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Spectroscopic Instrumentation using a Variable Focal Length, Scanning Focusing X-ray and
Magic Angle Spinning NMR

By

ANTHONY JOSEPH SOUKEY

DISSERTATION

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2024

Spectroscopic Instrumentation using a Variable Focal Length, Scanning Focusing X-ray and Magic Angle Spinning NMR

By
Anthony J. Soukey

Abstract

Instrumentation is the bedrock of spectroscopic investigation regardless of the location on the electromagnetic spectrum being studied. Although X-ray spectroscopy and Nuclear Magnetic Resonance (NMR) spectroscopy rely on different energies of electromagnetic waves, the goal of both types of spectroscopies is to use electromagnetic waves to excite an atom and to measure the resulting perturbation. X-ray nanochemistry follows the physical and chemical interactions between high energy photons used to excite electrons and the resulting chemical reactions from the electron depositing energy into the surrounding medium. These interactions are measured using chemical dosimeters, but can also be studied through calculations based on physical interactions. To improve the effectiveness of these studies, new instrumentation has been developed to control the location of X-rays to increase the dose enhancement at a specific location. This instrument can also be improved by using X-ray calculations that model sample dosimetry produced by an algorithm giving more accurate results. In Chapter 2, the development and implementation of an improved scanning focusing X-ray source with a variable focal length for extremely high dose enhancement of a sample containing AuNPs is discussed. In Chapter 3, calculations to simulate the scanning focusing instrument from Chapter 2 are demonstrated to accurately simulate the beam intensity, shape, and dose profile measured by the instrument.

Solid state NMR uses the rapid spinning of a solid sample at 54.74° in order to acquire spectra that would otherwise not be measurable in a static state using a process called magic angle spinning (MAS) [1,2]. This spinning uses specialized and expensive equipment. To improve the sampling signal for a low cost, widely available instrument, a 3D printed MAS rotor was developed. This device improves the signal from solid KBr and NaBr to produce narrow linewidths

that improve sampling signal. To further improve upon the existing spectroscopic method, the device was modified to allow for up to 8 samples to be measured simultaneously. This gives the instrument the ability to measure samples that it was otherwise unable to analyze for a few dollars per unit. In Chapter 4, the development of a 3D printed MAS probe for a low field NMR instrument is shown and the 3D printing techniques used to improve signal acquisition through a multiple stator design are demonstrated.

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Thank you to the Augustine lab that opened their arms to teach me new things well into my 4th year as a graduate student with minimal exposure to NMR. Without the weekly lectures from Brandon, and the willingness for Javier and Matthew to answer novice level questions, I was able to complete my project in significantly less time than expected. I would especially like to thank Professor Augustine for taking me under your wing. Although the circumstances regarding my previous PI's departure were not your responsibility, you supported me with the skills I had gained while encouraging me to not blindly follow NMR design convention.

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List of Abbreviations

3-CCA	3-Carboxycoumarin acid
7-OH-CCA	7-hydroxycoumarin-3-carboxylic acid
AA	Atomic Absorbance
AuNPs	Gold Nanoparticles
BE	Biological Enhancement
BMPO	3,4-dihydro-2-methyl-1,1-dimethylethyl ester-2H-2-carboxylic acid-1-oxide
CE	Chemical Enhancement
DEU	Dose Enhancement Units
DNA	Deoxyribonucleic Acid
DLS	Dynamic Light Scattering
EPR	Electron Parametric Resonance
GFP	Green Fluorescent Protein
MAS	Magic Angle Spinning
NIST	National Institute of Standards and Technology
NMR	Nuclear Magnetic Resonance
$O_2^{\bullet-}$	Superoxide Radical
$\bullet OH$	Hydroxyl Radical
OSTI	Office of Scientific and Technical Information
PE	Physical Enhancement
PEG	Poly(ethylene glycol)

PLA	Polylactic Acid
PMA	Polymethyl methacrylate
PMMA	Poly(methacrylic acid)
PTFE	Polytetrafluoroethylene
RMSE	Root Mean Squared Error
RNA	Ribonucleic Acid
ROS	Reactive Oxygen Species
RPM	Revolutions Per Minute
SIE	Surface-to-Isocenter Enhancement
T1PE	Type 1 Physical Enhancement
T2DI	Type II Deionized Water
T2PE	Type 2 Physical Enhancement
T3PE	Type 3 Physical Enhancement
UV-Vis	Ultraviolet-Visible
XEOL	X-ray Excited Optical Luminescence

Chapter 1: Introduction to X-ray Nanochemistry and its use in Dose Enhancement

X-rays have been instrumental in the fields of chemistry, physics and medicine. The first instrumental uses of X-rays were created by W. C. Röntgen which applied fundamental physics research to medical X-ray imaging [3]. While X-ray imaging had significant use for treating patients, the application of X-rays in the field of chemistry soon followed with the famous characterization of double helical structure of deoxyribonucleic acid (DNA) by Rosalind Franklin and Raymond Gosling [4].

X-rays are also capable of penetrating otherwise opaque structures which allows for the X-rays to interact with molecules deep inside of samples. However, working with X-rays can be a double-edged sword, since they can cause damage to living tissue, increase incidences of cancer, and in high enough doses, lead to death [5]. We seek to harness the ability of X-rays to deposit energy into materials to further understand the fundamental physical and chemical interactions needed for the next generation of X-ray therapeutics.

X-ray Nanochemistry combines the usefulness of X-ray penetration through materials with the ability of the nanoparticle to deposit large amounts of energy locally inside a sample. Such energy deposition can be used to deliver drugs without degradation to a specific location in the body via nanoparticles, then release the drug via mechanisms discovered using X-ray nanoparticle interactions [6]. Other X-ray Nanochemistry applications are directed towards either decreasing tumor growth or killing cancer cells through high Z nanoparticles releasing high amounts of energy to specific locations within the cells, thereby causing damage only to the desired target cells while limiting damage to nearby healthy tissue [7,8]. Such applications are on the forefront of both nanotherapeutics and X-ray therapeutics.

1.1 Attenuation of X-rays in Materials

X-rays can be attenuated by a material through absorption and scattering. While attenuation is the loss of X-ray intensity through a material, not all attenuated X-rays are converted into absorbed energy inside of the material. X-rays can be attenuated through three primary sources: coherent scattering, incoherent scattering, and photoelectric absorption [9]. Beyond the energy scope of X-ray Nanochemistry, higher energy processes can also occur at energies greater than 1 MeV such as pair production and photodisintegration [10]. Each element has been calculated for such energy reductions through attenuation cross sections that are listed in the National Institute of Standards and Technology (NIST) Standard Reference Database 126 [11]. The relationship between the loss of photon intensity based on the photon distance traveled through a material and the attenuation constants is

$$I/I_0 = \exp(-x \cdot (\mu/\rho)) , \quad (1.1)$$

where I_0 is the initial X-ray intensity, I is the intensity after passing through a material, x is the distance traveled through the material, μ is the attenuation coefficient of the material and ρ is the density of the material [9]. The attenuation coefficient to determine the amount of scattering and absorption occurring for a given element can be calculated for each element using

$$\mu/\rho = \sigma_{total}/m_a , \quad (1.2)$$

where the cross-sectional area of the atom is σ_{total} and the mass of the atom is m_a . The total cross-sectional area can further be split into individual photon interactions [12] as

$$\sigma_{total} = \sigma_{photo} + \sigma_{coherent} + \sigma_{incoherent} + \sigma_{high E} . \quad (1.3)$$

The total cross-sectional area corresponds to the sum of the individual scattering cross sections of σ_{photo} for the photoelectric absorption, $\sigma_{coherent}$ Compton scattering, $\sigma_{incoherent}$, Rayleigh

scattering, and $\sigma_{high E}$, combining all of the gamma ray energy interactions such as pair production. The last term in (1.3) can be ignored at energies below 1 MeV due to the minimum energy needed for a pair of electrons to be produced costing 1.022 MeV and therefore not used in the calculations for X-rays [10].

1.2 Energy Transfer of X-rays into Materials

While it is important to know the attenuation of X-rays in materials for beam shape and intensity, attenuation fails to determine an amount of energy deposited while traveling inside of a material. For this, the mass energy-transfer coefficient is used to determine the energy deposited from charged particles [13]. The dose is measured by a value kerma which is acquired by multiplying the mass energy-transfer coefficient (μ_{tr}/ρ) by the photon energy fluence at each X-ray energy [14]. The kerma is defined in ICRU Report 33 as the total kinetic energy of all primary charged particles released due to X-rays per unit mass of sample [15]

$$\mu_{tr}/\rho = (f_{photo}\sigma_{photo} + f_{incoherent}\sigma_{incoherent})/m_a. \quad (1.4)$$

The primary difference between μ_{tr} and μ is the missing terms for $\sigma_{incoherent}$ and $\sigma_{high E}$ with their respective scaling factors f_{photo} and $f_{incoherent}$. When calculating the total energy deposited into a material by X-rays, the coherent scattering becomes negligible since the energy entering the system is not transferred to a charged particle but exits with insignificant deposition of energy [16]. High energy interactions are also excluded for the same lack of energy required as stated in the justification for (1.3). This leaves photoelectrons and Compton scattered electrons as the primary sources of energy being transferred from X-rays to the sample. The energy transfer fraction for photoelectrons

$$f_{\text{photo}} = 1 - (X/E) \quad (1.5)$$

is directly proportional to the average energy of the exiting fluorescent radiation X emitted per absorbed photon with initial energy E [13]. Such fluorescent light scattering inside phantoms of low Z materials are insignificant due to the low energy of the characteristic X-ray edges absent in water shown in Figures 1.1a-d. However, the metals discussed do exhibit X-ray fluorescence due to the presence of characteristic X-ray edges in the keV range exhibited by the attenuation spikes shown in Figures 1.1a-c. Since the maximum energy of characteristic X-rays of hydrogen, carbon, and oxygen being less than 0.5 keV or less the fluorescence from these atoms excluded from ray tracing calculations [17–19]. In the case of added gold nanoparticles (AuNPs) in a sample, the gold fluorescence is not considered. Samples with AuNPs are being measured for energy deposition at the sample and not the shape and intensity of the beam after the sample. For Compton scattering, not only will the fluorescent radiation X be released, but it will also be accompanied by the incoherent Compton scattered light $\langle E' \rangle$ where [13]

$$f_{\text{incoherent}} = 1 - (\langle E' \rangle + X)/E . \quad (1.6)$$

Since the energy of fluorescent X-rays and Compton scattered X-rays produced in the attenuation must be lower than the input energy, μ_{tr}/ρ is therefore always equal to or less than the μ/ρ . Such differences can be seen in water above 10 keV shown in Figure 1.1b with the maximum difference found in the X-ray regime.

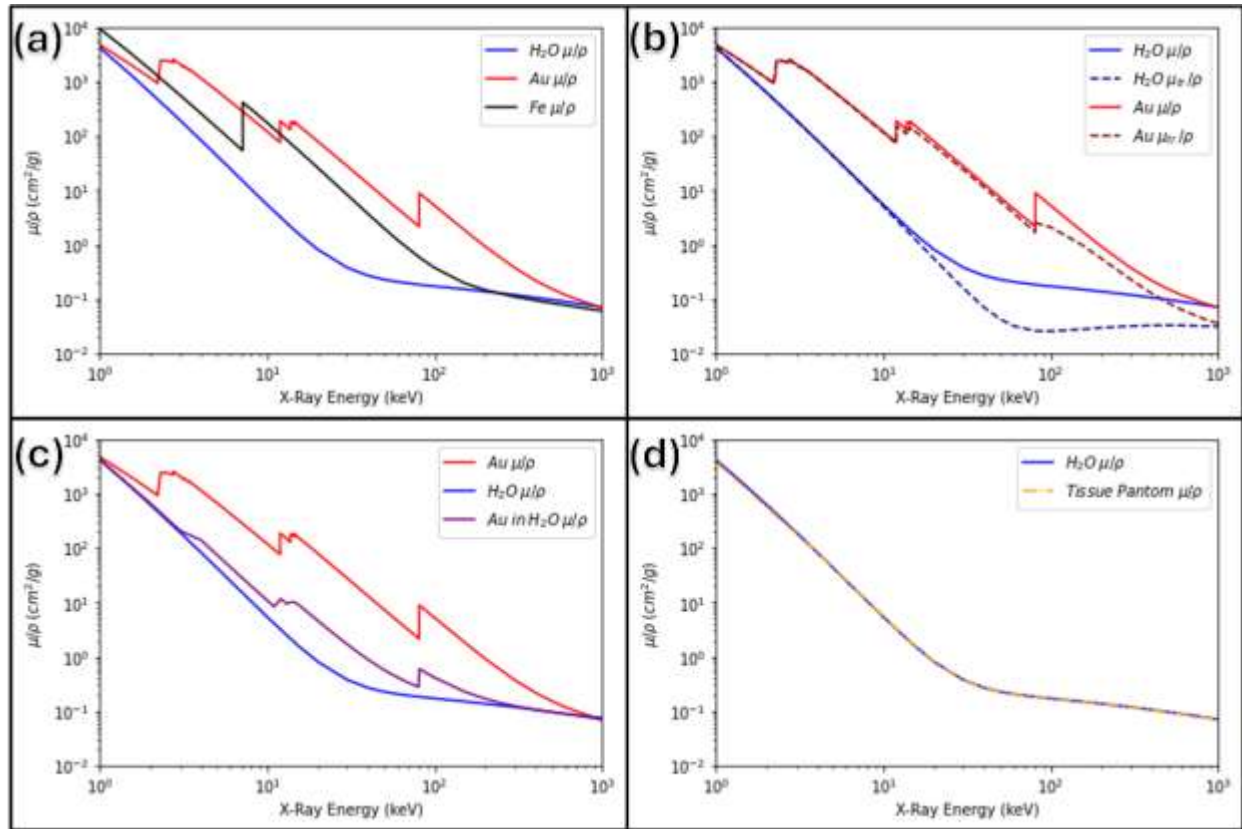


Figure 1.1: Attenuation and mass energy-absorption coefficients for elemental and molecular analytes [11]. Plots of the attenuation coefficients in (a) represent sample analytes gold and water as well as iron used as shielding. Comparisons of the attenuation and mass energy-absorption coefficients in (b) show that not all attenuated energy is directly transferred into the material for water and gold. The plot in (c) shows the increased attenuation of an added 5 wt.% Au in water compared to the individual bulk attenuations. Attenuation coefficients in (d) demonstrate that water and a tissue phantom can act as a replacement for soft tissue due to the high overlapping of attenuation coefficients.

Although (1.2) gives the intensity of a single element for a given isotope, the attenuation can be measured for mixtures using the same mathematical principles. For alloys, molecules, or other multi atom samples, the overall attenuation μ_{tot} and mass energy-transfer coefficient μ_{tr}/ρ

can be separated into the constituent elements' coefficients. A total coefficient can be achieved by scaling by each elements' weight percents w_i and summing across all the elements using [20]

$$\mu_{tot}/\rho = \sum_i w_i(\sigma_{total}/m_a)_i . \quad (1.7)$$

By introducing materials with higher absorption coefficients, we can improve the amount of energy entering the sample. This addition increases the average Z and therefore increases both the attenuation and absorption of X-rays inside of a material. This has been done with high Z elements such as gold, bismuth, and gadolinium nanoparticles [21–23]. Bulk gold has a calculated attenuation and mass energy-transfer coefficient greater than water as shown in Figure 1.1b. When a solution of high Z material such as gold are added at the weight percent scale, a noticeable increase in the attenuation coefficient above 10 keV is seen when compared to pure water as shown in Figure 1.1a. This effect can be further applied to tissues to increase the X-ray dosage inside of a tumor since water and soft tissue have similar attenuations as shown in Figure 1.1d.

1.3 X-ray Enhancement Using Nanomaterials

X-rays are capable of passing through most materials with the main factors affecting how many photons can transmit reliant upon the atomic mass of the material and the density of the material. Since the applications are primarily focused on using aqueous solutions or equivalent phantoms, the density remains near 1 g/cm³ and the only remaining option is to increase the average Z of the material. This can be done by adding nanoparticles to the solution being studied. The main nanoparticles used in X-ray Nanochemistry focus on AuNPs due to their straightforward synthesis, high Z and low cytotoxicity [24]. By adding enough nanoparticles on the order of weight

percents, solutions with nanoparticles can outperform water samples in terms of applied X-ray dose. To measure such an improvement in dose by the addition of a material, we use the measurement enhancement which is defined as

$$Enhancement = \frac{Resoponse\ with\ Nanoparticles}{Resoponse\ without\ Nanoparticles} - 1 . \quad (1.8)$$

The units for this ratio are defined as dose enhancement units (DEU) [25]. This gives a relative improvement for how well AuNPs can increase a measured response inside of a material and it is important to note that the calculated enhancement is not based on an agreed upon convention. Therefore, no direct comparison of enhancement results can be made between different authors. Comparisons must only be done after converting to the same method of calculating enhancement. An increase in a measured sample response with added nanoparticles will yield a positive enhancement whereas a decrease in such a response will give a negative enhancement. Such responses can be dependent on the sample analysis parameters such as the analyte, the nanoparticles, and the detection method. A change in response can also be based on the X-ray source, be it from a single wavelength, unfiltered bremsstrahlung, or source filtered [26]. Finally, if the response is negative, that means the nanoparticles hinder the response and is given a special case called anti-enhancement [27].

While an increase in dose can be beneficial when treating a tumor in radiotherapy, an important caveat must be addressed. Elemental gold in its (I) and (III) ionic forms is known to be cytotoxic in the concentrations needed to see an increase in overall dose [28]. This means that for gold to be effective, it cannot be delivered systemically and must be administered locally to cause damage to a tumor without having access to healthy tissue. Even if the gold is delivered locally, the increased dose in X-rays would not be the main reason for tumor death since the gold

itself is cytotoxic. This also leaves the possibility for the administered gold to spread beyond the intended target and cause damage to nearby tissue.

Gold nanoparticles on the other hand, have been shown to be biocompatible when the surface ligand is converted to poly(methacrylic acid) (PMA) or poly(ethylene glycol) (PEG) inside various cell types [29,30]. Further improvements have been made through pharmacokinetic studies with targeting of tumors via improved surface ligands [31]. This has been shown to improve uptake of AuNPS inside tumors but also important organs such as the liver, kidneys, and bladder [32,33]. By targeting a tumor with an X-ray beam instead of applying a general dose to the body, such as in the case of 3D conformal radiation therapy, lethal doses can be localized to a tumor while sparing the healthy surrounding tissue [34].

Enhancement of X-rays can be classified into main types: physical, chemical, and biological enhancements [25,26]. These different classifications are separated by the process of increased dose, method of measurement, and the distribution of the energy deposited. Physical enhancement (PE), follows the energy transferred from nanoparticles into the surrounding sample via electron or photon ejection from a nanoparticle interacting with an X-ray [25]. Chemical enhancement (CE), measures the catalytic interaction of the surface of the nanoparticle with its surrounding irradiated material [25]. Finally, biological enhancement (BE), measures the interaction between biological processes and X-ray irradiated nanoparticles [25].

1.4 Physical Enhancement

Based on the physical interactions between X-rays and nanoparticles, an increase in dose can be seen via electron deposition into a material [35]. The increase in energy deposited from X-rays via photon and electron interactions inside of the nanoparticles are classified as PE. PE can be further subdivided into different types based on the location and type of energy deposited into the surrounding sample. Type 1 PE (T1PE) is the energy carried far from the high Z nanoparticles via ejection of high energy electrons [36]. Type 2 PE (T2PE) measures the energy deposited near the surface of the nanoparticles due to the numerous but lower energy electrons [37]. Finally, Type 3 PE (T3PE) determines the improvement of scintillation or fluorescence of X-rays in a material using nanoparticles. While these subtypes are distinct, measurement of the different types of PE can be accomplished simultaneously for an overall PE or individually with type isolation [25].

The primary differentiator for T1PE is the ability for the energy deposited by a nanoparticle X-ray interaction to be distributed far away from the nanoparticle. This type of interaction dominates when nanoparticles are irradiated with high energy X-rays since the average energy of ejected electrons are high. This gives electrons the ability to travel and deposits energy far from the source nanoparticle on the order of microns [38]. To isolate T2PE and CE from T1PE, the AuNPs are covered in a lower Z, catalytically inactive coating such as silica to prevent the emission of low energy electrons into the surrounding water [27]. Therefore, only the higher energy electrons interact with the detection medium. If a sample has a uniformly distributed detection mechanism such as a fluorescent X-ray probe 3-carboxycoumarin acid (3-

CCA), the resultant enhancement measured will be predominantly T1PE, since dose is transferred uniformly throughout the sample [27].

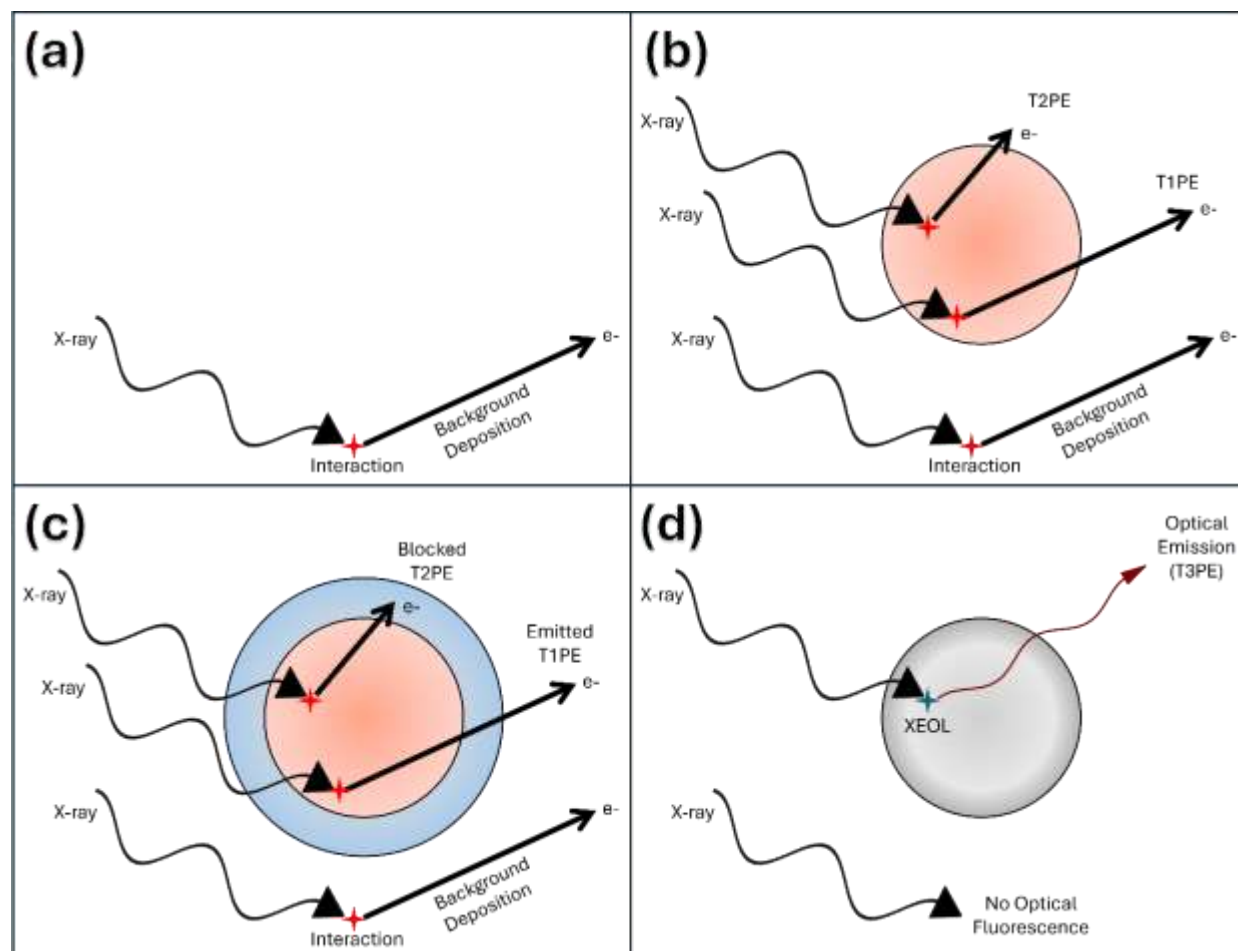


Figure 1.2: Depiction of the types of physical enhancement adapted from Ting Guo [26]. The diagram in (a) represents the background mechanism for energy deposition into a sample. The mechanism in (b) shows the different types of physical enhancement from a high Z nanoparticle and their energy deposition locations including the background dose that remains. The isolation of T1PE from the total PE by using a low Z shell covering of AuNPs to block low energy electrons is in shown in (c). T3PE from a scintillating nanoparticle in (d) exhibits X-ray excited optical luminescence (XEOL) in a non fluorescing medium [39].

