

# Development of Breast Tissue Phantoms for X-ray Diffraction Medical Imaging

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**Abstract**— Biomedical imaging has transformed breast cancer care by enabling earlier detection, more accurate staging, and minimally invasive treatment strategies. For non-metastatic cancer, breast conserving lumpectomy surgery is generally the best treatment option. Unfortunately, nearly half of these patients will require additional surgery due to the existence of residual cancer in the lumpectomy margin surrounding the tumor. Breast cancer pathology results can take several days leading to patient anxiety and treatment delays. Surgeons are therefore turning to new diagnostic approaches that allow tumor pathology to be performed in the operating room for immediate assessment and rapid treatment.

This research focuses on the development of non-biological tissue-mimicking material (TMM) phantoms to replicate x-ray diffraction spectra for active tissue involved in the treatment of breast cancer: adipose, fibroglandular, and cancerous tissue. These physical models that simulate human tissue will be fashioned into different shapes and replicant bio tissue combinations to optimize systems performance. A MATLAB® computer program was written to access a database of organic solvents and water spectra that when combined would produce superposed spectra similar to that of the bio tissue specimen. Spectra fitting involved minimizing the residuals - the difference between the superposed spectra and the bio tissue spectra. Interesting observations were made with regard to water content for each of the fitted bio tissue results.

**Index terms:** X-ray diffraction imaging, tissue-mimicking materials, biomedical imaging

## I. INTRODUCTION

Worldwide, there are an estimated 2.3 million cases of breast cancer diagnosed each year [1]. The American Cancer Society estimates approximately 320,000 new cases of invasive breast cancer will be diagnosed in U.S. women this year alone [2]. Breast cancer is the most common form of cancer in U.S. women, where one in eight women will be afflicted with this disease [3]. Early diagnosis is critical, offering a >99% survival rate,

reducing treatment intensity, and reducing long-term emotional distress. [4]

Biomedical imaging has transformed breast cancer care by enabling earlier detection, more accurate staging, and minimally invasive treatment strategies. For non-metastatic breast cancer (Stage III or lower), surgery typically involves either a lumpectomy or a mastectomy where a lumpectomy is the course of treatment for approximately 60% of surgeries [5]. Of importance is the re-excision rate or the percentage of patients who require additional surgeries (following a lumpectomy) to ensure the entire cancerous tissue is removed, which has been estimated to be nearly 40% of patients [6]. Once the tumor and the surrounding tissue (margin) have been resected, it is sent to a pathology lab to determine whether it is benign or malignant. Pathology assessment of lumpectomy margins aims to identify residual cancer to inform the surgeon of further surgery. Definitive pathology reports typically take 3 to 7 days which leads to patient anxiety and treatment delays [7].

Surgeons are turning to new diagnostic approaches that allow tumor pathology to be performed in the operating room for immediate assessment and rapid treatment. Frozen section analysis, intraoperative ultrasound, optical coherence tomography, fluorescence labeling, and Raman spectroscopy are a few examples of these [8, 9-11]. The research reported herein focuses on another promising technology, x-ray diffraction imaging (XDI), for the detection, diagnosis, and treatment of breast cancer. This imaging modality relies on X-ray diffraction (XRD) which leverages well-established scattering phenomena for materials structure determination. The underlying technology is the use of coded apertures that provide enhanced imaging resolution within the sampling volume [12-14]. Initial work on the development of tissue-mimicking materials (TMMs) for XDI instrument development is reported with the intention of assisting with identifying optimal imaging protocols and system enhancements for the treatment of breast cancer.

## II. X-RAY DIFFRACTION OF WATER AND ORGANIC LIQUIDS

In contrast to crystalline materials, amorphous solids and liquids possess only short-range order, lacking long-range atomic or molecular periodicity. The structural make-up of these materials can generally be described as disordered, isotropic, and homogeneous. XRD phenomena leading to characteristic spectral features for amorphous substances is reliant on coherent scatter and interference as observed for crystalline materials but tied to short range structural order.

The reproducible XRD features from amorphous solids and liquids give way to the means of determining spatial distributions of particles. The association of particles in liquids and amorphous solids is defined by the radial pair distribution function (RDF or, pair distribution function). RDF is used to determine bonding topology and the population of atoms in coordination spheres [15] – whereby a central particle is surrounded by an array of particles in the configuration of a sphere. Thus, pertinent data related to structure may be obtained from diffraction spectra. An example of coordination spheres is shown in Figure 1 for water showing the distance  $r_1$  from a reference molecule coincident with its first coordination sphere and  $r_2$  for the second coordination sphere. This highlights the probabilistic nature of first nearest neighbor distances, second nearest neighbor distances, and so on. Nearest neighbor positions are a consequence of particle size (indicated in this figure by a circle around each water molecule) and repulsive inter molecular forces given by the properties of the material. The desire to maximize particle density while minimizing short range repulsive forces leads to characteristic spectral features.

