L. Giger, H. Li, K. Suzuki and C. Sennett, "A dual-stage method for lesion segmentation on digital mammograms," *Medical Physics* **34**, 4180-4193 (2007).
- 97 Y. Ikedo, D. Fukuoka, T. Hara, H. Fujita, E. Takada, T. Endo and T. Morita, "Development of a fully automatic scheme for detection of masses in whole breast ultrasound images," *Medical Physics* **34**, 4378-4388 (2007).
- 98 N. Packard and J. M. Boone, "Glandular segmentation of cone beam breast CT volume images," *Medical Imaging 2007: Physics of Medical Imaging* **6510**, (2007).
- 99 H. Hoppe, T. DeRose, T. Duchamp, M. Halstead, H. Jin, J. McDonald, J. Schweitzer and W. Stuetzle, "Piecewise smooth surface reconstruction," *Computer Graphics* **28**, 295-302 (1994).
- 100 W. E. Lorensen and H. E. Cline, "Marching Cubes: A high resolution 3D surface construction algorithm," *Computer Graphics* **21**, 163-169 (1987).
- 101 "Rhinceros," <http://www.rhino3d.com/>,
- 102 Altair Hyper Works, *HyperMesh*, www.AltairHyperWorks.com/HyperMesh.
- 103 C. M. Li, W. P. Segars, J. Y. Lo, A. I. Veress, J. M. Boone and J. T. D. III, "Three-dimensional computer generated breast phantom based on empirical data," *Medical Imaging 2008: Physics of Medical Imaging* **6913**, 691314 (2008).
- 104 J. Chung, V. Rajagopal, P. Nielsen and M. Nash, "A biomechanical model of mammographic compressions," *Biomechanics and Modeling in Mechanobiology* **7**, 43-52 (2008).
- 105 J. Chung, V. Rajagopal, P. Nielsen and M. Nash, "Computational modeling of the breast during mammography for tumor tracking," *Medical Imaging 2005: Physiology, Function, and Structure from Medical Images* **5746**, (2005).
- 106 F. S. Azar, D. N. Metaxas and M. D. Schnall, "A Deformable Finite Element Model of the Breast for Predicting Mechanical Deformations under External Perturbations," *Academic Radiology* **8**, 965-975 (2001).
- 107 C. Tanner, J. A. Schnabel, D. L. Hill, D. J. Hawkes, M. O. Leach and D. R. Hose, "Factors influencing the accuracy of biomechanical breast models," *Medical Physics* **33**, 1758-1769 (2006).
- 108 A. Del Palomar, B. Calvo, J. Herrero, J. Lopez and M. Doblare, "A finite model to accurately predict real deformations of the breast," *Medical Engineering Physics* (2008).

- 109 F. S. Azar, D. N. Metaxas and M. D. Schnall, "A Finite Element Model of the Breast for Predicting Mechanical Deformations during Biopsy Procedures," *Journal* (2000).
- 110 A. Samani, J. Bishop, M. J. Yaffe and D. B. Plewes, "Biomechanical 3-D finite element modeling of the human breast using MRI data," *IEEE Transactions on Medical Imaging* **20**, 271-279 (2001).
- 111 Y. Zhang, Y. Qui, D. Goldgof, S. Sarkar and L. Li, "3D Finite element modeling of nonrigid breast deformation for feature registration in x-ray and MR images," 8th IEEE Workshop on Applications of Computer Vision 38-43 (2007).
- 112 C. Tanner, A. Degenhard, J. A. Schnabel, A. C. Smith, C. Hayes, L. I. Sonoda, M. O. Leach, D. R. Hose, D. L. Hill and D. J. Hawkes, "A method for the comparison of biomechanical breast models," *Mathematical Methods in Biomedical Image* (2001).
- 113 C. Tanner, M. White, S. Guarino, M. A. Hall-Craggs, M. Douek and D. J. Hawkes, "Anisotropic behaviour of breast tissue for large compressions," *Journal* 1223-1226 (2009).
- 114 C. Tanner, M. White, S. Guarino, M. A. Hall-Craggs, M. Douek and D. J. Hawkes, "Anisotropic behaviour of breast tissue for large compressions," *Biomedical Imaging: From Nano to Macro, 2009. ISBI '09. IEEE International Symposium on* 1223-1226 (2009).
- 115 V. Rajagopal, P. M. F. Nielsen and M. P. Nash, "Development of a three-dimensional finite element model of breast mechanics," *Engineering in Medicine and Biology Society, 2004. IEMBS '04. 26th Annual International Conference of the IEEE* **2**, 5080-5083 (2004).
- 116 N. V. Ruiter, R. Stotzka, T. O. Muller, H. Gemmeke, J. R. Reichenbach and W. A. Kaiser, "Model-based registration of X-ray mammograms and MR images of the female breast," *Nuclear Science, IEEE Transactions on* **53**, 204-211 (2006).
- 117 V. Rajagopal, P. M. F. Nielsen and M. P. Nash, "Modeling breast biomechanics for multi-modal image analysis—successes and challenges," *Wiley Interdisciplinary Reviews: Systems Biology and Medicine* **2**, 293-304 (2010).
- 118 J. A. Schnabel, C. Tanner, A. D. Castellano-Smith, A. Degenhard, M. O. Leach, D. R. Hose, D. L. G. Hill and D. J. Hawkes, "Validation of nonrigid image registration using finite-element methods: application to breast MR images," *Medical Imaging, IEEE Transactions on* **22**, 238-247 (2003).
- 119 F. S. Azar, D. N. Metaxas and M. D. Schnall, "Methods for modeling and predicting mechanical deformations of the breast under external perturbations," *Medical Image Analysis* **6**, 1-27 (2002).
- 120 P. Pathmanathan, D. Gavaghan, J. Whiteley, S. M. Brady, M. Nash, P. Nielsen and V. Rajagopal, "Predicting Tumour Location by Simulating Large Deformations of the