The size of nanoparticles can also be used to accentuate T1PE as the predominant source of enhancement. Since the nanoparticle itself can attenuate the energy of the electron, larger nanoparticles will favor higher energy electrons escaping due to lower energy electrons not having enough energy to escape the nanoparticle [40]. Finally, the X-ray spectra used can improve T1PE based on the background dose being produced. By filtering a polychromatic beam output such as from a bremsstrahlung X-ray source, lower energy X-rays can be removed, thus increasing the average energy of the beam [41]. By shifting the majority of the X-rays into the 10-200 keV range, the added AuNPs will show a greater impact since that is the range for the attenuation increase relative to water shown in Figure 1.1c.

The second type of PE focuses on energy deposited locally around the nanoparticle. T2PE is the energy deposited from low electrons primarily generated from the secondary effects of the initial ionization of nanoparticles [40]. A major source of low energy emitted electrons are Auger electrons which are produced after an X-ray removes a tightly bound electron such as in an Au 1s or K shell electron shown in Figure 1.3a [42]. This results in a relaxation of the atom shown in Figure 1.3b from a higher energy electron the filling of the now empty shell. The difference in energy can be released as fluorescent light shown in Figure 1.3c thus completing the process [43]. However, the energy could also be transferred to another electron, emitting said electron and allowing the relaxation process to repeat until all the energy has left the atom [44,45]. One relaxation process can release up to 35 Auger electrons ranging from hundreds of eV to keV which have energies deposited less than 1 μm away when originating on the surface of the AuNP [46].

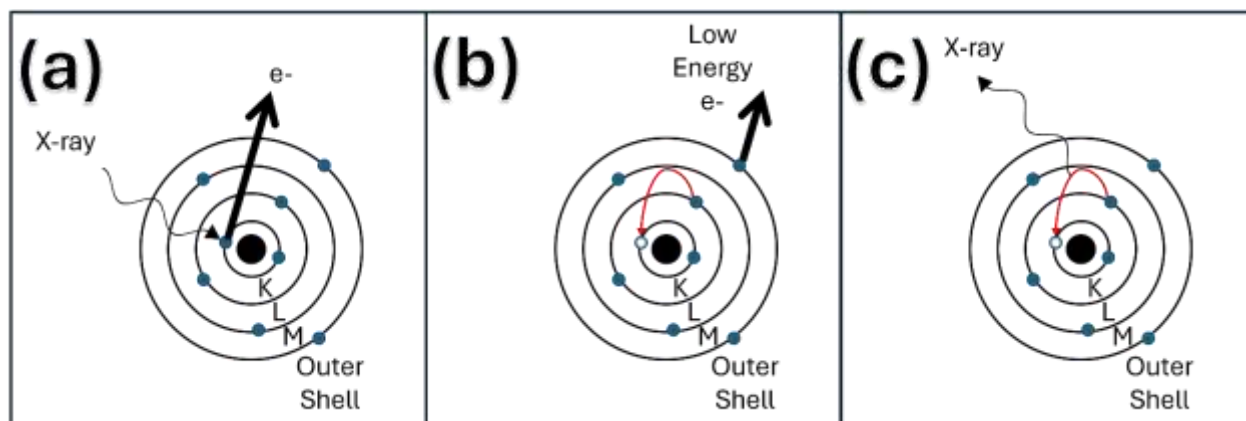


Figure 1.3: Depiction of the Auger relaxation process adapted from Gharibkandi Et al. [46]. The relaxation process starts with an excitation of the atom shown in (a) from an X-ray and the ejection of a photoelectron. The relaxation in (b) follows the Auger relaxation process of filling the vacancy left by the ionized electron and yields low energy electrons. Alternatively, the process shown in (c) instead releases a fluorescent X-ray, stopping the Auger relaxation.

Since T2PE is only measurable near the surface of the nanoparticle, in order to isolate the enhancement as T2PE, the method of detection must also reside close to the surface of the nanoparticle [47]. This has been done by measuring the single strand DNA breaks of green fluorescent proteins (GFP) attached to AuNPs. Since the detector, GFP is localized to the surface of the AuNPs, T2PE can be measured [48]. To further isolate from T1PE originating from electrons ejected from neighboring nanoparticles, tests are done at lower concentrations to avoid nearby electrons from being picked up from neighboring nanoparticles [35]. Since the T2PE electrons are low in energy to prevent attenuation before reaching the surface, smaller nanoparticles must be used such as the 3-6 nm nanoparticles [27].

The third and final type of PE that focuses on energy deposition related to X-ray detection using ultraviolet-visible (UV-Vis) detection. This type of enhancement is limited to high Z materials converting X-rays into visible photons which can be measured outside of the sample

[39]. This is different from T1PE and T2PE since the method of energy deposition is not based on energy transfer from electrons into the surrounding material. To isolate T3PE, the detection medium must only be triggered by electrons and unchanged by scintillated fluorescent light. While this type of enhancement is studied using XEOL, its implications and mechanisms are beyond the scope discussed in Chapters 2 and 3 [49,50].

1.5 Chemical Enhancement

Chemical enhancement is the improvement in the magnitude or rate of a chemical processes dependent on X-rays due to the introduction of nanomaterials. The primary focus of CE is the improvement of X-ray dose from X-ray byproducts being catalyzed by nanomaterials. The examples of CE to be presented all account for the possibility that an increase is due to PE. Such examples report single digit percent increases due to PE either theoretically or using PE controls, thus the remainder of the increase must be from chemical interactions with added nanoparticles. When a sample is irradiated with X-rays there are molecular interactions that take place as a result of charged particles depositing energy into the system [51]. The energy deposited generally causes the formation of reactive oxygen species (ROS) such as hydroxyl radicals ($\cdot\text{OH}$) and superoxide radicals ($\text{O}_2^{\cdot-}$) from which chemical probes can measure [52]. Depending on whether nanomaterials increase the number of ROS in the system determines the type of CE that is occurring.

T1CE is the increase in chemical yield that is not due to an increase in ROS [53]. This can be a result of increased catalysis of a nanoparticle that has been hit with X-rays. By becoming more reactive, the detection mechanism can be increased without necessarily being caused by

an increase in ROS. Such increases in reactivity also do not have to occur while being actively irradiated but can last after irradiation has stopped so long as the X-rays were the reason for the increased reactivity. Finally, the X-rays can also increase the reactivity of the reactant while not affecting the catalyzing nanoparticle.

An example of T1CE is the nanoparticle catalysis of 3,4-dihydro-2-methyl-1,1-dimethylethyl ester-2H-pyrrole-2-carboxylic acid-1-oxide (BMPO) after being irradiated with X-rays. BMPO can react with $\cdot\text{OH}$ produced in water when irradiated by X-rays to form the $\cdot\text{BMPO-OH}$ spin adduct that has a lifetime on the order of minutes [54,55]. Due to the long lifetime of the intermediate step, it can remain long after the initial X-ray irradiation occurs whereas the ROS produced by X-rays will disappear on the order of μs [54]. Upon the addition of AuNPs, the $\cdot\text{BMPO-OH}$ is catalyzed to form $\cdot\text{BMPO-H}$ which can be measured and compared for enhancement to the uncatalyzed $\cdot\text{BMPO-OH}$ using electron parametric resonance (EPR) spectroscopy [56,57]. This reaction was classified as T1PE since there was no measured increase in the ROS of the sample upon the addition of AuNPs. Since the ROS generation was only measured when X-rays were in the presence of the BMPO, the nanoparticles themselves never increased the concentration of ROS.

T2CE is reliant on either the production of or increased reactivity of ROS [53]. This was demonstrated using AuNPs irradiated in the presence of 3-CCA with a greater yield of products than were otherwise expected from PE. This was measured through the single strand breaks of DNA and ribonucleic acid (RNA) attached to AuNPs [58]. While this example did not measure an increase in the ROS reacting with the single stranded DNA, they did correct for the removal of ROS from the scavenging on surface of the nanoparticle [58]. After correcting for surface ligand,

nanoparticle material and local vs free DNA in water, they measured a 10-fold increase in single strand breaks from citrate gold nanoparticles in the presence of X-rays [58].

Another example of CE is the catalysis of aniline into polyaniline near Ag core-Au shell nanoparticles. The proposed mechanism suggests an activation of the nanoparticle from the $\cdot\text{OH}$ radical generated from X-rays transferring an electron with the core shell nanoparticle [59]. Having activated the surface of the nanoparticle, catalysis can be measured from the polymerization of aniline into polyaniline [60]. The polymerization with nanoparticles was measured at 28 times higher in the presence of the nanoparticles without X-rays but when combining the nanoparticles and X-rays, a 400 fold increase was measured [60]. Since there were no tests to determine whether the increase in polymerization was due to an increase in ROS, the type of CE in this example was not confirmed.

1.6 Biological Enhancement

Biological enhancement is the application of PE and CE to the biomolecular processes inside cells. The focus of BE is on how X-ray interactions combined with nanomaterials hinder the chemical cycles present in cells. This could be measured as a function of cell death, mitigation of tumor growth or a reduction of DNA repair [61,62]. Interactions studied in Chapters 2 and 3 are prepared in vitro or in silico as opposed to in cellulo, thereby removing the possibility of biological interactions as a source of enhancement. Biological enhancement is therefore outside the scope of this dissertation but fundamental phenomena discussed could be applied in molecular biology or biochemistry studies by future researchers.

2.1 Introduction:

X-rays have been used as a diagnostic tool, medical therapy, and as palliative care [63–65]. These applications rely upon the knowledge gained from studying the fundamental physical and chemical mechanisms related the attenuation and energy deposition of X-rays for their application in biology and medicine. These interactions can be harnessed to release drugs via X-rays and damage unwanted tissues like cancer [66,67]. However, X-ray interaction in vitro does not directly correspond to X-ray interaction in a body.

To bridge the knowledge gap, X-ray phantoms are used as a stand-in to experimentally emulate the human body attenuation of an X-ray therapeutic beam [68]. This most effects the energy spectrum and intensity of the X-rays reaching the sample target which can drastically change the mechanisms needed for a successful therapeutic result [69]. While these phantoms are conventionally made for generic organs and mass produced for consistency, 3D printing has opened the door to specialized X-ray phantoms [70]. Phantoms created using 3D printing allow for custom material properties to conform the plastic to the type of material being emulated.

Advancements in 3D printing hardware and software now allows for the printing of multiple materials simultaneously [71]. A phantom with multiple materials can emulate different parts of the body with their own unique X-ray attenuation properties. Such a phantom has been created with polylactic acid (PLA) emulating adipose tissue and polymethyl methacrylate (PMMA) used to emulate glandular tissue which can be designed and printed to represent geometries specific to a patient [72,73]. By making additions to the deposited plastic, phantoms are further expanded to emulate bones and other denser tissue by adding dopants like iron filings and CaTiO_3

into the 3D printed plastic [74,75]. By changing the amount of infill, one can tune the attenuation of a material [76]. Beyond therapeutic applications, 3D printed phantoms can also include radiochromic material allowing for the plastic in the phantom to act as a dosimeter [77].

By introducing the dynamic effects of an X-ray phantom, a different type of enhancement beyond the conventional CE and PE be explored. By spreading a dose across the surface of a phantom, an increase in the dose rate at a specific position can be achieved. This increase in dose at the center relative to the surface dose is called surface-to-isocenter enhancement (SIE) which has been measured through the use of a fixed focal length, dual rotation sample stage [78]. This device uses X-ray films and a previous enhancement measurement [35] to estimate a one mm diameter beam with a 7.5 wt.% AuNP solution to have an isocenter dose that was 295 times greater than the dose at the surface of the sample [78].

After adding an additional degree of freedom by moving the axes of rotation from the sample to the X-ray source and adding translational movement radially from the center axis, improvements compared to the study were made. This gives the instrument the ability to not only have an isocenter corresponding the focal point as was previously done but gives the ability to move the focal point anywhere along the top rotational axis. Additionally, a variable speed algorithm was developed to allow for an isometric surface dose instead of inconsistent deposition of X-rays across the surface of the sample.

2.2 Methods and Materials:

Mechanical and Chamber Design

The overall instrument design started with building a chamber that could mitigate the leakage of X-rays from the device to the surrounding area. This was done by building a box of 1-inch-thick steel to attenuate 95% of the highest energy stray X-rays already blocked by the collimating nose cone. For precise top rotation, an aluminum plate was attached just below the chamber top and a circular channel was milled to guide the assembly in a circle. Teflon blocks were designed within high tolerance to the width of the channel and were attached to the instrument assembly. When rotating about the top axis, and when properly aligned, the top axis drift for the beam center remained within 100 μm of a static beam. The top rotation for the azimuthal angle (ϕ) was achieved by attaching a stepper motor with a gear to the corner of the chamber and connecting it to a drive gear through a belt. This created a gear ratio of 12:1 which was necessary to achieve the torque required to prevent the stepper motor from skipping steps.

The linear translation (X) was achieved using an M-ILS150CC (Newport, Irvine, CA) servo motor which had a maximum translation range of 150 mm with 1.5 μm accuracy but when measured, could reliably reach 150.5 mm total travel distance without triggering the emergency end stops [79]. The altitude angle (θ) was controlled using a URS50BCC (Newport, Irvine, CA) rotation stage with 1.0 millidegree accuracy [80]. Both motion controllers were connected to the TUB00153-9A-W06 (Moxtek, Orem, UT) 70 kVp 12-Watt X-ray source and to the top rotation assembly through machined aluminum couplings and were aligned for both plumbness and centering. Motor control was achieved using an ESP3000 (Newport, Irvine, CA) universal stepper

motor controller and controlled via software using the native Newport motion control libraries in Labview.

X-ray Imaging and Beam Alignment

All imaging measurements were acquired using a Dream Sensor (Dentimax, Mesa, AZ) dental X-ray sensor. The sensor had working dimension of 1050 x 1580 pixels with the top corners tapered and a sensor consisting of square pixels with a width of 19 μm . For all alignment, the X-ray sensor was placed in the beam path and triggered simultaneously with the activation of the X-ray source. The resulting photo was exported and analyzed with python code using an edge detection algorithm to determine the X and Y location of the beam center. If the beam was not directly in the center of the sensor, the sensor holder was manually moved towards the previously measured beam center and the process was repeated until both centers matched.

When following the same procedure for a beam that was not at the isocenter, such as when measuring the conical shape of the scanning focusing beam, the resultant image resembled a ring. For such measurements, the edge detection algorithm not only acquired the outer edge for X and Y but also the inner edge of the beam. From those data, the outer diameter, inner diameter, center diameter of the beam, and top rotation center could all be determined.

Prior to use of the X-ray source, alignment of the beam was required. The designs for the couplings between the motorized parts were made with adjustable slots for screws to attach components together. The coupling between the X-ray source and the rotational axis stage had slots for adjusting the height of the X-ray. The height was set such that the X-ray source was as high as possible but did not knock into the top of the chamber when set to the highest theoretical

angle. After setting the height, the X and Y were adjusted by sliding the X-ray along the screw channels milled into on the aluminum plate holding the X-ray source to the rotational stage for Y and moved using the linear stage for X. Images were taken at $\phi = 0^\circ$ and $\phi = 180^\circ$ and the center X and Y locations were calculated. The difference between both center points were calculated and the X-ray was moved to the location between the previously measured points. Once the center points at $\phi = 0^\circ$ and $\phi = 180^\circ$ were within three pixels, the beam was considered aligned.

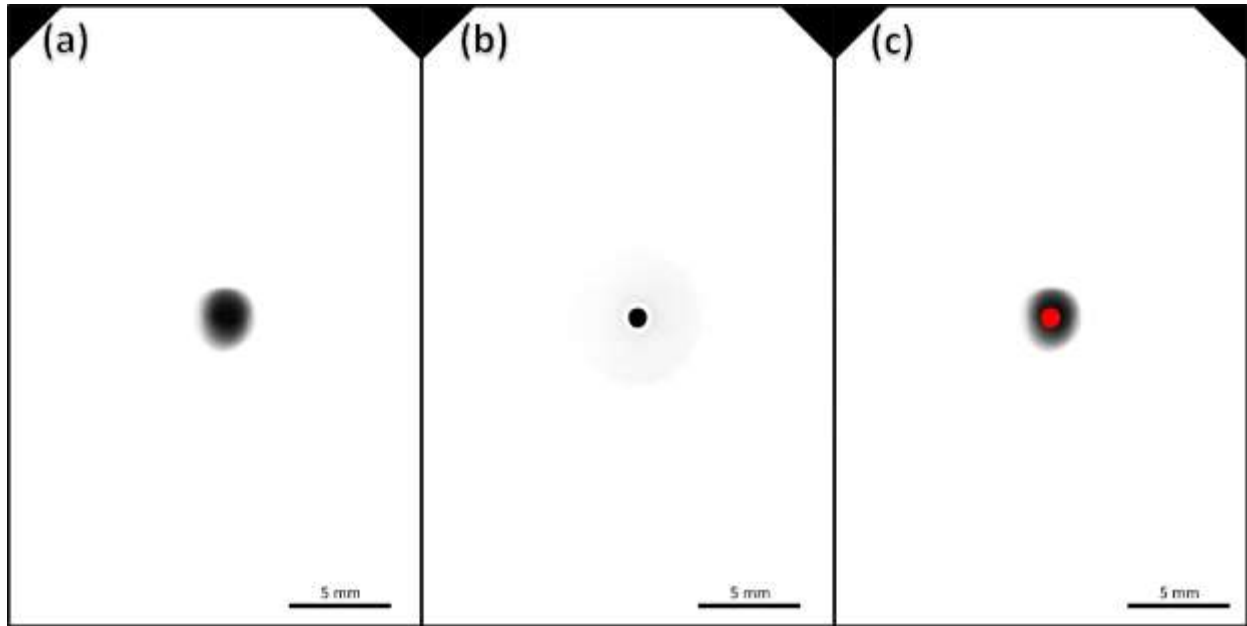


Figure 2.1: Top axis alignment using X-ray images at different heights above the bottom of the chamber. The X-ray image in (a) shows an image taken with the detector at the chamber floor and the image in (b) was taken with the detector 3.00 in from the bottom of the chamber. The overlaid image in (c) shows that both beam centers remain in the same location and therefore the beam center, ϕ axis, and Z axis are aligned. The image of the X-ray beam in (b) was edited from black to red to distinguish the two beams in (c).

The angle alignment was done by zeroing the angle using the built-in homing command and determining the required angle offset. To do this, a 3D printed holder for the X-ray detector was connected to a base with optical rails and placed at the bottom of the chamber. Images were taken at the bottom of the chamber shown in Figure 2.1a and with a 3.00-inch shim raising the X-ray shown in Figure 2.1b. The angle was adjusted by in 0.05° increments until the center of both beams were located at the same coordinates on the detector shown in Figure 2.1c. After all the offsets were determined from the alignment process, the Labview code included commands to move the θ and X to the offset values after homing.

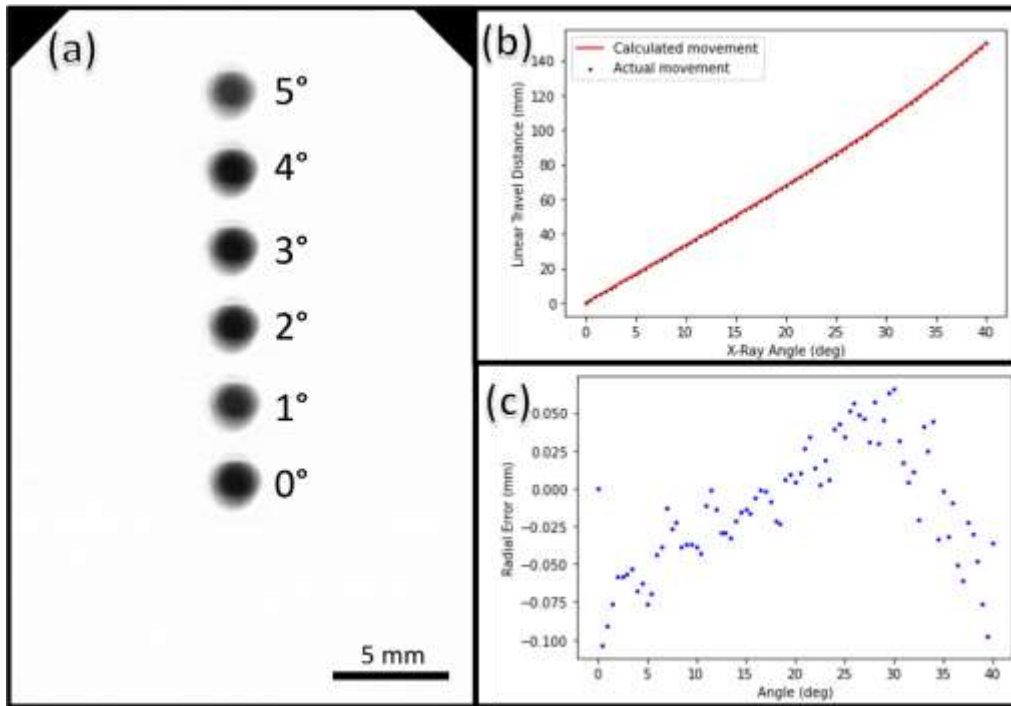


Figure 2.2: Determination of the R_0 and Z_0 values using images from the movement of the θ angle. Images were taken from 0 - 5° angle adjustments and overlaid in (a) to determine the movement of the beam with respect to θ . The expected movement locations and beam center displacements were calculated in (b) and used to measure center location differences in (c) between the theoretical and measured beam centers at each angle adjustment.

The offset values were measured by setting the angle and measuring the distance traveled by the beam using X-ray images with the first 5 degrees exemplified in Figure 2.2a. The detector image was analyzed using an edge detection python script to ascertain the beam center for each measurement. The measured X locations were compared to the expected beam center locations and R_0 and Z_0 were adjusted until the root mean squared error (RMSE) was minimized. Using 0.5° increments, the angle θ and distances X were changed using the movement algorithm described in detail below with results plotted in Figure 2.2b. The largest difference between the theoretical and measured center locations at $114\text{ }\mu\text{m}$ shown in Figure 2.2c have R_0 and Z_0 values of 38.25 mm and 192.8 mm, respectively. With these values, the beam path was constrained between 0° and 40° due to 40° needing 150.1 mm of travel which was within the 150.5 mm limit of the linear stage.

Variable focal lengths were achieved by changing the default Z_0 to a value other than 192.8 mm. By decreasing the value of Z_0 , the focal point was increased by the difference in height, whereas increasing the value of Z_0 resulted in a focal spot beyond the bottom of the chamber. Variable focal lengths were measured using a set of nested 3D printed holders for the Dentimax imaging sensor. Images were taken at heights in 2.5 cm increments above the bottom of the chamber and the beam was connected to the imaging sensor after each height adjustment. When imaging, the X-ray was swept across the full 360° ϕ axis at varying θ angles and focal lengths.