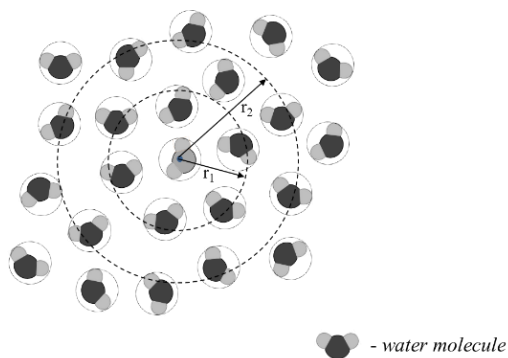


Fig 1. Illustration of water molecules and corresponding coordination spheres as indicated by the dashed lines. Distances from the reference molecule to each sphere are defined by a radial distance. The circles around each molecule signify their particle designation.

The diffuse patterns for liquids arise from non-periodic configuration and unconstrained movement of solutions of atoms or molecules. The X-ray diffraction spectra features for water and several organic solvents, shown in Figure 2,

disclose chemical properties and spatial distance information. The difference in the broad peak positions between water and those of the organic solvents is

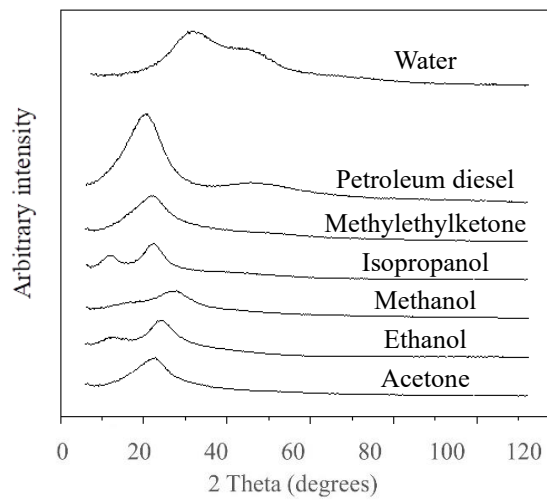


Fig 2. X-ray diffraction spectra for water compared to organic solvents.

attributed to the larger organic molecules and correspondingly larger molecule-to-molecule spacing and larger radial distribution distance. It is these spectra features that would be beneficial to the development of bio tissue TMMs.

## III. DEVELOPMENT OF XDI TISSUE MIMICKING MATERIALS

The XRD spectra shown in Figure 3 for active tissue involved in the treatment of breast cancer: adipose, fibroglandular, and breast cancer tissue [16], was selected to be fitted using our database of the six organic solvents and water shown in Figure 2. Future work will utilize a more comprehensive database of materials spectra.

A MATLAB<sup>®</sup> computer program was written to read each of the database materials, fit these to the bio tissue spectra - allowing the y-axis intensity to adjust to maximize the quality of the spectra fit, and then document this first replicant material. The program would then read the database materials in subsequent iterations to combine the spectra into superposed spectra to improve the quality of fit. The program seeks to minimize the residuals or differences between the spectra for the bio tissue targets and the superposed spectra from the selected database of materials. Ultimately, it is of interest for the materials that comprise the XDI TMMs to possess spectra features and peak positions suitable for replicating the spectra attributes of the bio tissue; to consider liquid + liquid mixtures (miscible and immiscible liquids), liquid + solid mixtures, and solid + solid mixtures; and TMM longevity/shelf-life. The motivation for producing TMMs is the challenge of

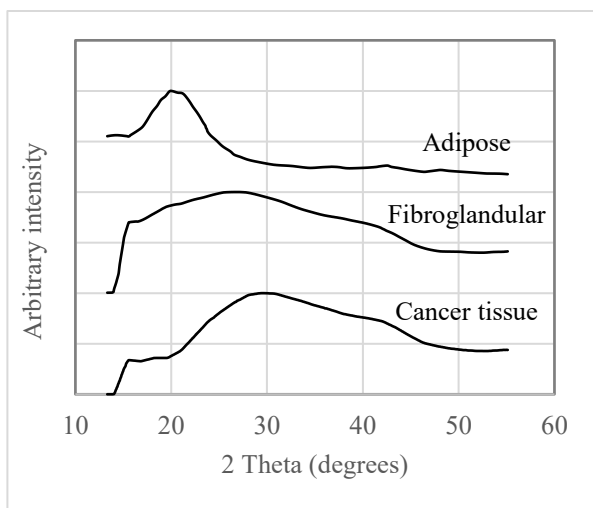


Fig 3. X-ray diffraction spectra for water compared to organics solvents. The authors extracted diffraction spectra reported by Araki and Miyoshi [16] reported in their work on endocrine therapy for the treatment of breast cancer.

accessing adipose, fibroglandular, and breast cancer tissue and limited handling time due to the tissue degradation. Biological tissue is highly perishable, degrading rapidly, and altering the inherent diffraction attributes.