- Breast Using a 3D Finite Element Model and Nonlinear Elasticity," *Medical Image Computing and Computer-Assisted Intervention – MICCAI 2004*, 217-224 (2004).
- 121 W. Lai, D. Rubin and E. Krempl, *Introduction to Continuum Mechanics*, London, UK, Butterworth-Heinemann, 1999.
 - 122 A. Gefen and B. Dilmoney, "Mechanics of the normal woman's breast," *Technology and Health Care* **15**, 259-271 (2007).
 - 123 LSTC, *LS-DYNA*, <http://www.lstc.com/lsdyna.htm>.
 - 124 C. Pailler-Mattei, S. Bec and H. Zahouani, "In vivo measurements of the elastic mechanical properties of human skin by indentation tests," *Medical Engineering & Physics* **30**, 599-606 (2008).
 - 125 M. Kwiatkowska, S. E. Franklin, C. P. Hendriks and K. Kwiatkowski, "Friction and deformation behaviour of human skin," *Wear* **267**, 1264-1273 (2009).
 - 126 P. C. Johns and M. J. Yaffe, "X-ray characterisation of normal and neoplastic breast tissues," *Physics in Medicine and Biology* **32**, 675 (1987).
 - 127 U. S. Natl. Bur. Stand, *Report of the task group on reference man: Anatomical values for reference man*, 1975).
 - 128 J. Hallquist, *LS-DYNA Theory Manual*, Livermore, CA, Livermore Software Technology Corporation, 2006.
 - 129 MathWorks - McDonald, B, *MATLAB Central - "surf2stl.m"*, <http://www.mathworks.com/matlabcentral/>.
 - 130 LSTC, *LS-PrePost 3.0*, <http://www.lstc.com/lsp/>.
 - 131 Musculoskeletal Research Lab - University of Utah, *FEBio*, <http://mrl.sci.utah.edu/software/febio>
 - 132 W. P. Segars, M. Mahesh, T. J. Beck, E. C. Frey and B. M. W. Tsui, "Realistic CT simulation using the 4D XCAT phantom," *Medical Physics* **35**, 3800-3808 (2008).
 - 133 J. Sempau, J. M. Fernandez-Varea, E. Acosta and F. Salvat, "Experimental benchmarks of the Monte Carlo code PENELOPE," *Nucl Instrum Methods Phys Res B* **207**, 107-123 (2003).
 - 134 G. Spyrou, G. Tzanakos, G. Nikiforides and G. Panayiotakis, "A Monte Carlo simulation model of mammographic imaging with x-ray sources of finite dimensions," *Physics in Medicine and Biology* **47**, 917-933 (2002).