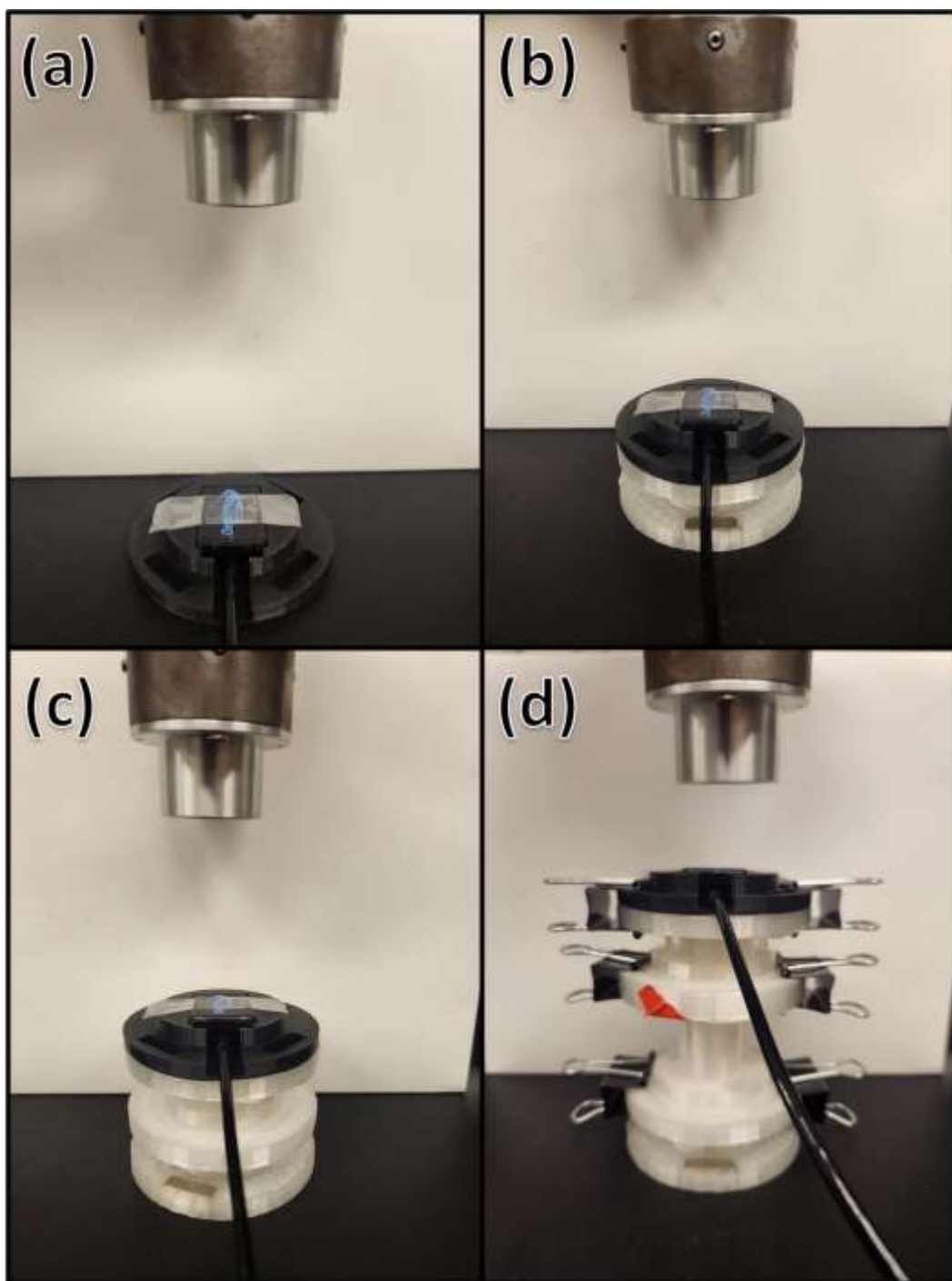


Figure 2.3: Setup used for imaging at different heights used in variable focal length tests. The images in (a-d) show the detector at the bottom of the chamber, 2.5, 5, and 7.5 cm above the chamber bottom, respectively.

Dosimetry

Instrumental dosimetry was measured using an Accugold AGMS-D+ diagnostic multisensor (Radcal, Monrovia, CA) attached to a 3D printed holder. The X-ray source was centered on the sensor using an image taken with the Dentimax which had a cutout for the imaging sensor. Once the beam was in the correct location, the imaging sensor was replaced with AGMD-DM+ sensor and the dose was measured using automatic triggering.

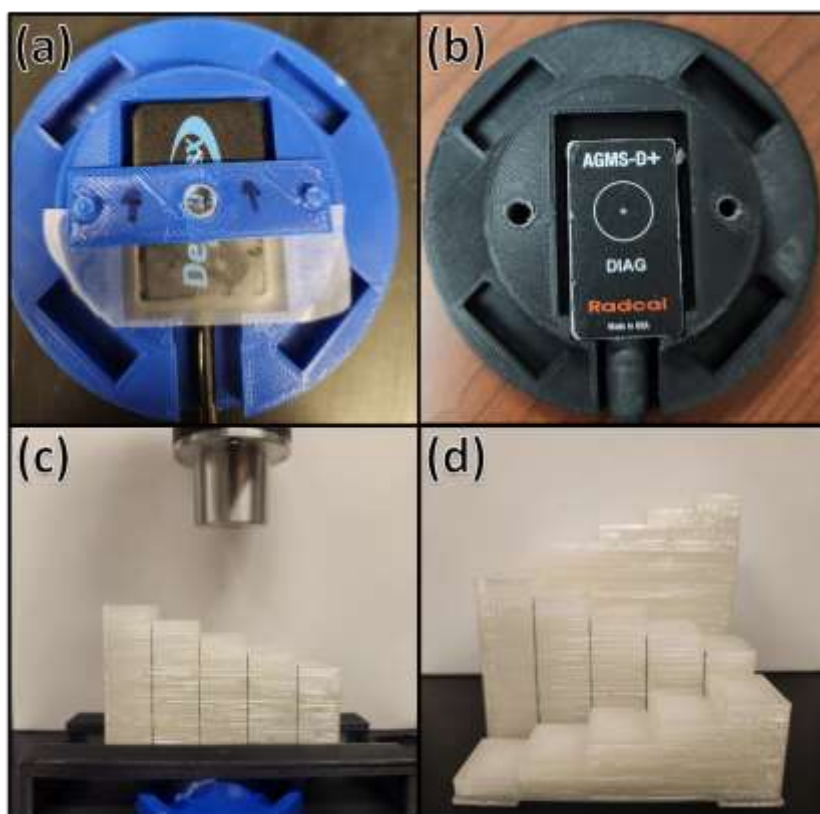


Figure 2.4: Schema for the devices used to measure dosimetry through PLA. The plastic holders show the alignment configuration in (a) using the X-ray imager with a solder ball above the detector center as well as the dosimetry configuration in (b) where the imager is replaced with a dosimeter. The plastic phantoms used in dosimetry experiments were placed above the dosimeter using an adaptor in (c) and different thicknesses were used ranging from 5 mm to 10 cm in 5 mm increments, as shown in (d).

Chemical dosimetry was measured using 3-CCA. While 3-CCA is only weakly fluorescent, when exposed to X-rays 3-CCA reacts to form 7-hydroxycoumarin-3-carboxylic acid (7-OH-CCA) which becomes much more fluorescent. This fluorescence was calibrated using known dose rates to measure the doses for unknown beams [81]. For each sample, a 20 mM stock was created in 80 mM phosphate buffer and diluted to a 3-CCA concentration of 2 mM for sample analysis. An aliquot of 30 μ L were added to a microcentrifuge cap and covered with a layer of parafilm.

Using a 3D printed detector holder and an accompanying 3D printed sample holder, images were taken of the beam. To find the center of the beam, a bead of solder was placed in the center of a centrifuge tube cap and placed in the sample holder. The detector was moved until the shadow of the solder was in the center of the beam. Once the center was found, the sample holder with the bead was replaced with the 3-CCA sample and irradiated. The 3-CCA samples were irradiated at 70 kVp and 171 μ A for maximum dose rate [82]. To prevent overheating, the sample was irradiated for 2.5 minutes then the detector was allowed to cool for 5 minutes.

The samples were calibrated using the Kevex PXS10-WB-10mm-40W source (Thermo Fisher Scientific, Waltham, MA) at 100 kVp and 250 μ A set at the 1.8 Gy/minute location in the chamber. The calibration standards were prepared in the same manner as the instrumental samples. After irradiation, samples were diluted to a 3-CCA concentration of 1 mM using the same 80 mM phosphate buffer used in sample preparation for fluorimetry. Fluorescence measurements were acquired using LS50B luminescence spectrophotometer (PerkinElmer, Waltham, MA) with excitation at 391 nm and emission peaks around 442 nm. The relative peak

absorbances of the standards were used to create a calibration curve and the sample dose was determined using the peak absorbance of the samples.

AuNP Synthesis and Sample Preparation

9.08 nm AuNP synthesis followed a modified procedure from Davidson and Guo to create mercapto gold nanoparticles [27]. In a round bottom flask, 34.6 μL of 30 wt.% Au (III) in dilute HCl was diluted to 5 mL of Type II Deionized (T2DI) water. While under vigorous mixing, 39.5 mg of sodium citrate in 5 mL of T2DI was added quickly. After reacting for 5 minutes, 1.6 mg of NaBH_4 in 10 mL of T2DI was added under vigorous stirring. After reacting for 45 minutes, 2 mL solution containing 10 mg of SH-PEG was added and stirred overnight and subsequently stored at 5 °C.

When the sample was ready to use, it was placed in a 10 kDa centrifuge filter and centrifuged at 6000 RPM for 10 minutes. The filtered supernatant was discarded and the sample was measured for wt.% concentration using flame atomic absorbance (AA). Flame AA samples were prepared by taking a 20 μL aliquot and adding it to 50 μL of freshly prepared aqua regia and let to react until the color changed from pink to pale yellow. The solution was then diluted to a final volume of 10 mL and the Au concentration was measured using the Varian SpectrAA FS-220 Flame AA (Agilent, Santa Clara, CA) using calibration standards prepared from 30 wt.% Au (III) in dilute HCl. The nanoparticle size was then characterized by diluting the concentrated nanoparticles 100:1 in T2DI and size was measured via dynamic light scattering (DLS) Zetasizer Nano S-90 (Malvern Panalytical, Malvern, UK) to confirm the size was between 5-10 nm.

Enhancement samples were prepared by filling microcentrifuge caps with 30 μL of sample solution. The samples were prepared by combining 15 μL of nanoparticle solution and 15 μL of 2

mMol 3-CCA. The nanoparticle solutions contained between 0 and 0.1 wt.% Au nanoparticles which were diluted from the 0.21 wt.% stock solution using T2DI. These samples were then irradiated and transferred to a microcentrifuge tube and a corresponding nanoparticle solution was added for a concentration of 0.05 wt.% in each tube. These solutions were then diluted to a final volume of 60 μL for sufficient volume in the 50 μL fluorimeter cuvette. For calibration using the Faxitron 43855A (Hewlett Packard, Palo Alto, CA) X-ray source sample preparation followed the same procedure but the volumes irradiated were scaled to 150 μL pre dose volume and the final volume was 300 μL with no further dilution after the second set of nanoparticle solutions were added. Samples were irradiated for 2 Gy for both X-ray sources for an irradiation time of 1 hour for Moxtek irradiated samples and 6 minutes and 40 seconds for Faxitron irradiated samples. Solutions were measured using the fluorimeter procedure used for dose calibration.

2.3 Results and Discussion:

To set the scanning focusing angle adjustment, an algorithm calculates the necessary change in X for a given change in θ to maintain the beam at the isocenter location of (X,Z)=(0,0). A simple calculation for changing X and Z based on the tangent angle is insufficient when applied to the instrument assembly. When rotating the X-ray source about the θ axis, there is a change in X and Z positions shown in Figure 2.5c since the X-ray beam does not sit at the center of the rotational stage axis. This beam offset calculates of the absolute X and Z positions using the experimentally measured values for R_0 and Z_0 shown in Figure 2.5b for the default focal length at the bottom of the chamber. The new locations for X and Z are then calculated using

$$X_{new} = R_0 - (R_0 \cdot \cos(\delta\theta)) \quad (2.1)$$

$$Z_{new} = Z_0 - (R_0 \cdot \sin(\delta\theta)), \quad (2.2)$$

which are dependent on the initial conditions R_0 , Z_0 , and the change in angle $\delta\theta$. This correctly calculates the new X position at the initial Z location as the movement of the θ stage determines the new location of the beam shown in Figure 2.5c. The translational stage is then moved by the distance δx calculated with

$$\delta x = (\tan(\delta\theta) \cdot Z_{new}) \cdot X_{new} \quad (2.3)$$

to get the beam from off centered, back to the isocenter as shown in Figure 2.5d.

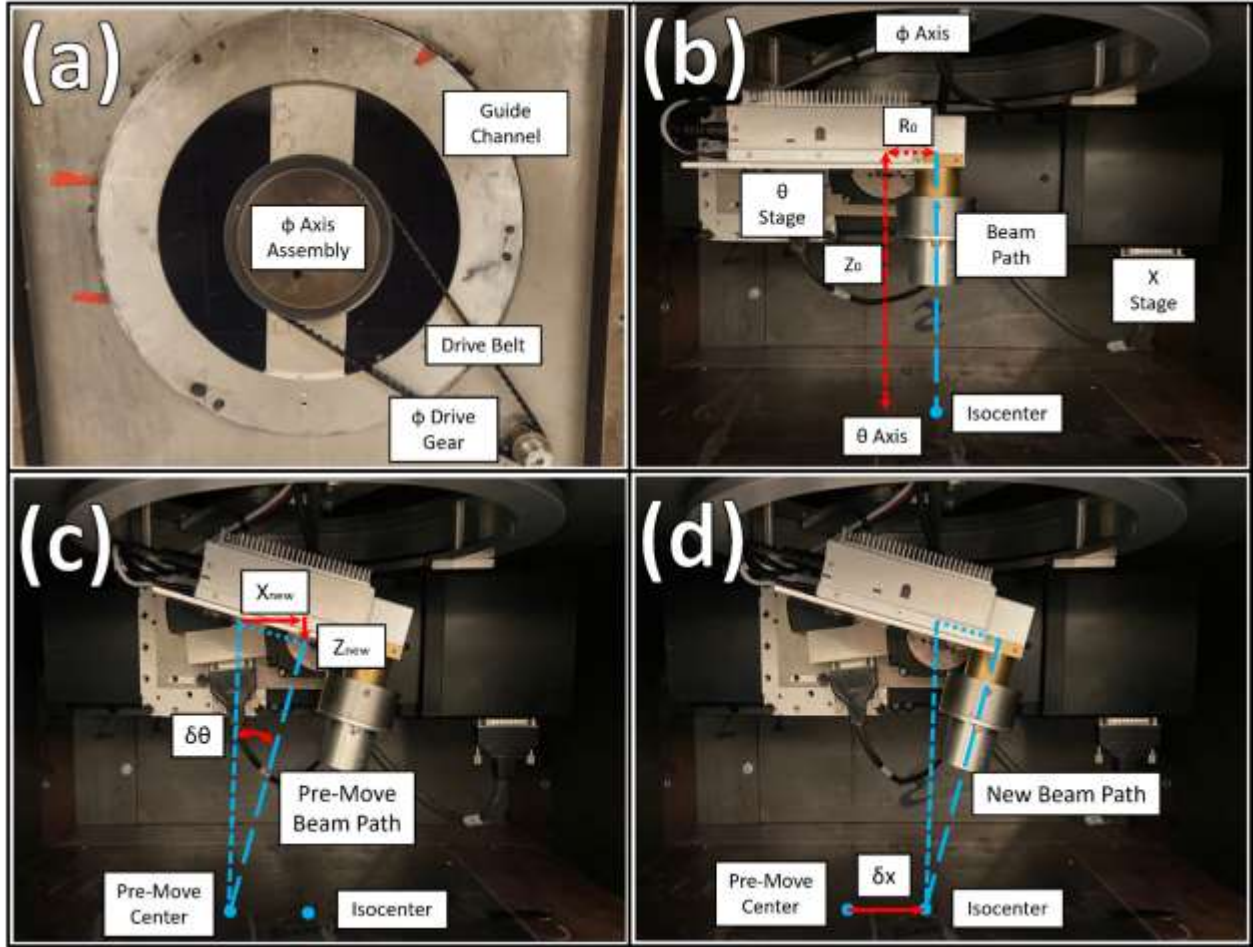


Figure 2.5: Picture of scanning focusing instrument showing axes, angle adjustment, and initial positions. The top axis assembly in (a) consists of a drive shaft and a driven shaft in a gear ratio to increase the torque delivered to the driven assembly. Initial conditions shown in (b) illustrate that the angle and position begin at the positions of $(x, \theta) = (0 \text{ mm}, 0^\circ)$ and have initial offset values of R_0 and Z_0 used for angle adjustment calculations. The beam in (c) is adjusted by $\delta\theta$ prior to movement of the X axis which moves the beam location away from the isocenter and is calculated using the beam line set by the X_{new} and Z_{new} . The δx vector is then calculated in (d) to show the movement of the beam from the angle adjusted position back to the isocenter.

The scanning focusing isocenter location shows stability across the altitude angle range of 0-40°. As illustrated in Figure 2.6d, the highest angle has blurring of the beam due to the detector and the beam no longer being parallel. However, when the angle is small, the beam is nearly perpendicular to the detector and casts a circular shadow shown in Figures 2.1a-c. As the angle increases, the static beam starts to show a more oval shape due to shadowing at higher altitude angles. This results in the beam shape shown in Figure 2.6d which has an inner shape nearly identical to the 0° beam but with a blurring effect at the edges of the beam. If the detector was capable of always remaining perpendicular to the beam, the shape would remain circular and there would be no beam blurring. However, this would have required drastically increasing the complexity and cost of the detection and would use two additional motorized stages.

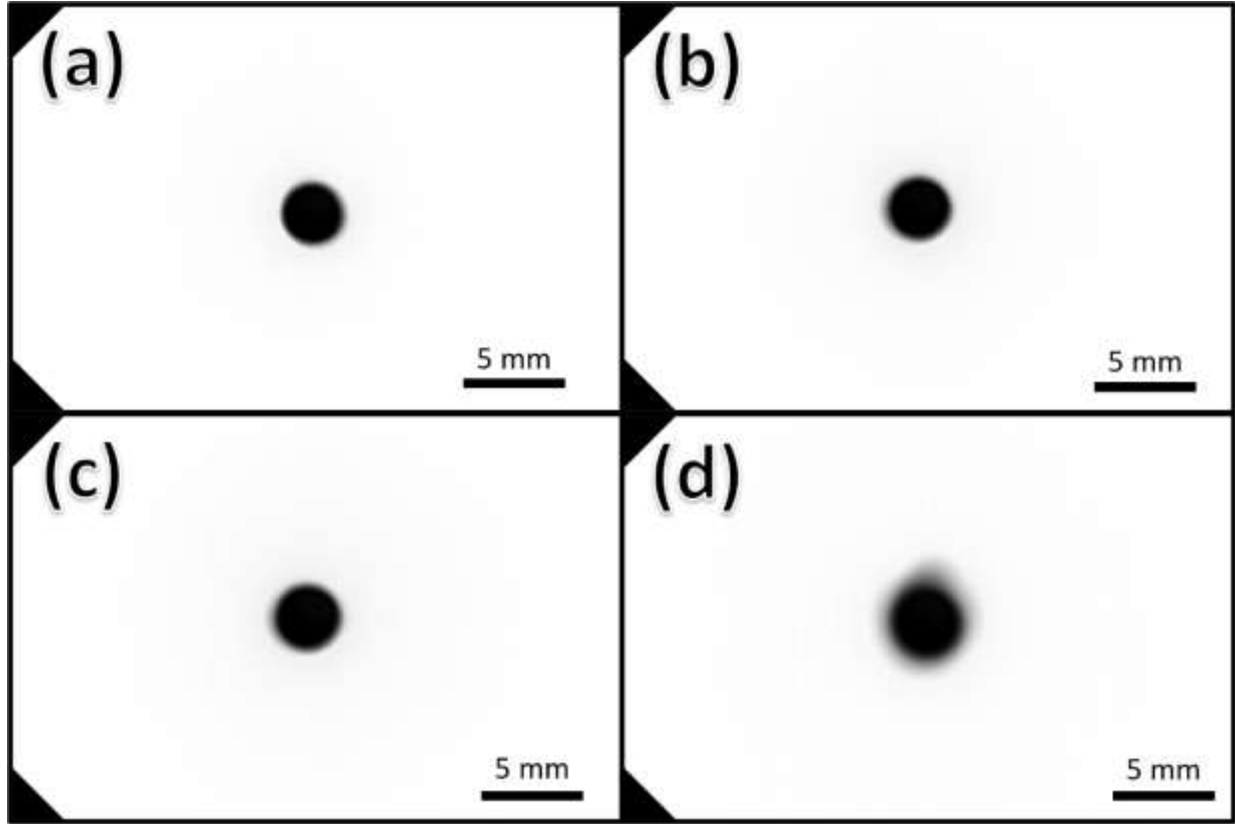


Figure 2.6: Images for the beam at the isocenter given full 360° at altitude angles. Images in (a-d) show top rotated X-ray images for θ values of 0° , 10° , 20° , and 40° , respectively.

Variable focal length images show the shape of the variable focal length cones produced by rotating about the top ϕ axis by one revolution. The images show that the beam is well aligned since all of the beams go through the center of the rotational ϕ axis for the first column in Figure 2.7 which is when the θ angle has not yet been adjusted. After adjusting the angle θ , even to the small angle of 5° shown in the second column of Figure 2.7, a cone of expanding rings begins to form. This cone continues to expand when set to 10° shown in the third column of Figure 2.7. However, the beam path is off the detector once the beam is 7.5 cm away from the isocenter due to the limited width of the X-ray imaging sensor.