Figures 4, 5, and 6 show XRD spectra as reported by Araki and Miyoshi [16] for adipose, fibroglandular, and breast cancer tissue along with the superposed fitted spectra performed by the authors. Information pertaining to the bio tissue and fitting parameters is shown in Table I. The adipose was fit using an effectively equivalent combination of ethanol and isopropanol spectra and to a lesser extent with water spectra. Adipose is body fat and characterized by a low water content. Therefore, it is not surprising that water spectra was not weighted heavily in this fitting routine. It is also important to note the strong peak at  $\sim 20$  degrees relative to the predominant peak in water spectra at  $\sim 27$  degrees. This is due to the larger spatial distances organic fatty tissue. Fibroglandular tissue showed a combination of organic tissue and water. This is a consequence of milk ducts/lobules and fibrous connective tissue where water content is much higher. Ethanol and water spectra were the main contributors to the spectra fitting. Finally, the cancerous tissue was optimally fit solely by water spectra. Restricting the predominant peak at  $\sim 27$  degrees for water to that to the strong peak in the cancerous tissue reveals the opportunity for additional material(s) to improve the quality of fit. Such material would require spectra features at higher 2 Theta values and will be examined in future work. It is interesting to note that prior work showed significantly higher water content in malignant breast tissue compared to healthy tissue [17] which is consistent with our findings.

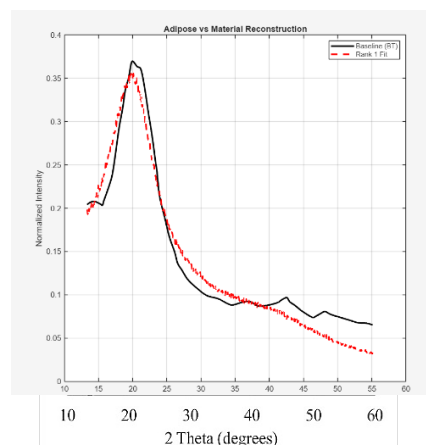


Fig 4. Plot of adipose fitted predominately with a combination of ethanol and isopropanol spectra (red, unsmoothed data).

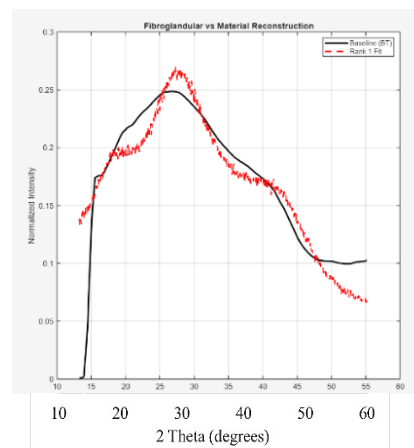


Fig 5. Plot of fibroglandular tissue fitted predominately with a combination of water and ethanol spectra (red, unsmoothed data).

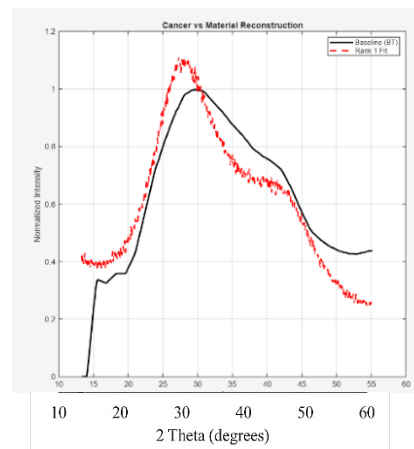


Fig 6. Plot of breast cancer tissue fitted predominately with a combination of water spectra (red, unsmoothed data).

Table I. Bio tissue spectra fitting

Bio tissue	Definition	Database material used to fit the bio tissue spectra	Spectra fit weighting factors	Reported bio tissue water content
Adipose	connective tissue (body fat) that exists throughout the body	Isopropanol Ethanol Petroleum diesel Water	51.6% 47.9% 0.3% 0.2%	10-20% [18]
Fibroglandular tissue	fibrous connective tissue and milk ducts/lobules in the breast	Ethanol Water Petroleum diesel	71.2% 24.9% 3.9%	up to 55% [19]
Breast cancer tissue	most common types: Invasive Ductal Carcinoma and Invasive Lobular Carcinoma	Water	100%	50-70% [17]

#### IV. SUMMARY

This research discussed development of non-biological tissue-mimicking materials (TMMs) to replicate x-ray diffraction spectra for active tissue involved in the treatment of breast cancer: adipose, fibroglandular, and cancerous tissue. A database of organic solvents and water spectra was used to fit the bio tissue spectra. The application of a MATLAB® computer program was used to determine liquid mixtures that replicate the XRD spectra features of the bio tissue. This approach was determined to be a time-efficient means of determining TMM replicants. The TMM phantoms will be used in a comprehensive parametric study to identify optimal imaging protocols and potential enhancements to XDI instrumentation.

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