- 135 J. M. Boone, T. R. Fewell and R. J. Jennings, "Molybdenum, rhodium, and tungsten anode spectral models using interpolating polynomials with application to mammography," *Medical Physics* **24**, 1863-1874 (1997).
- 136 T. Mertelmeier, J. Orman, W. Haerer and M. K. Dudam, "Optimizing filtered backprojection reconstruction for a breast tomosynthesis prototype device," *SPIE Medical Imaging: Physics of Medical Imaging* **6142**, (2006).
- 137 J. M. Boone, "Normalized glandular dose (DgN) coefficients for arbitrary x-ray spectra in mammography: Computer-fit values of Monte Carlo derived data," *Medical Physics* **29**, 869-875 (2002).
- 138 C. B. Caldwell and et al., "Characterization of mammographic parenchymal pattern by fractal dimension," 1990 Characterization of mammographic parenchymal pattern by fractal dimension *Phys. Med. Biol.* **35**, 235
- 139 J. W. Byng, N. F. Boyd, E. Fishell, R. A. Jong and M. J. Yaffe, "Automated analysis of mammographic densities," *Phys. Med. Biol.* **41**, 909 (1996).
- 140 Aguilar M, A. E. and M. A. Pancorbo, "Fractal characterization by frequency analysis: II. A new method," *Journal of Microscopy* **172**, 233-238 (1993).
- 141 Anguiano E, P. M. A. and M. Aguilar, "Fractal characterization by frequency analysis: I. Surfaces," *Journal of Microscopy* **172**, 223-232 (1993).
- 142 G. D. Tourassi, D. M. DeLong and C. E. Floyd, Jr, "A study on the computerized fractal analysis of architectural distortion in screening mammograms," *Phys Med Biol* **51**, 1299-1312 (2006).
- 143 J. I. Chen, B. Zheng, Y. H. Chang, C. C. Shaw, J. D. Towers and D. Gur, "Fractal analysis of trabecular patterns in projection radiographs," *Investigative Radiology* **29**, 624-629 (1994).
- 144 J. J. Heine and R. P. Velthuisen, "A statistical methodology for mammographic density detection," *Medical Physics* **27**, 2644-2651 (2000).
- 145 G. Wolberg, "Image morphing: a survey," *The Visual Computer* **14**, 360-372 (1998).
- 146 M. H. Davis, A. Khotanzad, D. P. Flamig and S. E. Harms, "A physics-based coordinate transformation for 3-D image matching," *Medical Imaging, IEEE Transactions on* **16**, 317-328 (1997).
- 147 D. Rueckert, L. I. Sonoda, C. Hayes, D. L. G. Hill, M. O. Leach and D. J. Hawkes, "Nonrigid registration using free-form deformations: application to breast MR images," *Medical Imaging, IEEE Transactions on* **18**, 712-721 (1999).

- 148 J. P. W. Pluim, J. B. A. Maintz and M. A. Viergever, "Mutual-information-based registration of medical images: a survey," *Medical Imaging, IEEE Transactions on* **22**, 986-1004 (2003).
- 149 K. K. Brock, M. B. Sharpe, L. A. Dawson, S. M. Kim and D. A. Jaffray, "Accuracy of finite element model-based multi-organ deformable image registration," *Medical Physics* **32**, 1647-1659 (2005).
- 150 Y. Guo, R. Sivaramakrishna, C.-C. Lu, J. Suri and S. Laxminarayan, "Breast image registration techniques: a survey," *Medical and Biological Engineering and Computing* **44**, 15-26 (2006).
- 151 S.-Y. Lee, K.-Y. Chwa, J. Hahn and S. Y. Shin, "Image Morphing Using Deformation Techniques," *The Journal of Visualization and Computer Animation* **7**, 3-23 (1996).
- 152 L. Roose, W. Mollemans, D. Loeckx, F. Maes and P. Suetens, "Biomechanically Based Elastic Breast Registration Using Mass Tensor Simulation," *Medical Image Computing and Computer-Assisted Intervention – MICCAI 2006*, 718-725 (2006).
- 153 B. P. Bergeron, L. Sato and R. L. Rouse, "Morphing as a means of generating variation in visual medical teaching materials," *Computers in Biology and Medicine* **24**, 11-18 (1994).
- 154 A. Krol, M. Z. Unlu, K. G. Baum, J. A. Mandel, W. Lee, I. L. Coman, E. D. Lipson and D. H. Feiglin, "MRI/PET nonrigid breast-image registration using skin fiducial markers," *Physica Medica* **21**, 39-43 (2006).
- 155 F. Maes, A. Collignon, D. Vandermeulen, G. Marchal and P. Suetens, "Multimodality image registration by maximization of mutual information," *Medical Imaging, IEEE Transactions on* **16**, 187-198 (1997).
- 156 J. B. A. Maintz and M. A. Viergever, "A survey of medical image registration," *Medical Image Analysis* **2**, 1-36 (1998).
- 157 J. M. Boone, T. R. Nelson, A. L. Kwan and K. Yang, "Computed tomography of the breast: design, fabrication, characterization, and initial clinical testing," *Medical Physics* **33**, 2185 (2006).
- 158 M. I. Miller, "Computational anatomy: shape, growth, and atrophy comparison via diffeomorphisms," *NeuroImage* **23**, S19-S33 (2004).