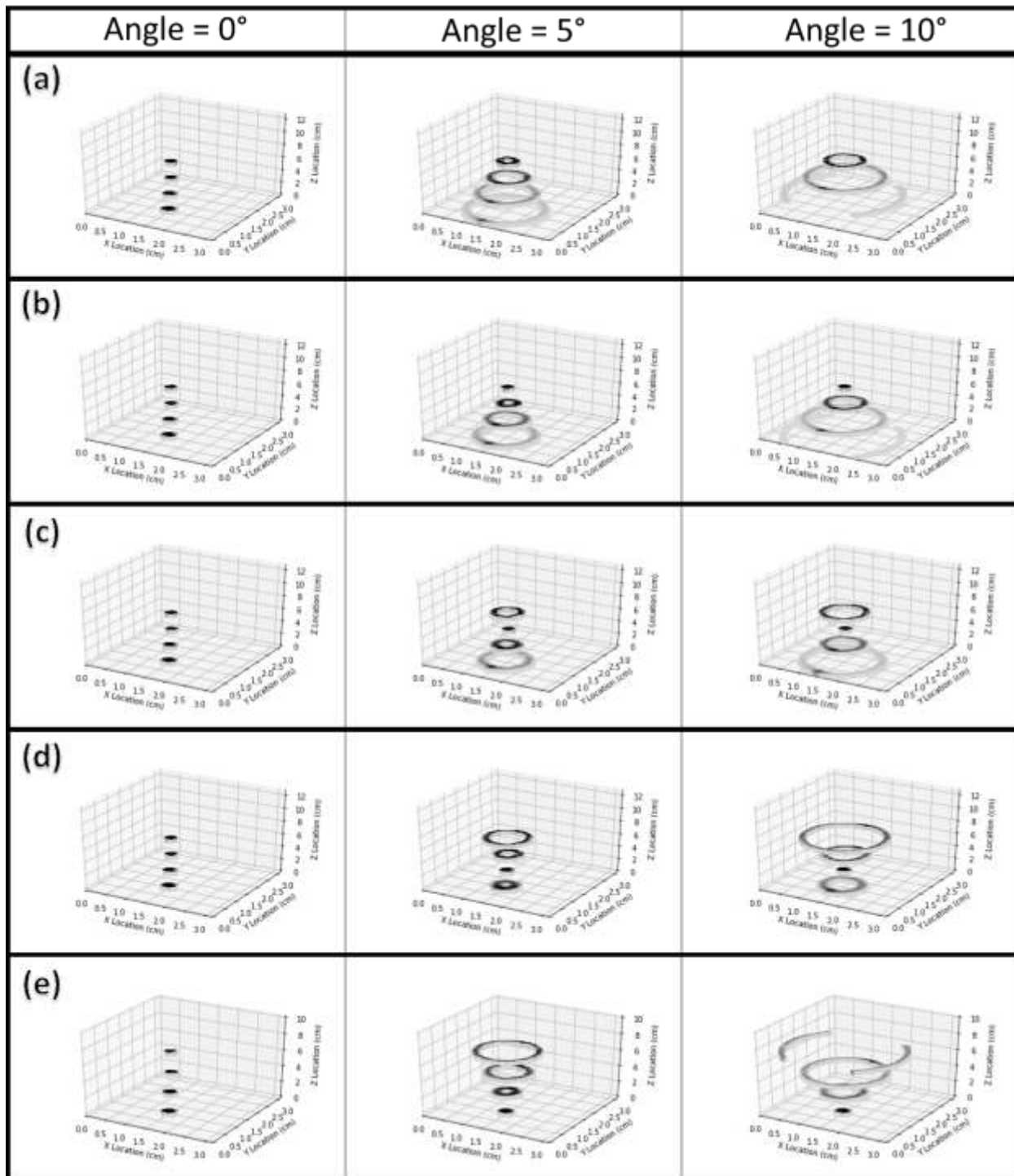


Figure 2.7: Variable focal length images of the scanning focusing beam. Columns correspond to the 0°, 5°, and 10° θ angles used. Rows (a-e) correspond to the focal lengths of 10 cm, 7.5 cm, 5.0 cm, 2.5 cm, and 0 cm above the chamber bottom, respectively.

When the isocenter is measured at the same height as the detector, near identical images are shown in Figures 2.7b-e when compared to the results measured at the same height but at a θ angle of 0° . These results prove that the isocenter is indeed present since the beam remains the same at all imaging heights that are equal to the focal length heights for θ angles measured. Figure 2.7a shows no such result because the imaging sides of the detector would knock into the nosecone of the X-ray when set at the 10 cm height thereby moving the beam relative to the detector. However, the conical shape of the beam still shows consistency with the expected beam cone diameters calculated using

$$| D | = 2 \cdot \delta Z \cdot \tan(\theta) \quad (2.4)$$

and shown in Figures 2.8a-d. The calculated beam diameter shows strong consistency with the measured beam diameters. The beam shows an increase in the rate at which the diameter changes when the detector is further from the isocenter which is expected since the diameter of the cone scales with height. Results for the beam diameter fail however when the beam is at low angles since the beam overlaps with itself, not yielding a doughnut shaped image. The edge detection software requires there to be a center unexposed to X-rays and thus cannot calculate a rotation diameter when no center appears. This only effects the isocenter diameter, which remain constant, and measurements at low θ angles. At high angles, measurements cannot be made due to the detector no longer being wide enough to measure the width of the beam. This leads to fewer samples at higher θ angles and for measurements further away from the isocenter.

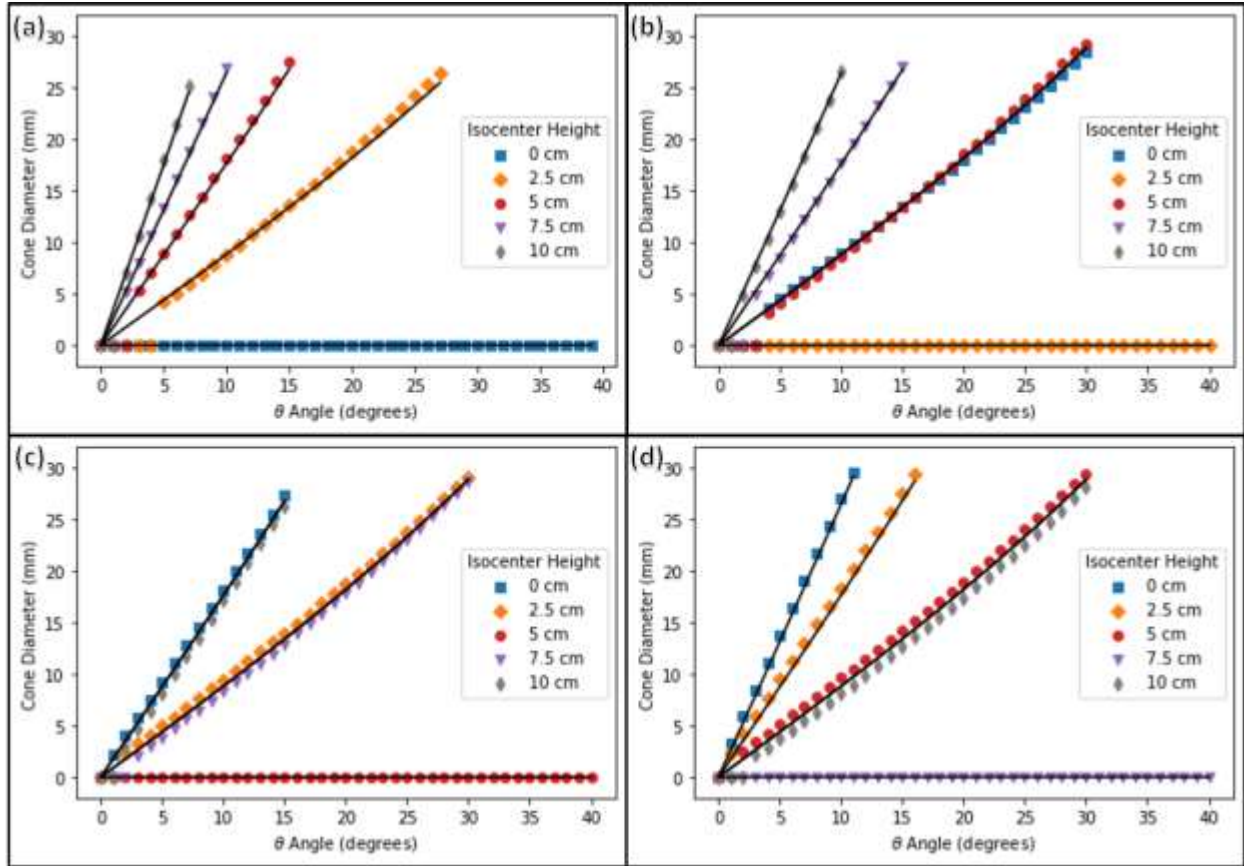


Figure 2.8: Variable focal length beam center locations at different combinations of isocenter and detector heights. Plots (a-d) correspond to detector heights of 0 cm, 2.5 cm, 5 cm, and 7.5 cm above the bottom of the chamber, respectively.

The number of unique theoretical and measured lines that do not overlap is dependent upon whether measurements were taken at equal distances relative to the height of the isocenter. For the images taken at the bottom of the chamber seen in Figure 2.8a, five unique lines form corresponding to the five unique distances above the isocenter. For Figures 2.8b-d, the isocenter has a detection at 2.5 cm above the isocenter and 2.5 cm below the isocenter leading to two overlapping lines since the diameter is only dependent on the absolute value of the distance from the isocenters. This overlapping occurs twice for Figure 2.8c since the height

of the detector is in the center of the distribution of chosen isocenter heights with distances from the isocenters at ± 2.5 cm and ± 5 cm.

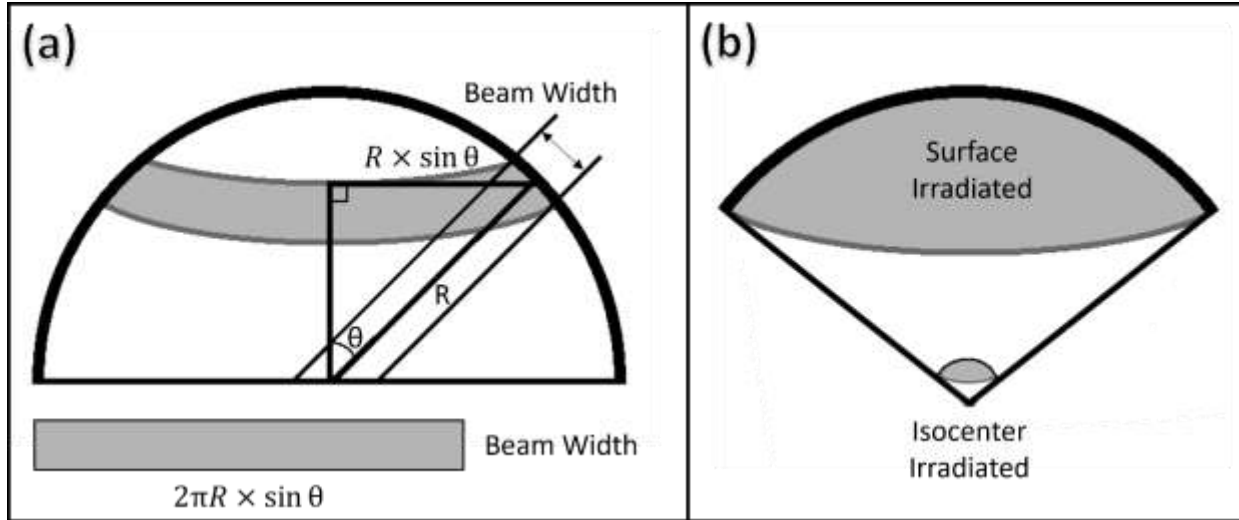


Figure 2.9: Schematic showing the surface area calculation for the irradiated surface at a given angle θ and the beam width W . The single ribbon surface calculation in (a) shows the area irradiated at a single angle θ . When added together without overlapping, the image in (b) illustrates the overall irradiation of the surface.

To calculate the ribbon corresponding to the surface area irradiated, the beam path must be mapped in spherical coordinates. Conventionally, the surface area of a ribbon on a sphere uses the arc length of the ribbon derived from a change in angle and the radius of the sphere. Since the width of the beam W is known experimentally, the area being irradiated is calculated using

$$Area = W \cdot (2\pi R \cdot \sin(\theta)) \quad (2.5)$$

where the angle θ , and the radial distance from the isocenter R to the surface is shown in Figure 2.9.

Although the calculation implies a trapezoidal ribbon due to the top having a smaller radius compared to the bottom, the beam width is negligible compared to the phantom radius such that the difference in area is orders of magnitude smaller than the overall area. This results in a length difference of less than 50 μm for a travel distance of 40 cm when calculating using a trapezoid vs the assumed rectangle for the most extreme case. After calculating the relative area at different angles, the rotational speed across the ϕ axis can be set such that the surface area per unit time is equivalent at all adjustment angles and therefore equivalent in dose regardless of the surface area irradiated.

The surface dose program uses a motorized timing control program for consistent X-ray irradiation timing between rotations and for the prevention of overheating of the X-ray source. The program allows the user to specify the rotation speed in revolutions per minute (RPM) and the off-time delay to specify the time that the X-ray must remain off for cooling and adjustment of the longitudinal angle. The program first calculates the total distance needed to travel for 1 full rotation as well as the distance needed for acceleration/deceleration. For even irradiation across the surface of the sample, the X-ray is only turned on once the top rotation has reached a constant velocity then and turned off while accelerating, decelerating, or when adjusting the longitudinal angle with the timings shown in Figure 2.10. Although the X-ray downtime can be controlled by the user, a constant acceleration period of 2.5 seconds is used regardless of the velocity and was included in the X-ray off time chosen by the user. The maximum velocity is set by dividing the number of steps per full rotation by the top rotation time and the number of extra steps needed for acceleration and deceleration uses the maximum velocity times the time needed to accelerate or decelerate.

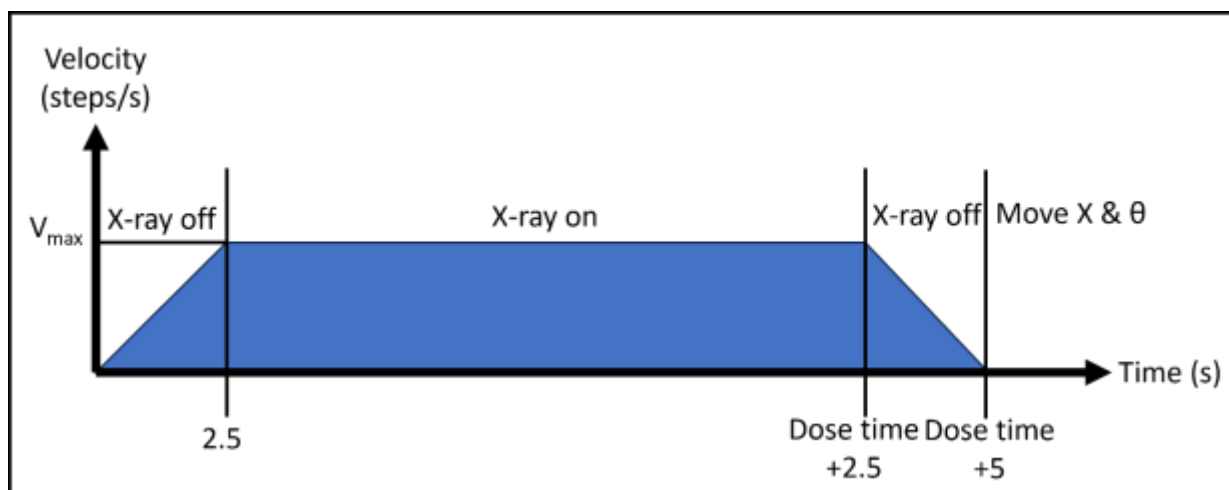


Figure 2.10: Timing schematic for constant dose across the sample surface. The total number of steps, movement time, and acceleration are all based on the maximum velocity set by the desired dose and surface irradiated by the beam. The beam is only turned on while at the maximum velocity and thus turned off during the acceleration, deceleration, and while waiting to adjust the angle of the source.

X-ray dose measurements show the effect of different combinations of voltages and currents. The highest combination allowed by the manufacturer has the highest dose at 222 mGy/hour for a kVp of 70 kV and 171 μ A current for the highest rated power of 12 W. Due to the measurement detector measuring over an area of 0.79 cm², and the beam only covering a 3.2 mm diameter as measured by imaging, the area compensated dose per unit area is 2.17 Gy/hour at the isocenter shown in Figure 2.11a. After the dose calibration using a calibrated dosimeter, chemical dosimetry validation was prepared. The doses measured with respect to the known calibrated dose rate using the Kevex source show relatively similar results to the Accugold dosimeter.

After fitting the results to a line of best fit using the built-in least squares fit function in provided in the numpy python library, the slope representing the dose rate shows a deficiency of

0.56 Gy/hour. Since the line of best fit shown in Figure 2.11c includes an offset such that a dose would be measured prior to irradiation of X-rays, a depression in the dose rate is seen. This error is likely due to the extremely long irradiation times needed to measure at such a low dose rate. In comparison to sources used in previous studies, the dose per minute is orders of magnitude smaller due to the extremely thin beam profile and low power output [27,83]. The chemical detection method developed for the higher-powered instruments are effective at experiment durations on the order of minutes, replicate studies require many hours of irradiation due to the low dose rate and the cooling cycling required to irradiate at significant doses. To solve for these issues, a second line of best fit in Figure 2.11c has been driven through the origin in order for the dose to correspond to experimental conditions since the lower times had better linearity just above the minimum doses needed to calibrate. This correction shows a similar dose rate using the slope of the chemical dosimetry when compared to the Accugold dosimeter with a relative percent difference of 8.15%.

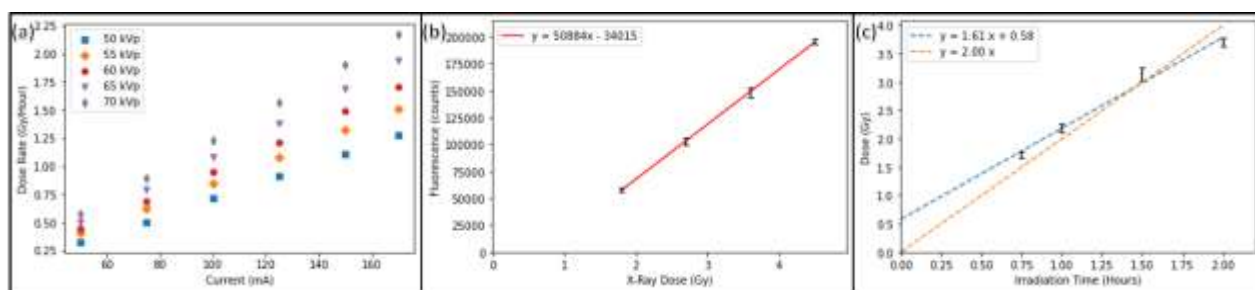


Figure 2.11: Dosimetry measurements for Moxtek and Kevex X-ray sources. The dosimetry results in (a) show the Moxtek calibration using an Accugold AGMS-D+ diagnostic multisensor. The chemical calibration in (b) uses the Kevex X-ray source and 3-CCA at a rate of 1.8 Gy/minute. The results from (b) were used as a standard for the chemical calibration for the dose of the Moxtek X-ray source, as shown in (c).

Characterization of the AuNPs in Figure 2.12a show a peak diameter of 9.08 nm from DLS with a small secondary sub nm peak. This size is comparable to but slightly larger than the AuNP dimeters used in Cheng Et al. which had 7.0 ± 1.3 nm AuNPs and is the basis for enhancement comparison [83]. Although the measured nanoparticle sizes are larger, the enhancement results shown using the same X-ray source at a different dose rate are comparable. After size characterization, concentration analysis via flame AA in Figure 2.12b show a post filtering concentration of Au at 4.2 PPM. After accounting for the digestion and dilution volumes, a stock concentration is 0.21 wt.% when accounting for digestion and dilution volumes. This concentration was used to create AuNP dosimetry used to measure enhancement.

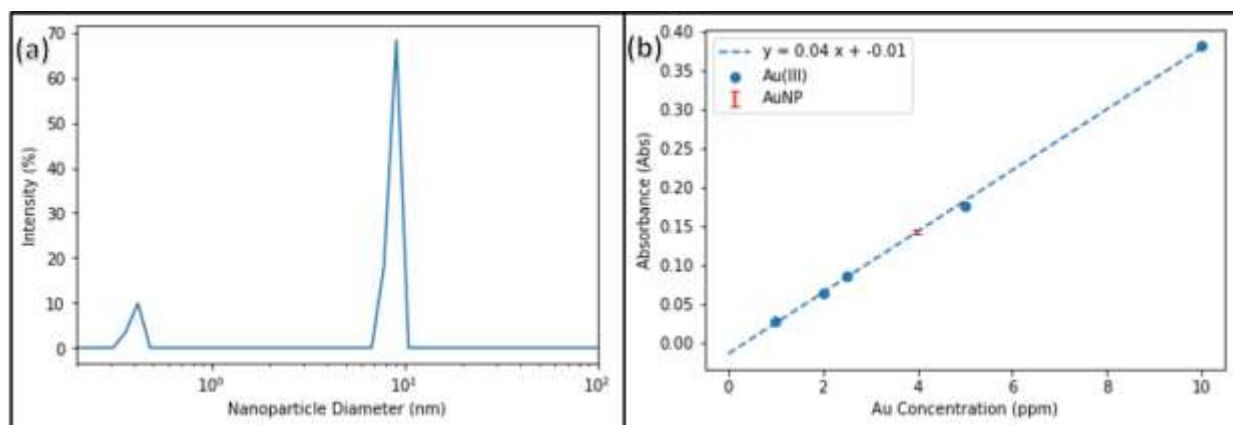


Figure 2.12: Characterization of AuNPs using DLS and Flame AA. The DLS results in (a) for the AuNPs show a peak intensity at 9.08 nm with a minor peak at 0.42 nm, a similar size as the edge length of a gold unit cube and smaller than AuNPs. The flame AA calibration in (b) shows the concentration of 1:500 diluted AuNPs.

Enhancement results from the Faxitron source show similar results to previously reported CE values measured by Cheng Et al [83]. Although modifications in the methodology were made, Figure 2.13a shows enhancement increasing linearly below 0.01 wt.% which flattens off to

approximately 0.5 DEU at the maximum measured concentration of 0.1 wt.%. These results are consistent even though the X-ray source deposited only a 2 Gy dose instead of a 100 Gy dose due to the Moxtek X-ray being limited by its low maximum dose rate. The voltage potential is also lower at a maximum allowable 70 kVp instead of the previously used 100 kVp for the Faxitron X-ray source. Even with these changes, the enhancement measurements still tapered to approximately the same enhancement value. The combination of the two changes shows a likely minimum dependence on dose can be reached by lowering the dose rate below the lowest value tested by Cheng Et al [83].

The Moxtek enhancement results in Figure 2.13a show that the beam used for the scanning focusing X-ray source measures higher enhancement when compared to the Faxitron X-ray source used in method validation. This improvement is likely due to modifications related to the sample preparation and the profile of the X-ray. The primary difference between the Moxtek and Faxitron sample preparation is the smaller sample volumes irradiated with the Moxtek X-ray source at a depth of 300 μm deep compared to the 900 μm deep samples irradiated with the Faxitron X-ray source. This 3-fold decrease in depth due to sample holder size and volume constraints from the Moxtek beam lowers the attenuation through the sample giving a smaller background signal, leading to a higher enhancement in comparison. Another change is the needle beam created using the nose cone collimator. While the dose rate overall is lower, the beam that is reaching the isocenter is unfiltered and which is more affected by the decreased background signal due to passing through a thinner sample.

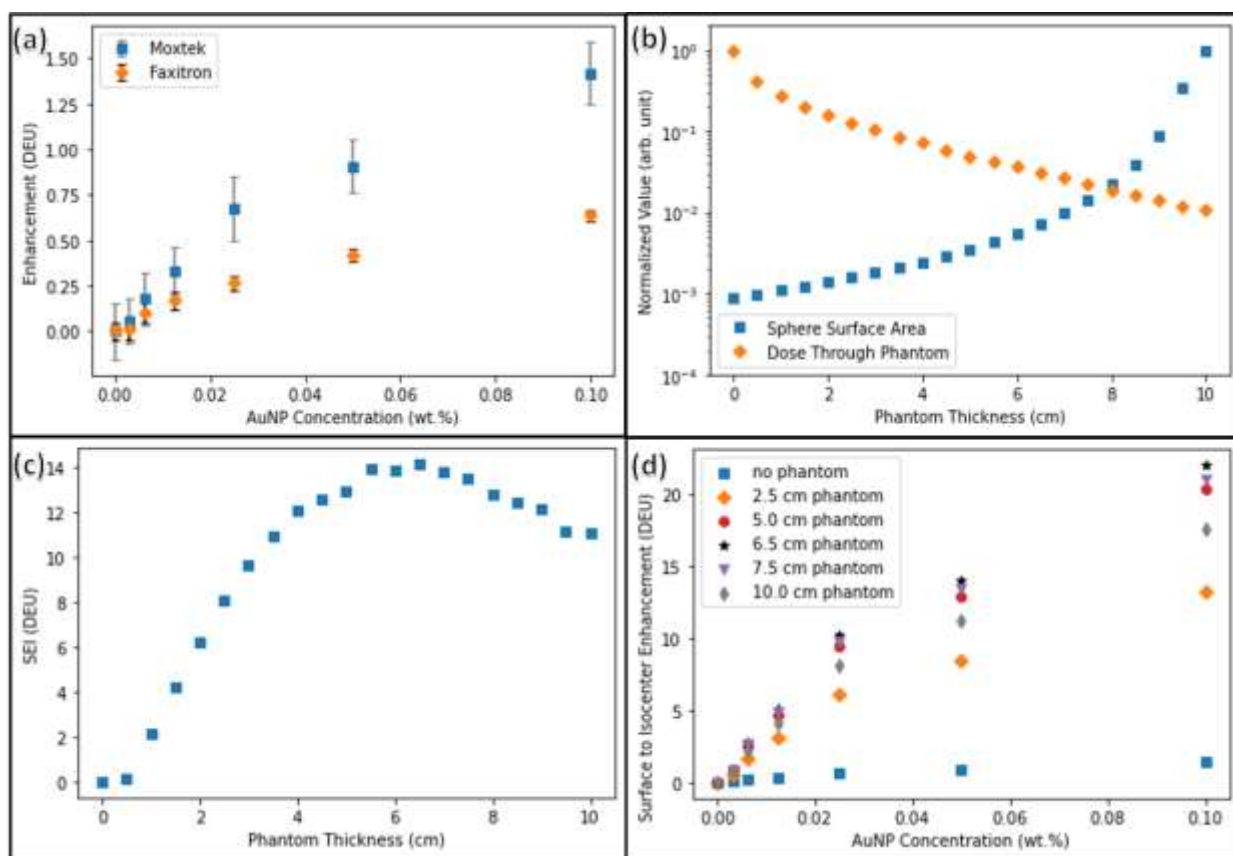


Figure 2.13: Enhancement of AuNPs from 70 kVp X-rays from scanning focusing measurements and calculations. The plot in (a) shows the enhancement of AuNPs without a phantom, with higher enhancement for the Moxtek X-rays source compared to the Faxitron source. The irradiated surface area and measured dose in (b) show changes as a function of phantom diameter. The plot in (c) shows the relationship between sample depth and SIE. The enhancement results from (a) and (c) are combined in (d) to show the highest overall enhancements at different phantom diameters.

Although the measurement of CE using this method is not new, the ability to move the beam source relative to the surface of the sample creates new scenarios for measuring X-ray nanochemical interactions inside of phantoms. This pushes the boundary to measure how the chemical and physical processes relating to how X-rays change after being attenuated by a body equivalent. By spreading the dose across the surface of a simple spherical phantom, a targeted

dose results in an accumulation of dose at the isocenter of the phantom then would otherwise be possible using a static beam. Higher relative surface area doses are possible at the isocenter because the relative surface area of the phantom increases faster than the rate at which the dose decreases when passing through more material. After traveling through 10 cm of a PLA phantom, Figure 2.13b shows the dose deposited at the isocenter is reduced to 1% of the dose deposited at the surface. The movement of the beam from 0-40° allows for spreading of the higher surface dose across a much greater surface than the area at the isocenter. This spreading of the dose is summed at the isocenter but divided across the surface of the phantom giving to a per area surface dose that is 0.11% of the dose deposited to the isocenter. The per area dose can be calculated at both the isocenter and surface of the phantom

$$\text{Relative Isocenter Dose} = \frac{\text{Isocenter Surface Area}}{\text{Isocenter Dose}} \quad (2.6)$$

$$\text{Relative Surface Dose} = \frac{\text{Surface Surface Area}}{\text{Surface Dose}}. \quad (2.7)$$

These ratios are used to calculate the SIE mentioned in the introduction to this chapter as

$$\text{SIE} = \frac{\text{Relative Isocenter Dose}}{\text{Relative Surface Dose}}. \quad (2.8)$$

Such enhancements are based on the size of the phantom, the angle swept by the X-ray, the energy spectrum of the X-ray, and the diameter of the X-ray beam. If measuring SIE at the highest settings for a given X-ray source, the only way to improve enhancement is by decreasing the skin dose relative to the isocenter. Such an increase is maximized by irradiating the entire surface of the sphere. Although the scanning focusing X-ray source is limited to 0-40° of angle adjustment and 150 mm translation, future improvements of the design can be made to increase the degrees of freedom, such as using a 6-axis robotic arm, but would greatly increase costs and complexity

of the device. Another surface area ratio improvement is possible by shrinking the beam diameter. Since SIE is dependent on the ratio of the isocenter surface relative to the phantom surface area, an increase can be seen by shrinking the isocenter at a fixed phantom radius. Since the surface area of a sphere is scaled by the radius squared, this means SIE will also scale by the radius of the isocenter squared. However, there are two main drawbacks to such an improvement: cost and dose time. The nosecone of the scanning focusing instrument uses an aperture diameter of 10 thousandths of an inch which requires specialized equipment, skilled labor and extreme precision for manufacturing all of which are expensive. Even a relatively small decrease in the diameter of the aperture can balloon costs due to the precision required for such small holes to be properly aligned. With a 10-fold decrease in the diameter of the beam for the scanning focusing X-ray source, a massive 150 DEU enhancement seen in Table 2.1 can be theorized. Even if a smaller beam is used, the time at which it takes to deposit a significant enough dose will be greatly increased since the aperture will be blocking more X-rays. To compensate, dose times must increase to maintain the same flux of X-rays at the isocenter to see a measurable dose.

Given a static beam and X-ray spectrum, it is expected that SIE would always increase relative to an increasing radius, however the SIE shown in Figure 2.13c has a maximum SIE for the 6.5 cm phantom diameter. This unexpected result corresponds to when the rate at which the relative area increases becomes larger than the rate at which the dose decreases. This means the isocenter can be tailored to a given material and diameter by changing the energy spectrum of the beam such that the rate crossing occurs at the radial distance of the isocenter thus maximizing the enhancement.

Table 2.1: Theoretical increases in enhancements given maximum possible improvements to the initial conditions.

AuNP Concentration	Original SIE (DEU)	SIE Using 1 mm Skin Phantom (DEU)	SIE Using 0.3 mm Beam (DEU)	SIE Using Skin Phantom and 0.3 mm Beam (DEU)
Without AuNPs	15.1	39.7	150	397
0.1 wt.%	22.0	59.2	220	579
7.5 wt.% [27]	76.5	224	832	2190

By combining the CE through the addition of AuNPs in the sample and movement of the X-ray beam across the surface of the phantom the enhancements compound, giving the greatest overall enhancement. For the scanning focusing X-ray, this occurs at the maximum concentration AuNPs with an enhancement of 1.5 DEU and with a phantom thickness of 6.5 cm yielding an enhancement of 14.1 DEU for a combined enhancement of 22.0 DEU shown in Figure 2.13d. Further improvements can be made by applying these results to literature data beyond the concentrations tested here. Such an improvement can be seen by the 5.5 DEU enhancement measured by Davidson and Guo using silica coated AuNPs at a 7.5 wt.% concentration [27]. Another way to improve the SIE ratio is by placing a skin phantom on top of what would be the skin of a patient. Since the majority of the energy absorbed by X-rays will be within the first mm of depth, a lot of effort has put into the understanding of skin-depth X-ray deposition [84].

To circumvent the 2 Gy peak entrance skin dose used in X-ray guided interventions, application of a thin skin equivalent layer can be used to absorb such a damaging dose [85]. This allows for the enhancement calculation to begin at the lower dose located 1 mm below the sacrificial surface, drastically decreasing the dose deposited in a theoretical skin of a patient

without significantly decreasing the surface area irradiated. This could also be done by filtering the X-rays through a low Z metal like copper or aluminum to block the low energy X-rays, thus achieving a similar result using same phenomena [41]. With the addition of a sacrificial phantom skin, a decrease in the distance through which the peak SIE will occur lowers from 6.5 cm to 2.5 cm while increasing the SIE itself to 39.7 DEU. By combining the sacrificial skin phantom with a 0.3 mm beam while at the highest measured nanoparticle enhancement, an astounding 2190 DEU can be realized for a target 2.5 cm into a sample. This means that the dose into the healthy skin of a patient would only experience a maximum dose of 28 mGy across the skin while still allowing for the release of a drug from a nanoparticle drug carrier at the isocenter requiring 50 Gy for a therapeutic release [86]. Even the AuNPs themselves can increase the efficacy for dose dependent AuNP tumor therapy by scaling tumor damage to effective dose [87].

2.4 Conclusion:

Although the results show lower enhancement for the 12W Moxtek source under similar experimental conditions, improvements have been made both with dosimetry and usability of the scanning focusing device. The X-ray beam is not limited to a fixed location inside of the phantom allowing for more control of the surface dose of a phantom and opening the door to new geometries to improve SIE. The rotational speed can also be changed to deposit an equal dose across the surface of the phantom. This dose control, along with an improved dose calibration using a radiometric dosimeter and further validation using a secondary X-ray source, gives greater control of both isocenter and surface doses. Combining these experimental design improvements with the addition of a sacrificial skin phantom, an enhancement of 2190 DEU can

be realized. Such a high enhancement when combined with other X-ray therapies can greatly improve the effectiveness of localized treatments while minimizing deleterious effects.

3.1 Introduction:

X-ray spectroscopy has important uses in academic, medical and industrial venues. The ability of X-rays to observe the contents of otherwise opaque objects, comes with occupational hazards [88]. By simulating X-rays, spectroscopic methods can be tested prior to laboratory implementation alleviating any risk to workers or causing wear to equipment. These simulations require accurate inputs for X-ray energy spectra used for beam shape intensities as well as material attenuation and absorption coefficients. To simulate an accurate X-ray spectrum for a continuous source such as a benchtop X-ray, the shape of the beam can be approximated from Kramer's Law [89]

$$I_0 d\lambda = iK \left(\frac{\lambda}{\lambda_{min}} - 1 \right) \frac{1}{\lambda^2} d\lambda. \quad (3.1)$$

The distribution intensity $I_0 d\lambda$ for a metal target scales proportionally to the atomic mass of the target by a scaling factor K and the X-ray current i . The overall shape of the spectrum is dependent on the minimum wavelength set by the maximum voltage potential kVp and the conversion of energy in keV to frequency in pm with the Duane-Hunt law [90]

$$\lambda_{min} \approx \frac{1239.8 \text{ pm}}{kVp}. \quad (3.2)$$

However, for calculations using keV instead of X-ray wavelength, (3.1) can be converted from wavelength to energy using the same frequency to energy conversion. This gives the intensity of the beam I_0 in terms of X-ray energy E and the maximum voltage of the X-ray applied E_{max} as

$$I_0 = iK \left(1 - \frac{E}{E_{max}} \right) \frac{1}{E^2} \quad (3.3)$$

and plotted in Figure 3.1a.

Although a continuum of X-ray energies would be produced from 0 to E_{max} , the X-rays must first escape the target material and exit the device producing the beam. Even with a micron of target material and a window of a highly transparent medium like beryllium, there is still attenuation of the beam for low energy X-rays as described in Chapter 1 [91]. This significantly lowers the intensity of X-rays at low energies and results in the humped beam shown in Figure 3.1c.

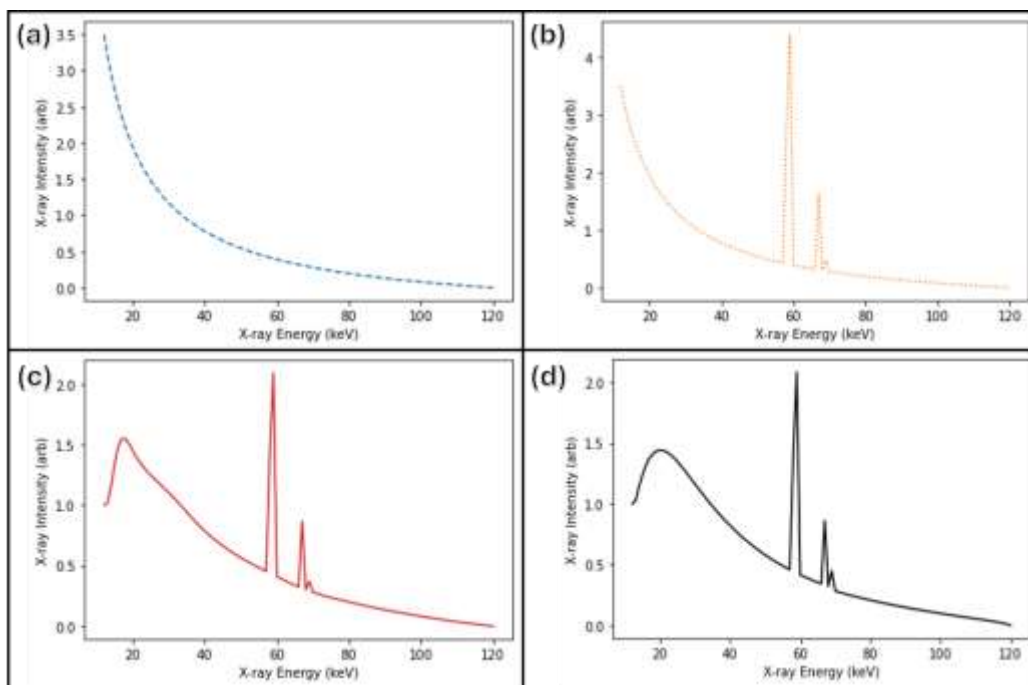


Figure 3.1: Spectra developed using Kramer's Law with the addition of characteristic X-rays compared to SpekCalc. The X-ray spectrum in (a) is produced using Kramer's law only, while the spectrum in (b) combines the results from (a) with the calculated characteristic X-rays. The plot in (c) takes the spectrum from (b) and attenuates using a 1 mm beryllium window and 1 micron of tungsten to correct for lower energies. SpekCalc software with the same variable inputs as (a-c) was used to acquire the plot in (d) [92–94].

Along with the bremsstrahlung X-rays, characteristic X-rays are produced based on the electron binding energies of the target and the voltage applied to the instrument. These characteristic X-rays are produced at specific energies and with very narrow linewidth [95]. Such X-rays are produced due to collision events between the accelerated electrons and the electrons of the X-ray target material [96]. This ionization event produces the same Auger relaxation process discussed in Chapter 1 but with the release of a fluorescent X-ray rather than additional electrons. These fluorescent X-rays result in large spikes in X-ray intensity at specific energies in the spectrum the intensity of which can be approximated with [90]

$$I = i \left(\frac{E_0 - E_c}{E_0} \right)^n . \quad (3.4)$$

The intensity of the characteristic beam is proportional to the current of the X-ray and the relative difference between the transition energy E_c and the maximum X-ray voltage E_0 to the power n , which has been acquired experimentally to be between 1.5 and 2 [97]. The scaling of n is dependent on the element and the edge that is measured [97].

Table 3.1: X-ray energies and transitions for a tungsten X-ray target characteristic X-ray peaks [98].

Edge	K α 1	K α 2	K β 1	K β 2	K β 3
Electronic Transition	$1s_{1/2} \rightarrow 2p_{3/2}$	$1s_{1/2} \rightarrow 2p_{1/2}$	$1s_{1/2} \rightarrow 3p_{3/2}$	$1s_{1/2} \rightarrow 4p_{3/2}$	$1s_{1/2} \rightarrow 3p_{1/2}$
Edge Energy (keV)	59.300	57.981	67.244	69.101	66.952
Binding Energy (keV)	10.207	11.544	2.281	0.424	2.573
Relative Intensity	100	58.3	21.9	4.8	11.4

With an accurately simulated X-ray spectrum, attenuation of the X-rays can be calculated using (1.1) with X-ray coefficients from a database. Although this will give the transmitted beam, the resulting beam will neither resemble the correct shape nor the intensity of a beam passing through a given material. To calculate a beam that better resembles real transmission of X-rays through a material, scattered X-rays must be considered for calculations. While X-rays are scattered both coherently and incoherently for energies between 1 and 120 keV, the primary difference between these types of scattering are whether the interaction is relativistic or nonrelativistic.

Thomson scattering is the nonrelativistic scattering of an X-ray interacting with an electron in an atom through classical acceleration [99]. Under the classical principle of electromagnetic waves being produced by an acceleration or deceleration of a point charge, the excitation from an X-ray with wavelength λ accelerates an electron that in turn creates an electromagnetic wave with an equal scattered wavelength λ' [100]. This scattering angle θ is independent of the incoming X-ray energy but only occurs for lower energy X-rays [101]. At higher X-ray energies, incoherent Compton scattering becomes more prevalent but both types of scattering can occur for some X-ray energies [102].

Compton scattering is the incoherent scattering of X-rays approximated by an elastic collision between a photon and an electron [103]. This scattering results in the ejection of an electron and an X-ray scattered in the opposite direction of the collision plane with a lower energy than the incident X-ray shown in Figure 3.2a [104]. This loss of energy can be calculated using the Compton equation [104]

$$\lambda' - \lambda = \left(\frac{h}{mc} \right) (1 - \cos \theta) \quad (3.5)$$

where λ' is wavelength of the scattered X-ray, λ is the initial wavelength of the X-ray, θ is the angle at which the X-ray is scattered, h is Planck's constant, m is the rest mass of an electron, and c is the speed of light. Although (3.5) is useful for calculating the spectra after scattering, it does not give the likelihood that an X-ray is scattered to the angle θ .

To acquire the angular dependence necessary to determine the final locations of both coherently and incoherently scattered X-rays, the Klein–Nishina formula

$$\frac{d\sigma}{d\Omega} = \frac{r_e^2}{2} \left(\frac{1 + \cos^2(\theta)}{1 + \alpha(1 - \cos^2(\theta))} \right) \left(1 + \frac{\alpha^2(1 - \cos(\theta))^2}{(1 + \cos^2(\theta))(1 + \alpha(1 - \cos(\theta)))} \right) \quad (3.6)$$

can be used. This equation uses the differential cross section of the electrons in the scattering material and can approximate incoherent Compton scattering for high energy X-rays and coherent Thomson scattering when α is zero [105]. In (3.6) r_e is the classical electron radius, α is the kinetic energy divided by the rest mass of an electron for the incident X-ray, and θ is the scattering angle of the X-ray. The differential cross section $\frac{d\sigma}{d\Omega}$ corresponds to the solid angle $d\Omega = 2\pi \sin(\theta) d\theta$ that the photon passes through relative to the incident beam area $d\sigma$. Since the goal is to compute the probability that a photon is scattered at an angle rather than an area, $\frac{d\sigma}{d\theta}$ must be computed. By integrating over the entire solid angle, the total cross section σ can be determined using

$$\sigma = \int \frac{d\sigma}{d\Omega} d\Omega. \quad (3.7)$$

By substituting the definition of $d\Omega$, the total cross section can be defined in terms of $\frac{d\sigma}{d\Omega}$ and the scattering angle θ as [106]

$$\sigma = \int_0^\pi 2\pi \frac{d\sigma}{d\Omega} \sin(\theta) d\theta. \quad (3.8)$$

Since the integration of $\frac{d\sigma}{d\theta}$ over all θ is equivalent to the initial value σ , the overall expression for

$\frac{d\sigma}{d\theta}$ is given [107]

$$\frac{d\sigma}{d\theta} = 2\pi \frac{d\sigma}{d\Omega} \sin(\theta). \quad (3.9)$$

With (3.9) a probability density function can be calculated by solving from 0 to 180° and normalizing to an area of 1. This yields an angular dependence for Compton scattering when α is larger, as shown in Figure 3.2b where scattering is most probable at the lowest and highest angles of deflection. The scattering probability is lowest perpendicular to incoming beam, and for larger angles, decreases as α increases.

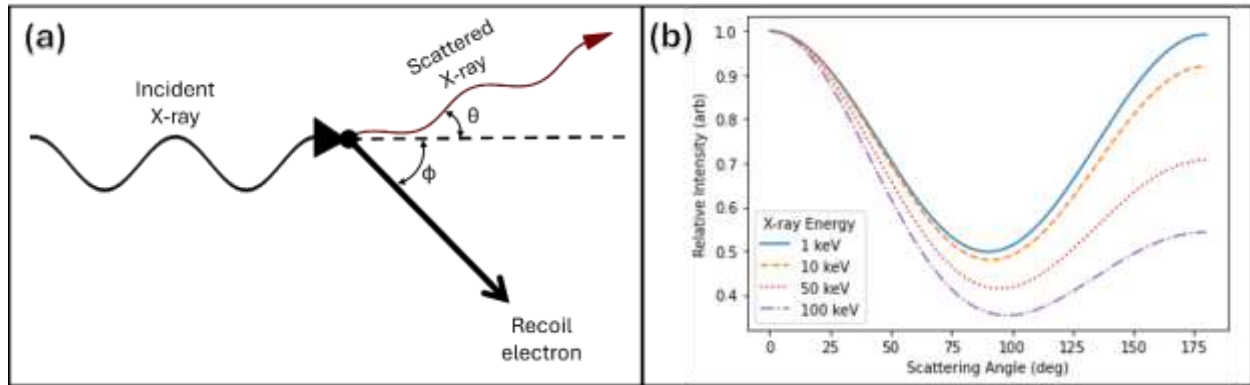


Figure 3.2: Scattering of X-rays due to interactions with electrons in an atom adapted from Compton [104]. The schematic in (a) depicts Compton scattering, where an incident X-ray hits an electron leading to a lower energy X-ray scattered at an angle θ and an electron scattered at an angle ϕ . The plot in (b) shows the relative intensity of scattered X-rays across all available angles using (3.9) with 1 keV electrons approximating coherent Thomson scattering.

Using the scattering probabilities and previous experimental results, an algorithm for calculating the X-ray dosage inside of a material has been developed. Calculations using this

algorithm improve upon previous simulations used for a scanning focusing X-ray beams for measuring the chemical interactions between X-rays and nanoparticles. Through the implementation of surface area calculation, a uniform surface dose can be set to determine the maximum surface-to-isocenter dose for a variable focal length scanning focusing X-ray instrument. The improved scattering algorithm using ray tracing allows for a more accurate beam to be calculated and improves the spatial accuracy of X-ray energy deposition in a material. Simulated spectra can be used to direct iterative improvements on existing scanning focusing instrumentation. These improvements can be applied to guide future experiments in the subject of X-ray Nanochemistry.

3.2 Methods and Materials:

X-ray spectra were acquired using the SpekCalc X-ray simulation software. X-ray spectra used in calculates were attained for 70 kVp and 120 kVp with filter depths set using the software [92–94]. Absorption coefficients for water were acquired from the NIST database of X-ray attenuations and the attenuation coefficients were acquired using Mucal [108].

Experimental Beam Parameters

X-ray beam shape was determined using X-ray images acquired at different heights above the isocenter. Tolerances in the machining led to imperfect alignment and slight deviations leading to the beam shaking slightly as it was rotated about the top ϕ axis. Since these deviation errors were random, simulations used the static beam shape and assumed that the instrument will be improved to handle higher tolerances when testing the theoretical results. The beam

diameter used the edge detection software described in Chapter 2 to measure the inner and outer edge of a beam set with an isocenter above the X-ray detector while adjusted to a low, but nonzero θ angle. The difference in the outer edge and inner edge of the resultant beam was determined to be the static beam diameter.

For the dose profile of the isocenter at the bottom of the chamber, the same procedure using the imaging sensor and dosimeter holder from Chapter 2 was used. The dosimeter and X-ray source were simultaneously triggered and dose was measured across a 30 second period and measured at varying increments using the translational stage.