Biography

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PEER-REVIEWED PUBLICATIONS

C. M. Li, W. P. Segars, G. D. Tourassi, J. M. Boone and J. T. Dobbins III, "Methodology for generating a 3D computerized breast phantom from empirical data," Medical Physics **36**, 3122-3131 (2009).

J. T. Dobbins, III, H. P. McAdams, J. Song, **C. M. Li**, D. J. Godfrey, D. M. DeLong, S. Paik and S. M. Martinez-Jimenez, "Digital tomosynthesis of the chest for lung nodule detection: Interim sensitivity results from an ongoing NIH-sponsored trial " Medical Physics **35**, 2554-2557 (2008).

J. T. Dobbins, III, H. P. McAdams, D. J. Godfrey and **C. M. Li**, "Digital Tomosynthesis of the Chest," Journal of Thoracic Imaging **23**, 86-92 (2008).

CONFERENCE PROCEEDINGS

P. Madhav, **C. M. Li** and M. P. Tornai, "Development of in vivo characterization of breast tissues through absolute attenuation coefficients using dedicated cone-beam CT," Medical Imaging 2010: Physics of Medical Imaging **7622**, 762209-762211 (2010).

J. T. Dobbins III, J. R. Wells, W. P. Segars, **C. M. Li** and C. J. N. Kigongo, "Initial investigation into lower-cost CT for resource limited regions of the world," Medical Imaging 2010: Physics of Medical Imaging **7622**, 76223C-76229 (2010).

C. M. Li, W. P. Segars, J. Y. Lo, A. I. Veress, J. M. Boone and J. T. Dobbins III, "Computerized 3D breast phantom with enhanced high-resolution detail," Medical Imaging 2009: Physics of Medical Imaging **7258**, 72580S-72588 (2009).

C. M. Li, W. P. Segars, J. Y. Lo, A. I. Veress, J. M. Boone and J. T. Dobbins III, "Three-dimensional computer generated breast phantom based on empirical data," Medical Imaging 2008: Physics of Medical Imaging **6913**, 691314-691318 (2008).

C. M. Li and J. T. Dobbins III, "Methodology for determining dose reduction for chest tomosynthesis," Medical Imaging 2007: Physics of Medical Imaging **6510**, 65102D-65110 (2007).

C. M. Li and J. T. Dobbins III, "Preliminary assessment of the temporal subtraction of tomosynthesis images for improved detection of pulmonary nodules," Medical Imaging 2006: Physics of Medical Imaging **6142**, 61425C-61428 (2006).

PUBLICATIONS IN PREPARATION

C. M. Li, M. L. Palmeri, W. P. Segars, A. I. Veress and J. T. Dobbins III, "An analysis of the mechanical parameters used for finite element compression of a high-resolution 3D breast phantom", submitted to Medical Physics.

C. M. Li, M. L. Palmeri, W. P. Segars, and J. T. Dobbins III, "Utilizing morphing techniques to generate a suite of three-dimensional breast phantoms from empirical data", in preparation.

FELLOWSHIPS

Pre-Doctoral Breast Cancer 3-year Fellowship, Department of Defense Award W81XWH-06-1-0732 "Temporal Subtraction of Digital Breast Tomosynthesis Images for Improved Mass Detection"	2006-2009
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HONORS AND AWARDS

Duke University Hatch Incubator Resident	2009
SEBIO BIO/Plan competition – Grand Prize Winner	2008
University of Maryland Business Plan Competition – 1st place overall	2008
USF International Business Plan Competition – 2nd place overall, 1st Place Elevator Pitch	2008
Start-Up Challenge – Health Care Track and Overall Grand Prize Winner	2008
Duke University Graduate School Conference Travel Fellowship – SPIE Conference	2008
Duke Start-Up Challenge – 1st Place Phase I Lifescience/Healthcare/Bio- Tech Executive Summary	2007
Duke University Graduate School Conference Travel Fellowship – SPIE Conference	2007

IEEE-BIBE Program Committee	2007
Duke University Graduate School Conference Travel Fellowship – SPIE Conference	2006

PROFESSIONAL MEMBERSHIPS

Member, SPIE	2006-2010
Member, International Society of Intelligent Biological Medicine	2007-2008