Ray Tracing Algorithm

Ray tracing calculations for the nosecone consisted of a 2 mm wide emitter and a 2 cm wide detector, each with bins of 50 μm . Lines were calculated from the center of each bin at the emitter to the center of each bin at the detector to simulate all the discrete possible X-ray trajectories from the source that would reach the sample. If a line did not pass through the boundary set by the aperture used in the experimental setup, the X-ray spectrum was added to the bin array of the detector. If a linear trajectory led to the X-ray passing through the boundary set by the steel beam stops, the length at which the X-ray traveled inside the material was calculated. The distance, the initial X-ray spectra, and the attenuation coefficients were then used in (1.1) from Chapter 1 to calculate the transmitted intensity for each X-ray energy and the spectra was added to the bin array of the detector.

The simulated X-rays that traveled through the phantom also used (1.1) to measure the transmitted X-ray intensity but the total intensity also needed to account for the scattered X-

rays. Since the attenuation coefficient is the sum of the individual types of attenuation as described in Chapter 1 and stated in (1.3), calculations were be done to quantify the distribution of X-ray events: transmission, photoelectric absorption, coherent scattering, and incoherent scattering. Since the material changes the spectra depending on the thickness, a new spectrum was calculated between each incremental thickness step of 50 μm . The intensity of the beam was calculated for the incoming spectra and after passing through the pixel and saved as an input for the next pixel. The individual event coefficients were used to get the probability of a photon being attenuated by each event type, the sum of which was always one. Using these location probabilities, the probability that a scattered X-ray reaches the detector was calculated. Given a scattering event occurred at a specific height, the minimum and maximum angles at which the X-ray reaches the detector can be calculated using

$$\theta_n = \tan^{-1} \left(\frac{\left(\frac{W_{bin}}{2} \right) + (n \cdot W_{bin})}{H} \right) \quad (3.10)$$

where W_{bin} is the width of the detector bin, n is the integer value of the bin relative to the center of the detector and H is the height above the detector at which the scattering event occurs. The angular probability distribution of scattered rays can be determined at each X-ray energy for any given angle. The probability,

$$P_n = P_H \cdot \left(\frac{P_{\theta_n} + P_{\theta_{n-1}}}{2} \right) \cdot (\theta_n - \theta_{n-1}) \quad (3.11)$$

was determined with the numerical integration of the probability density function from the maximum and minimum angle needed to hit the detector determined using (3.10). In (3.11), P_n is the probability that the scattered X-ray reaches the n th detector bin, θ_n and θ_{n-1} are the maximum and minimum angles allowed for the X-ray to reach the edges of the detector bins, P_{θ_n}

and $P_{\theta_{n-1}}$ are the scattering probability density function values at θ_n and θ_{n-1} , and P_H is the probability that the scattering event takes place at the height H . The probability density functions for coherent X-rays were calculated using (3.6) and applied to (3.9) with $\alpha=0$ whereas the incoherent scattering was calculated with the same equation but required the α to be calculated at each X-ray energy. Since the probability was symmetrical about the Z axis, the probabilities were mirrored for the negative values of X . This symmetry means that P_0 , which had half of the bin on each side of the Z axis, only needed to be calculated once, but was doubled as

$$P_0 = 2 * \theta_0 \cdot P_{\theta_0} \quad (3.12)$$

to account for both sides of the axis. After simulating the spectra that transmitted through the material, simulated dosimetry at the detector was calculated for the energy absorbed into a 50 μm deep sample of water. To calculate a dose at each detector bin, the product of the end spectrum and the absorption coefficients of water were summed across all X-ray energies. For relative dose comparisons, all energies were normalized to the measured 2D dose Gaussian peak using the X-ray settings from scanning focusing experiments.

Dose Through Phantom Calculation

With the beam shape, spectra, and attenuation through the phantom all acquired, the dose at any given point inside of a phantom was calculated. Doses were summed for all points within the phantom by defining an array of X , Y , and Z coordinates as voxels in 3D space. By iterating all points through the angles of θ and ϕ , the dose at any given point can be calculated. The focal point of the X-ray source P_e shown in Figures 3.2a-c was first converted from spherical coordinates to a cartesian coordinate point with the known distance R and the input angles θ and

ϕ . The orthogonal line connecting the voxel location P to the line between the origin and the emitter point P_e was then calculated which gave the radial distance from point P to the center of the beam shown in Figure 3.3b. The point where the orthogonal line crossed the center of the beam P_o was then used to determine how far away the beam was. This distance gave the beam width from experimentally measured rate at which the beam diverged. With the distance from the beam center and a Gaussian with a width equal to the beam width, the spectrum of X-rays was determined at the voxel location shown in Figure 3.3c. The dose at the voxel was then calculated using the same method as the simulated dosimetry.

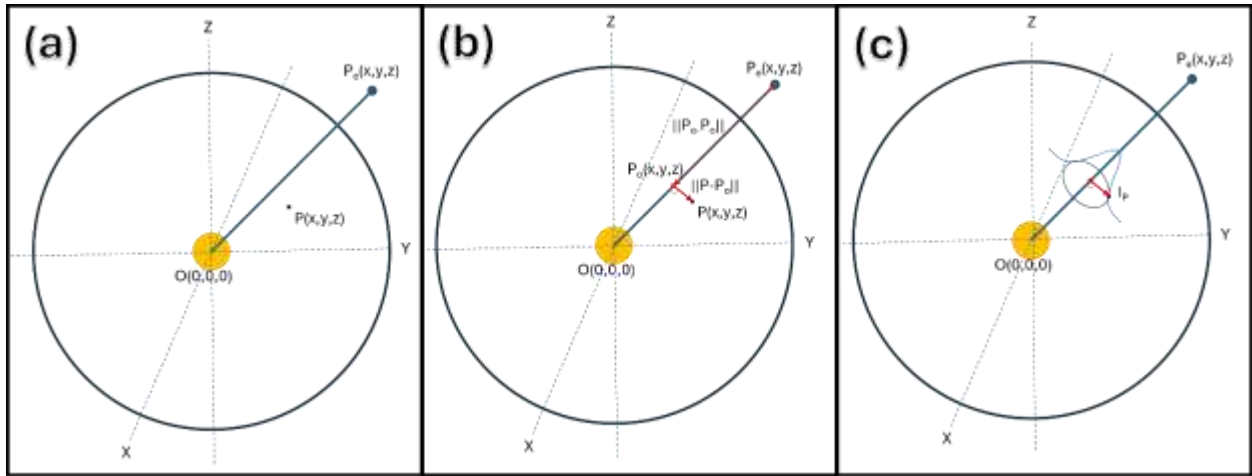


Figure 3.3: Representation of necessary points and distances used in the measurement of the dose through a phantom. The schematic in (a) shows the three inputs to the algorithm, the origin O , the point at which the dose was calculated P , and the location of the X-ray emitter P_e . The diagram in (b) illustrates the calculated line that passes through point P and is orthogonal to the line going from O to P_e , with the point of the intersecting lines defined as P_o . The distances between P_o and P gives the distance from P to the center of the beam, and the distance between P_o and P_e gives the distance from the X-ray source used to determine the width of the diverging beam. The Gaussian in (c), based on the parameters in (b), is used to determine the intensity of the beam for the dose calculation at point P .

Although the program was capable of measuring points in 3D, the time needed to carry out such calculations was untenable without parallelization of code on multiple cores and access to cluster computing. Therefore, all calculations were done in the XZ plane and measurements were not rotated about the ϕ axis but used the radial symmetry of the phantom and the surface area calculations from Chapter 2 in order to acquire results in a reasonable amount of time.

3.3 Results and Discussion:

Ray tracing results show a total of 0.25 inches of steel is unable to fully attenuate the initial X-ray beam. This results in bleed through of the beam widening the overall beam with a lower flux of higher energy X-rays. While it is possible to create an aperture of 0.01 inches using advanced machining, this capability is limited by the depth of the steel. It is however possible to improve the aperture by stacking the desired number of fixed length apertures to reach the total depth desired. Producing these parts requires micromachining, which is expensive and requires specialized equipment. In order to guarantee alignment of the apertures requires even higher precision on the location of the center with respect to the outer diameter. The aperture can further be improved by using an even higher Z material, such as tungsten or lead. However, tungsten requires specialized drilling equipment and lead incurs additional costs associated with its toxicity.

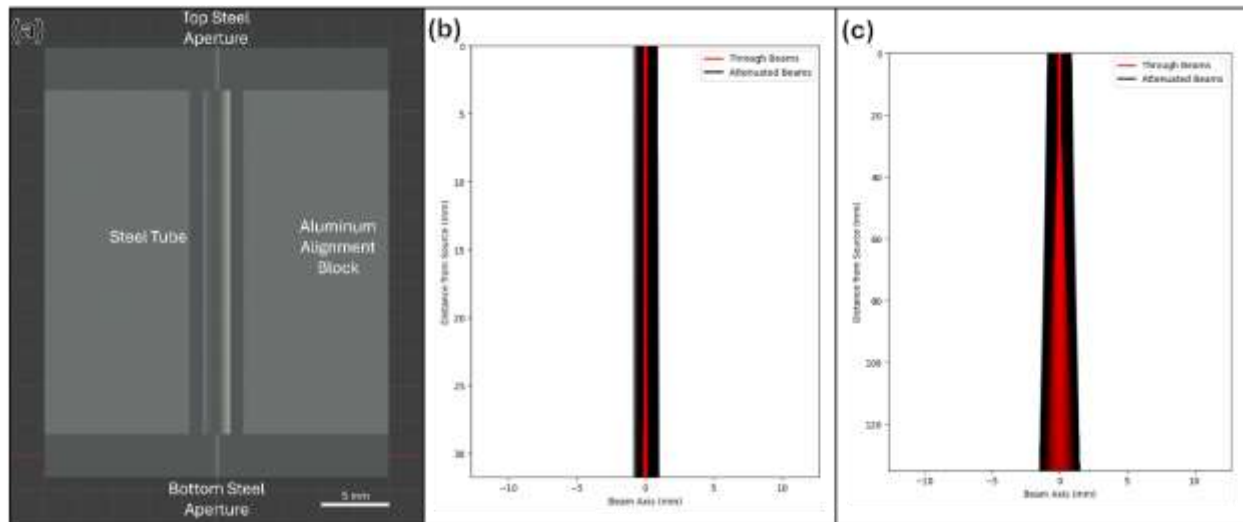


Figure 3.4: Aperture design with simulated ray tracing results. The top and bottom steel apertures of the nosecone shown in (a) have diameters of 10 thousandths of an inch and a spacer steel tube aperture of 2 mm inside the aluminum spacer. The ray tracing results shown in (b) depict the X-ray beam passing through the nosecone, and is equivalent in scale to the schematic from (a). The ray tracing results in (c) show the continuation of the beam beyond the nosecone aperture to the isocenter location.

Due to the aperture design, a diverging beam forms, leading to a calculated beam diameter that is 456 μm while at the surface of the 10 cm phantom and 3 mm at the isocenter for the 70 kVp Moxtek X-ray source. By back calculating the width of the beam using the images from experimental results, Figure 3.5 shows the source linearly diverging from a focal point. This focal point uses the extrapolation of the beam width reaching a 0 mm width at the X intercept. This point is the sum of the 10 cm distance to the bottom of the nosecone, the 0.25-inch distance from the edge of the nosecone to the top of the aperture disk, and half of the thickness of the aluminum 1 inch spacer. This results in the focal point measured at 11.85 cm above the isocenter being nearly equivalent to the sum of the expected distances at 11.91 cm above the isocenter.

Since the nosecone cannot sit at exactly 10 cm in order to not rub against the tallest phantom, there is a small gap which can account for the discrepancy in distances.

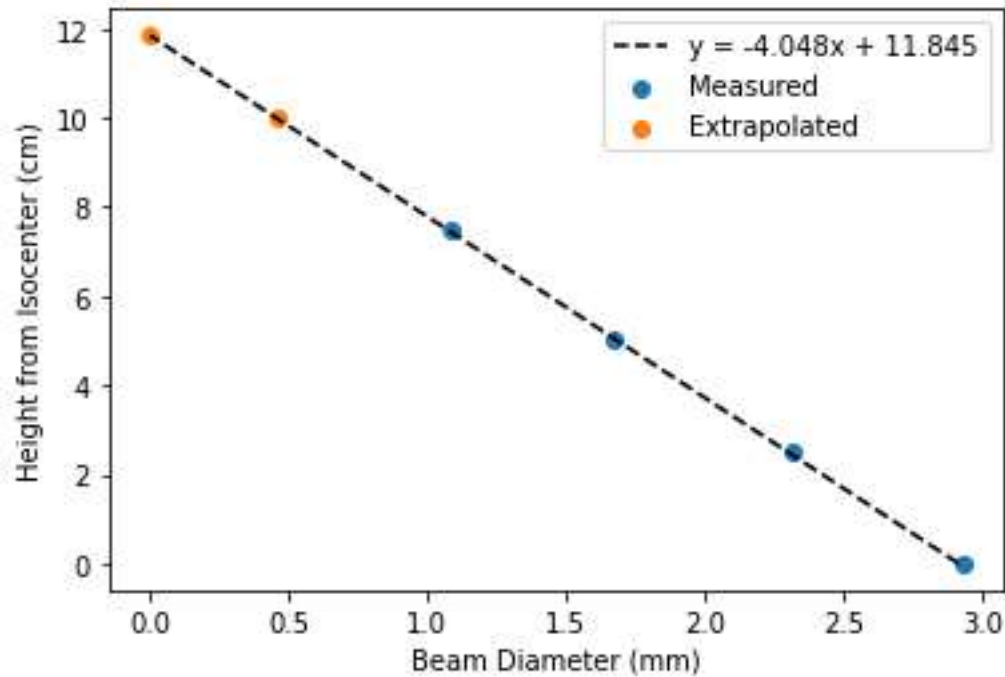


Figure 3.5: Linear fitting of the beam diameter relative to the distance from the isocenter. The fit corresponds to a cone with a focal point height equal to the y-intercept and an average widening angle of 0.705° acquired from the diameter and the distance from the isocenter.

Although knowing the overall dose of the beam is important, the detectors used in Chapter 2 show no spatially relevant information due to the width of the chemical detection method being larger than the beam itself. The dose measurements results show that as the beam moves away from the dosimeter center, the dose remains stable when the beam is fully within the range of the detector but drops as a function of overlapping area when the beam is only partially on the detector. Based on the ray tracing results, the relative intensities of the dose as a function of distance from the isocenter highly resembles a Gaussian shape.

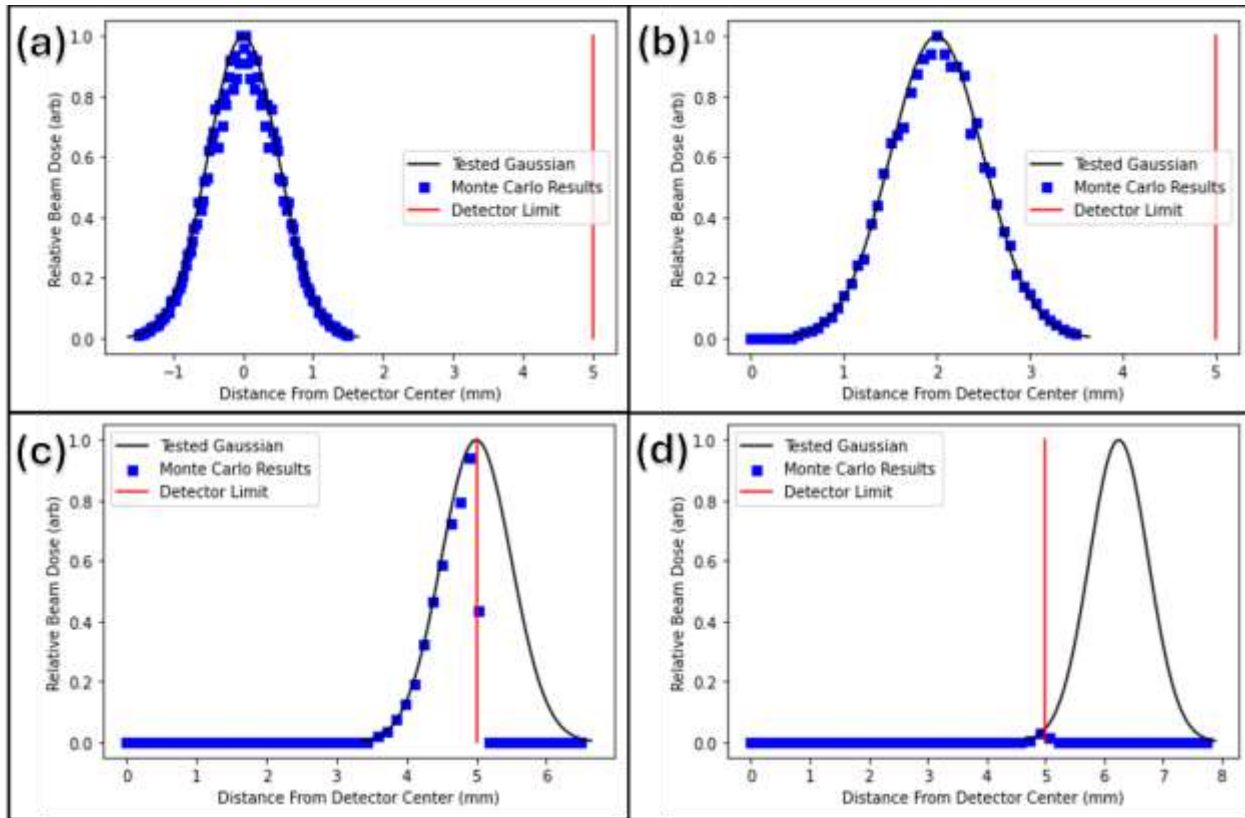


Figure 3.6: Gaussian fits used to estimate X-ray beam width. Plots in (a) and (b) show the fitted Gaussian at the initial position of the X-ray beam at the center of the detector and offset by 2 mm, respectively. The beams shown in (c) and (d) are partially inside the 5 mm range of the detector with a portion of the X-rays reaching the sensor.

To fit the dose values to a Gaussian, the Monte Carlo program uses the experimental dosimetry data and fits it at each point to different Gaussians with varying standard deviations. Figures 3.6a and b show that when the beam is completely within the radial range of the X-ray detector, all the points that are fit to the Gaussian are nonzero. When summed, both the measured and simulated beams fully inside of the detector shows normalized sums shown in Figures 3.7a and c remain stable until the edge of the beam reaches the edge of the detector as denoted by the vertical red line.

Once the overlap of the beam becomes partially outside of the radius of the detector, the points outside of the detector shown in Figures 3.6c and d become zero, leading to fewer points with nonzero values. This results in the lowering of the normalized sum shown in the “s” shaped curves of Figures 3.7a and c, flattening to near zero once the entire beam is outside the range of the detector.

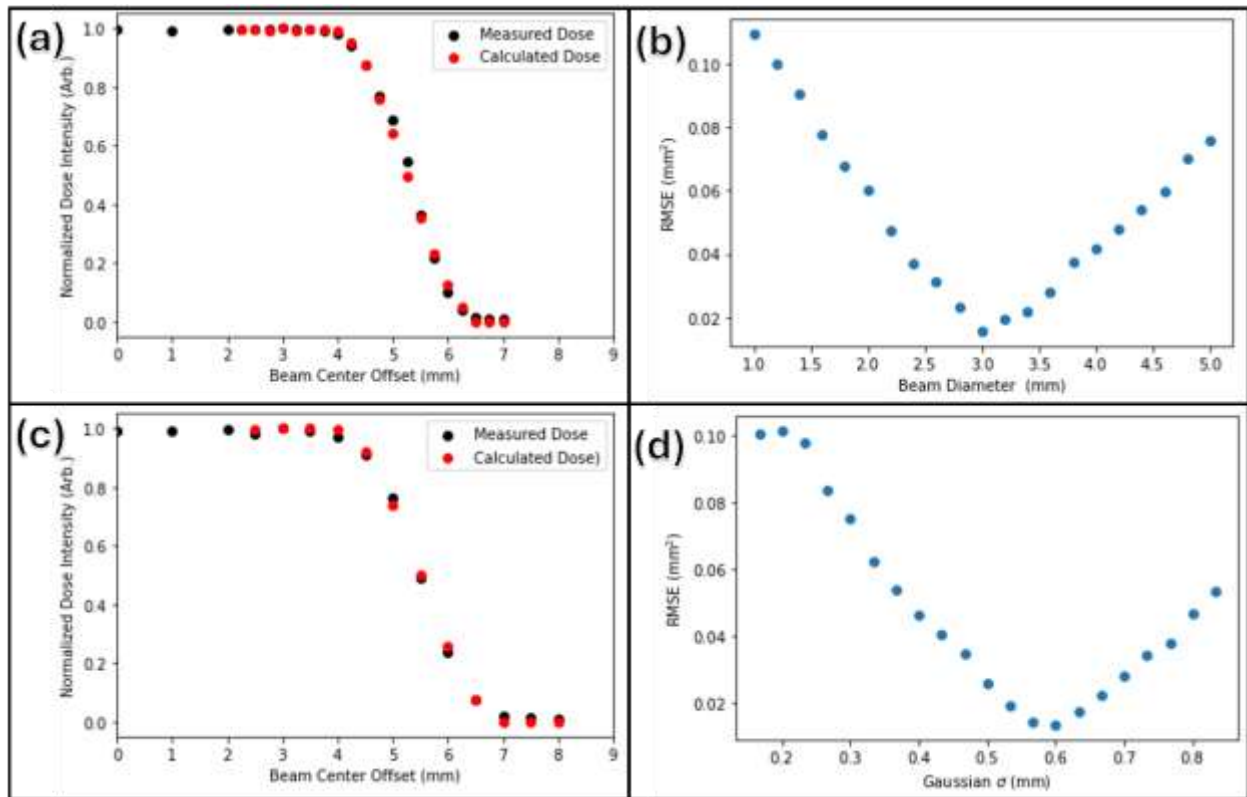


Figure 3.7: Fitting of the Accugold dosimeter approximated as a Gaussian beam. The top plots in (a) and (b) show the fitting of the unattenuated beam and the bottom plots in (c) and (d) show the fitting of the dosimetry results at each beam movement location after passing through 10 cm of a PLA phantom. The right plots in (a) and (c) show the best fitting results corresponding to the minima of the RMSE plots in (b) and (d), with standard deviations of 0.5 mm for the unattenuated beam and 0.6 mm for the beam passing through the phantom.

Using the normalized sums of the simulated Gaussians and the normalized doses from experimental results, the RMSE for the differences in these results is calculated. By varying the standard deviation of the simulated Gaussians, the σ with the lowest RMSE gives the best fit for the Gaussian beam profile. For the unattenuated beam shown in Figure 3.7b, the lowest σ is 0.5 resulting in 99.7 % of the beam residing within a diameter of 3.0 mm. When an X-ray beam is attenuated by a material, not only will there be transmitted photons in the same shape as the initial beam, but there will also be X-rays that scatter to widen the overall beam. This beam widening can be seen in Figure 3.7d showing that the RMSE minima for σ increases to 0.6 increasing the shape of the beam when passed through 10 cm of PLA to a diameter of 3.6 mm.

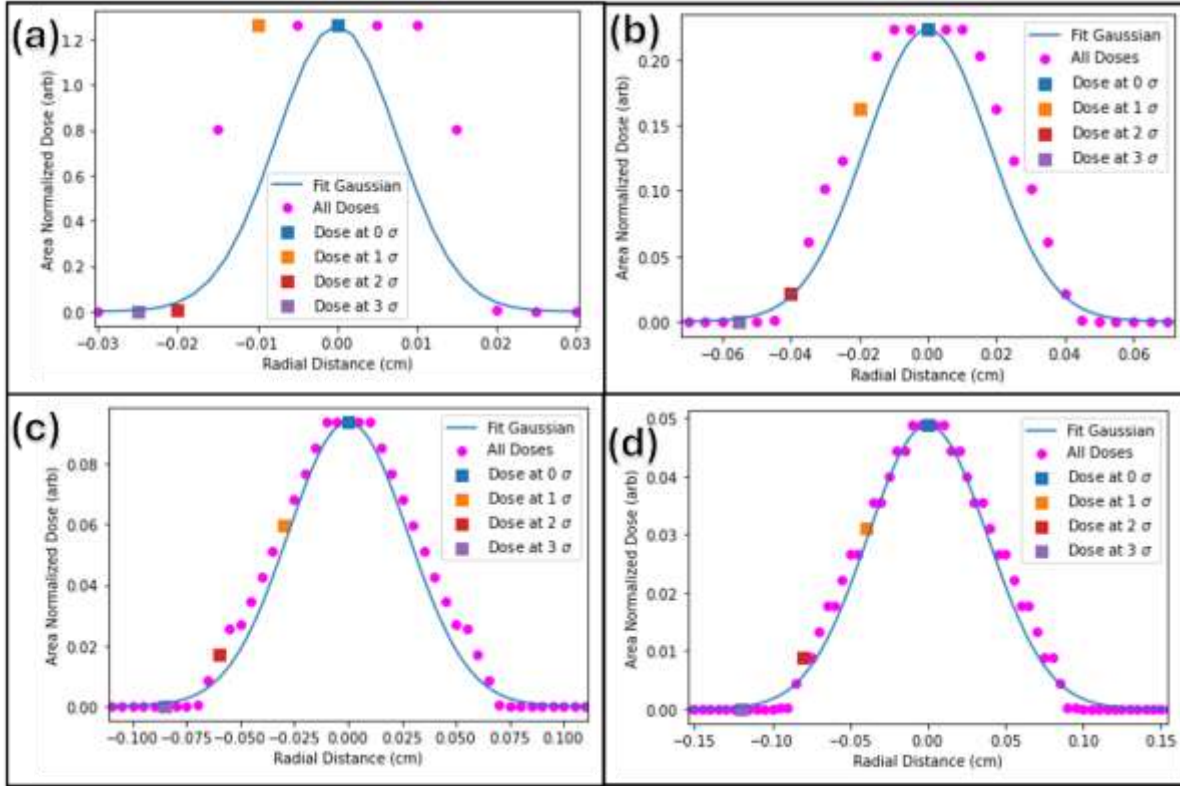


Figure 3.8: Gaussian fitting results for different heights above the isocenter. At the surface of the 10 cm phantom, the Gaussian fitting in (a) fails to accurately represent the ray tracing profile dose. The Gaussian fitting improves with a detection depth of 2.5 cm in (b) and nearly fits with a 5 cm detection depth in (c). The Gaussian accurately fits 95% of the beam width shown in (d) when detected at 7.5 cm into the phantom.

Since shape of the X-ray beam can be modeled as a Gaussian, the coverage of the beam on an X-ray surface of a phantom cannot be assumed to be equal across the diameter of the beam for the purposes of equal dosage of the surface. When beams are close to the aperture of the X-ray, the normalized dose across a diameter of the beam shown in Figure 3.8a have a near step function behavior showing near equal dose across the width of the entire beam for a detector at the surface of the phantom. As the detector is moved to different positions such as Figures 3.8b-d, the shape of the beam better resembles a Gaussian as the detector moves further

from the nosecone. This means for a phantom with a diameter of 5 cm or less, if the change the θ angle is such that the beam moves by one diameter like in Figure 3.9a, it will result in some areas getting high doses and others little to no dose. By overlapping Gaussian beams, the difference between the highest and lowest doses shown in Figures 3.9b and c decreases. When overlapping to as small of steps as possible such as the overlapping in Figure 3.9d, the difference across the irradiated surface except for the edges receives a near equal dose.

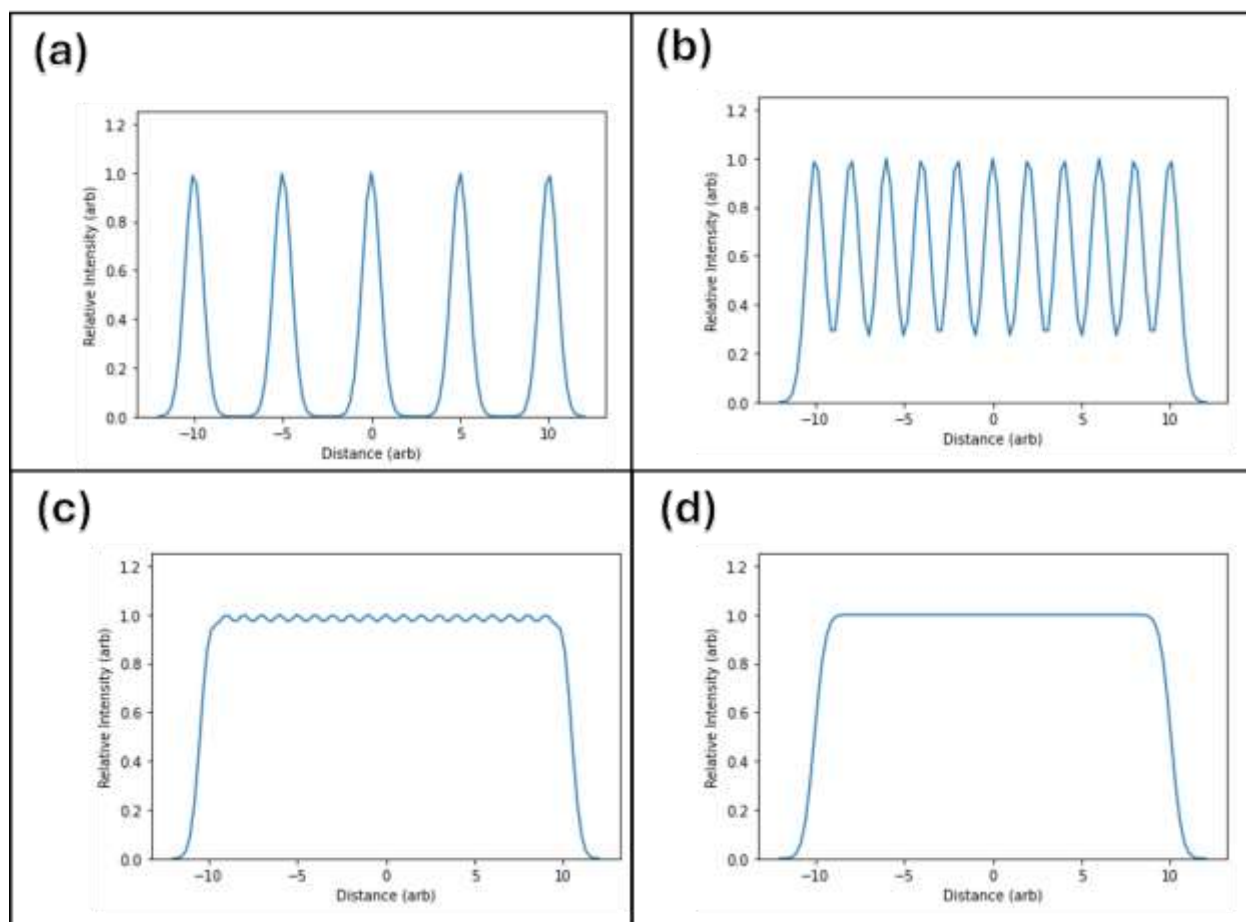


Figure 3.9: Example Gaussians showing the effect used to get uniform surface coverage from a Gaussian beam. The Gaussians in (a) are spaced so that no overlapping can occur, whereas in (b) and (c) the Gaussians overlap at intervals where there is full coverage, but the overlapping beams lead to low spots between peaks. With extreme overlapping shown in (d), the surface has near isometric coverage.

By combining the Gaussian modeling of the X-ray beam and the experimentally acquired attenuation through PLA, the ray tracing model accurately simulates the scattering of the X-rays to form a widened beam. Individual spectra are calculated for each detector point shown in Figures 3.10b and c, with the spectra near the center of the beam having more photons relative to the spectra at 3σ and beyond. The average energy of the attenuated spectra also increases. This improves the ability for the beam to show higher localized enhancement since T2PE

improves with higher X-ray energy and fewer lower energy background X-rays [25]. The simulated dose corresponding to the background dose is measured using the mass energy absorption of water and the spectra saved at each detector bin. This gives the energy deposited in simulated water phantom at the simulated detector locations.

The experimental dose rate for the beam without a phantom is 45.8 $\mu\text{Gy}/\text{second}$ and when passed through 10 cm of PLA the dose lowers to 0.59 $\mu\text{Gy}/\text{second}$ across the entire detector. By assuming the overall dose is equivalent to the integrated Gaussian over the area of the detector, the peak of the Gaussian for the beam without a phantom is used to normalize to the simulated X-ray doses. Since the relative heights of doses are set by the unattenuated normalization of the beam, the fit for the Gaussian to the normalized dose shown in Figure 3.10a is nearly identical from $\pm 2\sigma$ or 95.5% of the diameter of the beam. After calculating the scattered X-ray trajectories, measuring the dose, and normalizing the attenuated dose to the peak unattenuated dose, the peak height for the beam passing through PLA shows only a 1.8% difference between the estimated Gaussian peak and the calculated dose peak and shows a beam shape nearly identical to the simulated Gaussian.

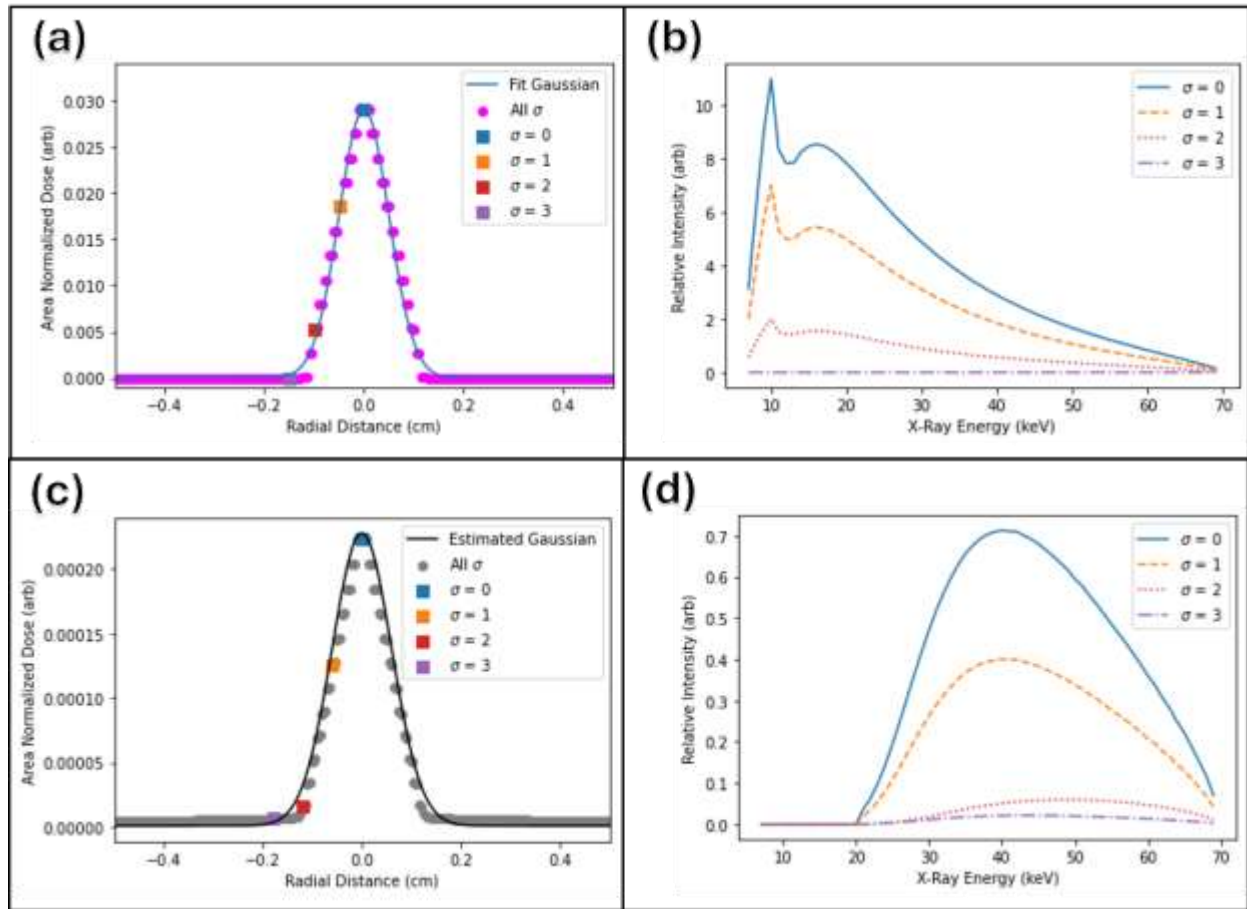


Figure 3.10: Fitting of X-ray beams both with and without passing through the PLA phantom. The unattenuated beam in (a) has a Gaussian shape with the integrated dose equivalent to the experimentally measured dose. The new beam shape in (c) shows the beam after attenuation and scattering through 10 cm of PLA and normalized to the unattenuated experimental dose from (a). The individual spectra shown in (b) and (d) were used to calculate the detector doses corresponding to the first three standard deviations of the fitting Gaussians from (a) and (c).

When using the attenuation coefficients library from the Office of Scientific and Technical Information (OSTI) for PLA and the density provided by the manufacturer, significantly less transmission of the X-rays is observed, resulting in an unexpectedly lower dose [108]. Although 3D prints with 100% infill are assumed to be solid PLA, small gaps due to imperfect deposition of the plastic decreases the actual density of the 3D printed part. By measuring the actual density

of the 3D printed phantoms using water displacement, the correct density of 1.19 g/cm^3 results in the Gaussian shown in Figure 3.10c.

After successfully simulating the dose and shape of the X-ray beam through a PLA phantom, results for different materials and input spectra show where improvements in Enhanced dose can be made. Figure 3.11a shows by using 120 kVp X-rays, the initial dose going into the phantom results in a lower skin dose due to the higher average X-ray energy. These results show that the experimental results can be improved by switching to a 120 kVp beam and following the exact same applied dose to a phantom, due to the dose deposited at the skin being lowered. The results are further improved with the 120 kVp beam due to the higher deposited dose at the isocenter shown in Figure 3.11b as well. This is likely because of the larger number of transmitted X-rays as the average energy of the spectrum is higher at 120 kVp, and higher energy X-rays favor scattering rather than being photoelectrically absorbed. This gives an overall higher dose due to the greater number of absorbing X-rays present at the isocenter. Finally, a higher dose at the isocenter is seen when comparing the same initial 70 kVp spectrum attenuating through the phantom PLA from experiments when compared to a more anatomically realistic water phantom. Although PLA and water share very similar attenuation coefficients in the 1-70 keV range, water has slightly lower attenuation and therefore higher transmission occurs in Figure 3.11b when given the same input X-ray spectrum.

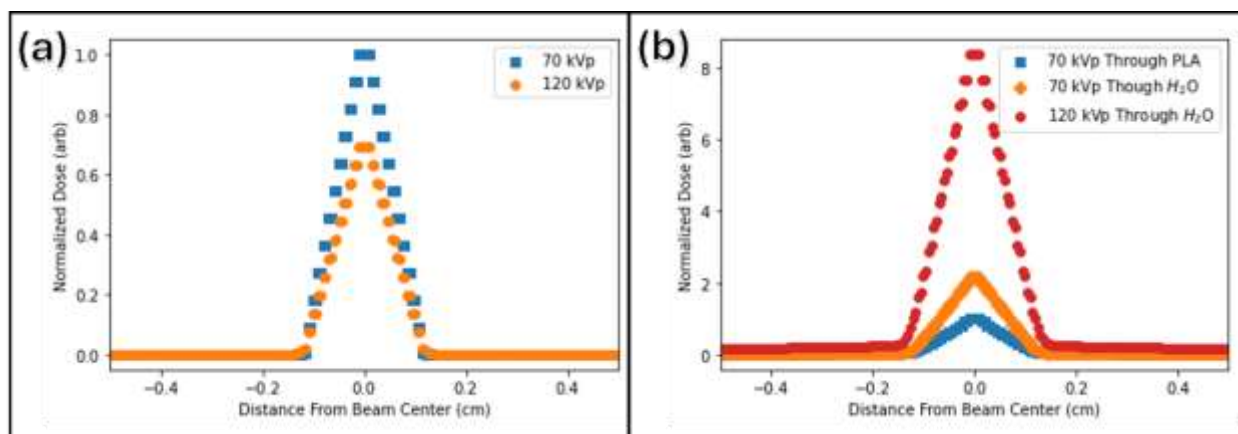


Figure 3.11: Dose measurements for simulated dose through a phantom. The simulated dose results in (a) use unfiltered X-rays at 70 kVp and 120 kVp. The simulated doses in (b) use attenuated X-rays at 70 kVp through both PLA and water, and 120 kVp through water. All doses are normalized to the experimentally derived dose through PLA at 70 kVp.

After acquiring the necessary parameters to accurately simulate an X-ray beam passing through a phantom, the spatial dose profile can be calculated. The results simulating the 70 kVp parameters from the Moxtek X-ray source at the maximum allowable θ angle of 40° shown in Figure 3.12a has an average dose of 17.9 DEU at the isocenter when normalized to the average dose at the surface. This enhancement improves to 112.9 DEU in Figure 3.12c when applying the enhancement from 0.1 wt.% AuNPs experimentally acquired in Chapter 2. The first improvement that can be made to increase the enhancement is by increasing the angle that the instrument sweeps up to 90° . This is simulated in Figures 3.12b and d to show enhancements with and without nanoparticles at 70 kVp increases to 26.2 DEU and 164.8 DEU, respectively.

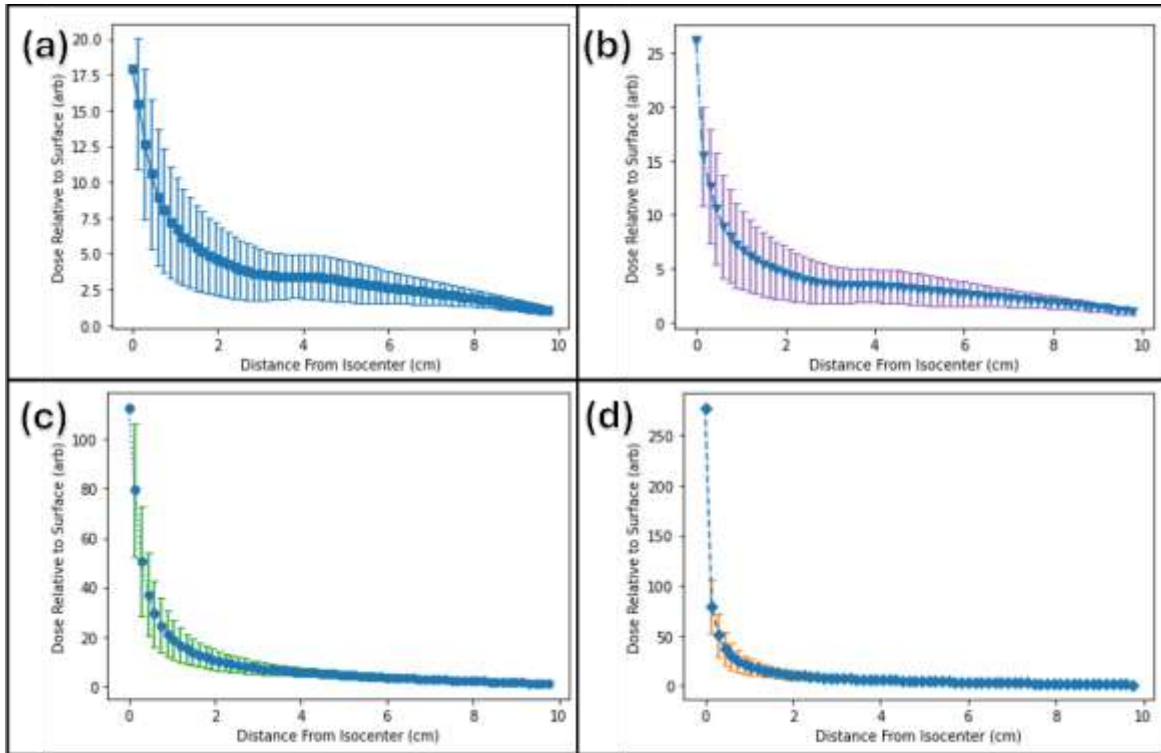


Figure 3.12: X-ray dose normalized to the surface for different scanning focusing sweep angles both with and without nanoparticle enhancement. The average doses relative to the surface dose use sweep widths of 0-40° in (a) and (c) and 0-90° for (b) and (d). Plots (a) and (b) are the baseline data using only the water phantom. Plots (c) and (d) show the enhancement with the addition of 0.1 wt.% AuNPS located within 1 beam radius from the isocenter.

When analyzing the dose maps in Figures 3.13a and b for the change in the spatial distribution of the dose, the dose near but not at the isocenter is much higher for the 40° swept calculation. This is due to the overlapping of beams being greater as they approach the isocenter. For the simulations in Figures 3.13c and d where AuNPs are included at the isocenter, the overlapping is less of an issue due to the greater difference between the enhanced isocenter dose and the area surrounding the isocenter. Due to computer memory limitations, the voxel widths in Figures 3.13 and 3.15 are limited 150 μm , which does not accurately portray the radial

dose. Because of this limitation a fixed dose across the beam width is used, but future simulations with adequate hardware can simulate with voxel widths that can accurately approximate a fit Gaussian minimizing overlap just outside the isocenter.

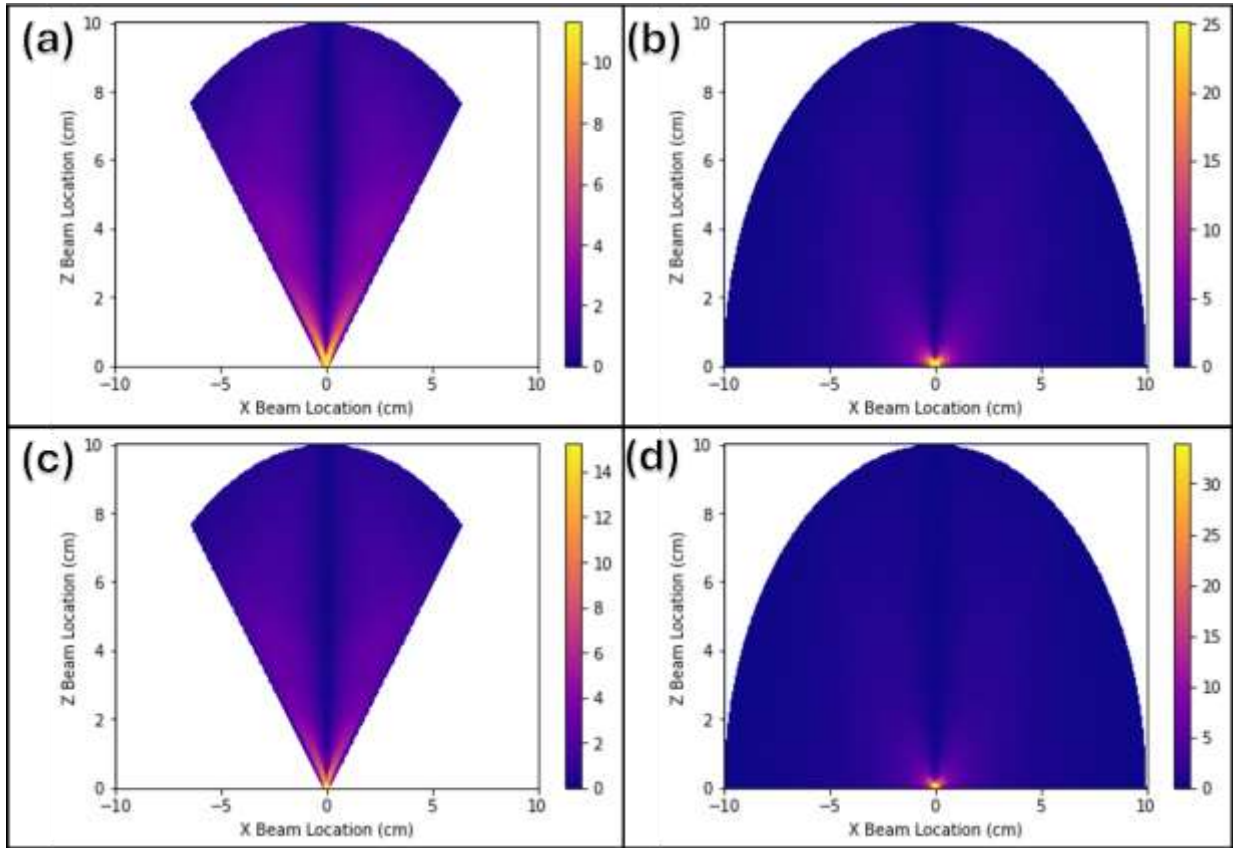


Figure 3.13: X-ray dose heatmaps for different scanning focusing sweep angles both with and without nanoparticle enhancement. Dose heatmaps using θ angle increments equal to the beam width at the surface and sweep from 0-90° for (a) and (c), and 0-40° for (b) and (d). The maps in (a) and (b) use the baseline data with only the water phantom. The maps in (c) and (d) show the enhancement with the addition of 0.1 wt.% AuNPS located within 1 beam radius from the isocenter.

The next improvement tested uses a simulated 120 kVp X-ray beam and the 90° sweep already shown to improve results. This energy is used to compare results to previously simulated

scanning focusing X-rays and uses the same maximum enhancement of 5.5 DEU when AuNPs are present [27]. By changing to an unfiltered 120 kVp beam, as already shown in Figures 3.11a and b, the surface dose is lower while the dose 10 cm inside of a material is higher than the unfiltered 70 kVp X-rays. These improvements shown in Figures 3.14a and b demonstrate a higher average normalized isocenter dose of 160.4 DEU for 120 kVp X-rays compared the average normalized dose of 26.2 DEU using 70 kVp X-rays. This is further improved when comparing the maximum experimentally acquired enhancement of 1.42 DEU using 0.1 wt.% AuNPs with 70 kVp X-rays to the 5.5 DEU enhancement measured with 7.5 wt% AuNPs at 120 kVp from previously published results [27]. By applying these enhancements, the doses at the isocenters shown in Figures 3.14c and d, have total enhancements of 277.7 DEU and 882.2 DEU for 70 kVp X-rays and 120 kVp X-rays respectively.

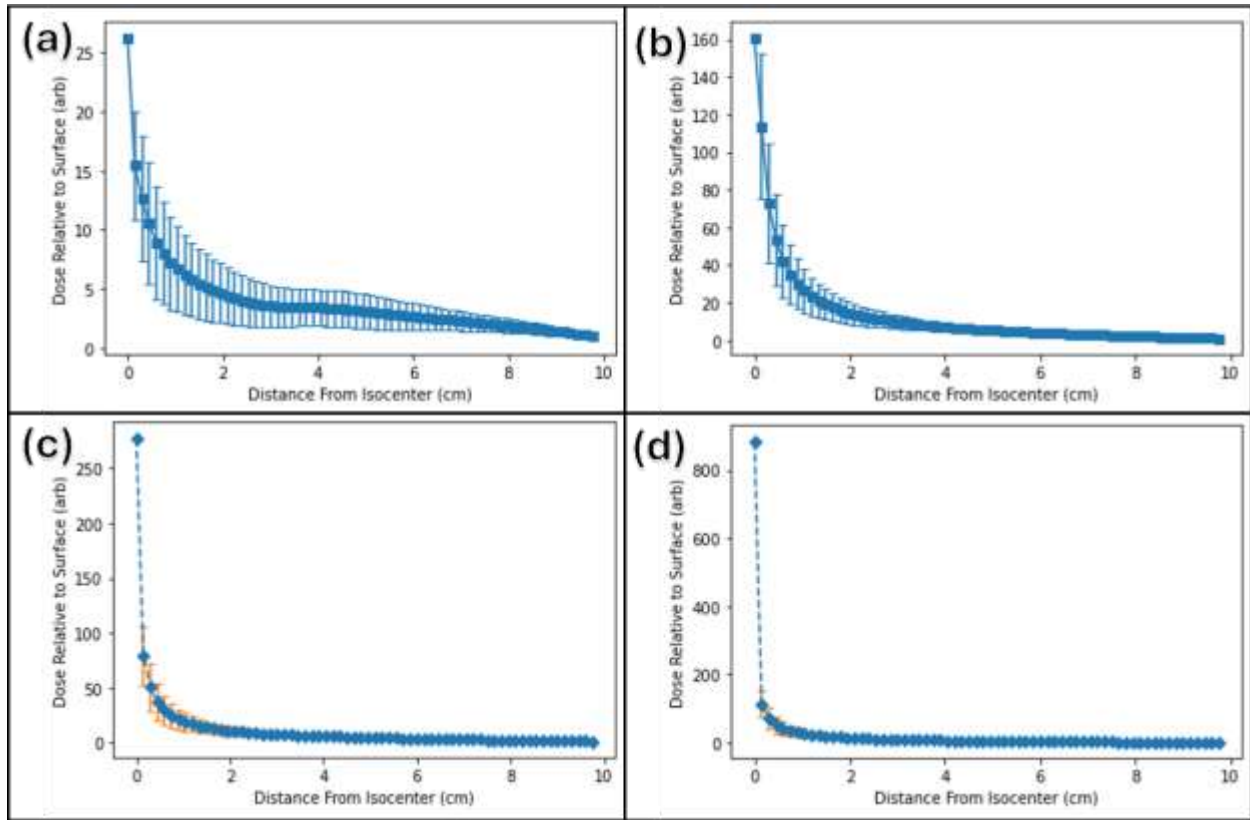


Figure 3.14: X-ray dose normalized to the surface for 70 kVp X-rays (left) and 120 kVp X-rays (right). The plots in (a) and (c) show the average doses relative to the surface dose for 70 kVp X-rays without AuNPs and with 0.1 wt.% AuNPs, respectively. The plots in (b) and (d) show the average doses for 120 kVp X-rays relative to the surface dose without AuNPs and with 7.5 wt.% AuNPs, respectively [27].

The 882.2 DEU calculated is much lower than the published 1622 DEU of enhancement published for a 1 mm wide beam through 5 cm of a plastic phantom [78]. However, the calculations presented in Figures 3.12 and 3.14 properly consider the surface dose and compensates the dose rate so that the overall dose on the surface is uniform. By iterating across small θ and ϕ for the most even dose coverage discussed in Figure 3.9, including the correct beam shape and intensity using the ray tracing discussed in Figures 3.10 and 3.11, the most accurate dose calculations can be made for guiding future experimental results.

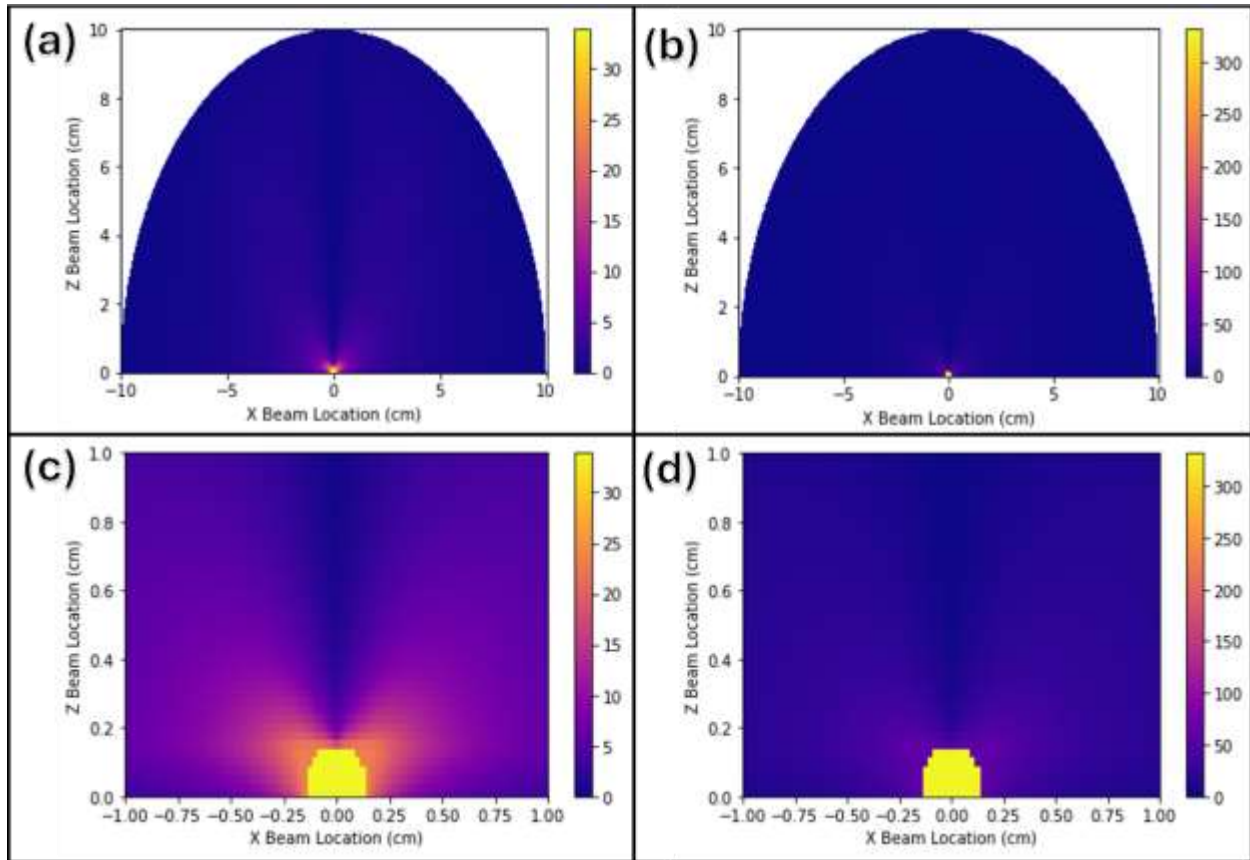


Figure 3.15: Dose heatmaps of AuNP enhancement overall (top) and zoomed in (bottom) through a water phantom. The left heatmaps in (a) and (c) show the heatmaps with the enhancement of 70 kVp X-rays using experimentally derived doses, spectra, and 0.1 wt% Au enhancement values from Chapter 2. The right heatmaps in (b) and (d) use calculated doses, spectra, and 7.5 wt.% AuNP enhancement using 120 kVp X-rays [27].

Most scanning focusing results consider maximizing the surface-to-isocenter dose as a static beam generates the highest dose within the first mm after entering a material. Future applications of the scanning focusing simulation software should be directed towards minimizing the isocenter dose to the next highest dose location. After standardizing the skin dose shown in Figures 3.15a-d, a new highest dose not at the isocenter is now less than 1 mm outside the

isocenter radius. Since the X-ray beams overlap more as they approach the isocenter, the dose accumulates the most just outside of the isocenter, creating the new highest dose location.

When calculating the enhancement relative to the dose just outside of the isocenter, the enhancement quickly drops to only 7.8 DEU for the best-case scenario of 120 kVp and 7.5 wt.% AuNPs. This phenomenon was not discussed in previous works since no effort was made to equalize surface dose and assumed an even dose across the width of the X-ray beam while also calculating enhancement based on an average dose across the surface [78]. Further calculations using the full capabilities of the algorithm should be done to strike a balance between surface dose and the dose surrounding the isocenter to minimize the difference in dose between the isocenter and surrounding material.

3.4 Conclusion:

An algorithm to simulate an X-ray beam was successfully developed using ray tracing. The algorithm shows excellent fitting of X-ray dosimetry results of a Gaussian from $\pm 2\sigma$ when fit to a beam at 10 cm from X-ray aperture. Using the beam shape and intensity algorithm, the dose inside of a material can be calculated for a beam moving in 3D space and is verified through radial symmetry. Although the highest calculated dose inside of a water phantom from the algorithm does not exceed previously published findings, the improvements based on beam shape and surface dose show that the assumptions made in previous work led to inaccuracies in their results [78]. This algorithm results in a maximum surface dose to isocenter dose enhancement of 882.2 DEU, but also results in a complication with using the surface dose to calculate overall enhancement. The high dose just outside the isocenter lowers the improvements that adding

AuNPs generates by two orders of magnitude. Future work should use this algorithm to focus on minimizing the next highest dose regardless of location with respect to the dose at the isocenter to remove the discovered deleterious effect.

4.1 Introduction:

Commercially available solid state NMR probes are designed primarily for high speed and high field applications. While these devices are able to acquire spectra precisely and with high resolution, the cost of equipment is limited to institutions with large budgets [109,110]. Due to the high initial investment [111] and upkeep cost of this equipment [112], focus has been directed towards upgrading existing lower field magnets with 3D printed stators [113,114]. 3D printed stators can be printed quickly, in mass, and for the unit cost of only a few dollars. With a 3D printed probe, a damaged stator can be printed and deployed within a few hours and at a fraction of the replacement costs. These 3D printed stators and rotors are offered as an alternative to the commercially available products and thus imitate the design to accommodate seamless integration into existing systems to reliably replace damaged high field MAS stators [115,116]. This gives researchers the ability to quickly and cheaply sustain solid state capabilities while minimizing downtime.

3D printers are able to build complex geometries with unique materials [117–120] at extreme resolutions [121–123], and high spinning speeds [124–126]. With these recent improvements, printers can create final products equal to or better than injection molding and comparable to conventional machining [127–129]. Since multiple devices can be printed simultaneously, minor edits to the same device can be tested in quick succession for design optimization. This ability to quickly and cheaply design, print, and test devices in-house, allows for extremely fast prototyping and the ability to design 3D printed NMR adaptors [130,131] and NMR related tools [132–134]. By using materials such as polytetrafluoroethylene (PTFE) or

ceramics, stators and rotors can even be created without significant unwanted background NMR signals [135–138].

Lower field instruments underperform their higher field counterparts due to permanent magnets having higher inhomogeneity [139] and lower magnetic field strength [140]. This makes benchtops insufficient for higher resolution ^1H NMR applications, but benchtop systems can still perform sufficiently when measuring simple chemical shifts and even measure expected anisotropy [141,142].

While lowering the cost of expensive high field instruments is important, focus has been directed towards improving existing benchtop NMR capabilities for price and portability. Price has drastically reduced from the low field magnets first used in NMR through advancements in the cost and quality of permanent magnet arrays [143,144] and through development of low cost controllers with open source access [145,146]. These devices provide a low cost alternative for student use [147], pollutant monitoring [148], and plastic degradation [149].

Focus has also been directed towards miniaturization of NMR instruments. Simple designs for benchtop systems have been created using strong, yet small permanent [150], or using the magnetic field of the earth [151], and controlled using a single chip circuit [152]. Portability has seen new field applications for NMRs such as industrial quality control [153], automated classification of food [154], and drug delivery research [155]. These devices vary wildly in terms of size, shape, and form factor requiring specialized designs for different instruments. The use of 3D printing allows for rapid prototyping and adaptation into these unique form factors.

4.2 Materials and Methods:

Stator Assembly Design

All 3D models were designed using Blender v3.4 and 4.0 (Blender Foundation, Amsterdam, Netherlands) and sliced using Chitubox v1.9.4 (Chitu Systems, Shenzhen, CN). Designs were printed with an Anycubic Photon SQ using Anycubic SLA resin (Anycubic, Shenzhen, CN). Final designs for all stators and angle adjustment housings included scaffolding for the hose barbs for devices to be printed directly on the print bed without external supports. Attempts were made for scaffoldless rotors, but due to initial layers having long exposure times and therefore light bleed passing into adjacent pixels, scaffolding was required to maintain rotor wall tolerances.

Two full sets of single spinning rotors, stators, coilforms, and angle adjustment housings are typically printed simultaneously in roughly 30 minutes. When printing only stators, a single build plate could hold 12 single stators and would scale down with multiple rotor spinners. However, when printing only rotors, the small footprint allowed for printing approximately 100 rotors on one build plate. Post processing of the 3D printed parts required soaking in 99% isopropyl alcohol and blowing high-pressure air on the surface and hose barbs to dry the surface and to remove uncured resin from the air ducts. This cleaning was repeated 3-6 times or until the surface showed no uncured resin on the surface of the parts. Once dried, parts were set under direct sunlight for a minimum of 15 minutes to fully cure.

The primary physical constraint of the AI-60 (4IR Solutions, Or Akiva, IL) is the available sample probe depth of 15 mm. The rotor was designed for the 4 mm diameter form factor used commonly in commercial stators. Due to the depth constraint, a standard 18 mm length rotor

could not fit within the probe body once rotated to the magic angle while still having room for air ducts. Since a standard rotor was not available, a 3D printed 4 mm diameter rotor was designed to an outer length of 15.5 mm after maximizing the available space for the drive air, a coliform, and air bearing ducts.

Rotor and Accessory Design

The sample rotor dimensions had an inner diameter of 3 mm and a length of 11.5 mm. The rotors designed yielded a total inner volume of 81.3 μL and an active volume of approximately 32 μL within the 4.5 mm long coil. Samples were prepared by pouring powdered bromide salts into a 3D printed funnel then tamping with a 3D printed plunger until the desired mass in the rotor was reached. The sample was then closed by adding 10-15 mg of UV resin and left in direct sunlight until cured.

The impeller designs used to drive the rotors were designed as one piece for sample holders and used a modified drive cap from Xu et al. 2021 [113]. Other rotor designs were made with the same specifications and process but use other published 3D printable drive caps [156,157]. These were not used for samples, but validated that different rotor heads were capable of rotational frequencies equivalent the rotor design used for samples.

A removable coil form was designed to allow for coil swapping and removal of the stator from the probe body without any changes to the circuitry. All coils had 10 turns with 27 AWG copper wire at a diameter of 5.5 mm and were held together to the coil form using UV cured resin. For multiple sample coliforms, all coils were wound in the same direction to a 10% maximum relative percent difference in measured inductance. All coils were soldered into an LC

tank circuit. When multiple coils were used, the inductors were in parallel with the tuning capacitor which was in series with a matching capacitor. The coil holder was aligned by a groove in the stator and locked in place using brass M2 screws for easy alignment.

Device Validation

Speed control of the rotor was measured by painting half of the rotor black and the other half with a reflective paint. The stator was designed with two 1 mm holes for fiber optic cables at the top opening. A red LED was epoxied to the end of one of the fiber optic cables and the other was glued to a 3D printed threaded cover for a Thorlabs APD410A2. The APD signal was connected to a Tektronix TDS724D oscilloscope and the voltage response from the reflective paint was used to acquire a spinning frequency. An alternative method for measuring spinning speed was done by using the Spectroid spectrum analyzer app. The audible frequency of the rotor was compared to both the APD and observed side bands to validate the accuracy of the audible frequency and accompanying harmonic frequencies to the observed speed.

Angle adjustment was achieved using a 3D printed housing that allowed the stator to freely rotate and assembled as shown in Figure 4.1d. The housing held the stator 0.5 mm above the probe body bottom and allowed for the adjustment of the angle for $\pm 2.5^\circ$ with an M3 screw. The angle was adjusted by 0.2° increments and the ratio of the center peak to first order peak was recorded. Although the first order peak is known to be less sensitive to the magic angle adjustment, the second order peak was more impacted by the noise compared to the first order peak [158].

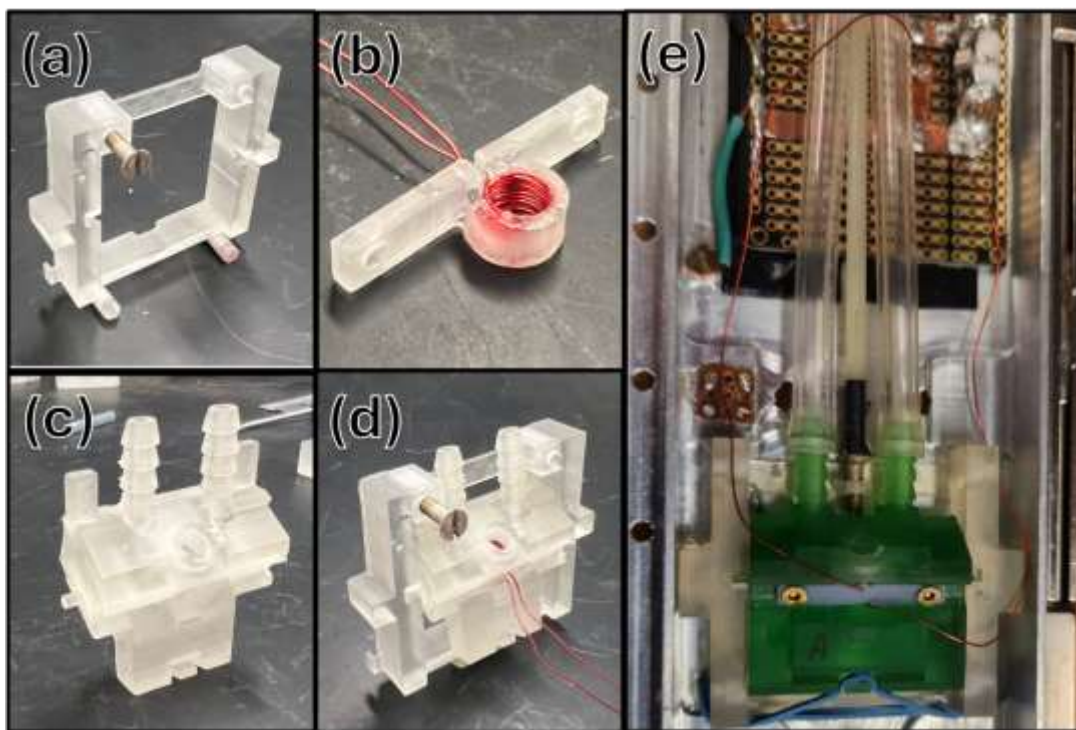


Figure 4.1: Images of the 3D printed stator assembly as separate components and installed together. Images (a-d) show the outer rotation fixture with adjustment screw, the self-aligning coilform, the stator body, and a fully assembled stator, respectively. The image (f) depicts the prototype stator assembled inside the AI-60 probe body with circuitry and air hoses attached.

The single stator design had two air bearing channels, each with 12 cylindrical $250\ \mu\text{m}$ diameter exit holes and one drive channel with 8 angled $500\ \mu\text{m}$ exit holes. Due to size constraints on the duct width, the drive inlets were curved to exit lower than what straight pipes would allow for, which increased the available rotor length. After validating results for a single stator, the design was modified into a unit cell stator that minimized the size to be copied, mirrored, and joined together to create 3D printable stators with multiple rotor capabilities. For the odd numbered stators, the cells were all the same chirality giving all rotors the same direction of rotation. The even numbered spinners were designed by mirroring the unit cell to have opposite spinning rotors across the mirror plane.

4.3 Results and Discussion:

The sample spinning frequency validation from the NMR spectra uses the distance between side bands in Figure 4.2, this difference is equal to the actual sample rotational frequency and is consistent with the audio and oscilloscope frequencies. When connected to the house compressed air regulated down to 45 PSI for the drive air pressure and 60 PSI for the gasket air pressure, the single rotor is reliably capable of accomplishing a 7 kHz rotational frequency without damage to the rotor or stator. Speed is controlled by changing the pressure of both the drive and gasket air pressure and the stable range of speeds is between 2 and 7 kHz. While lower speeds are possible, the frequency stability drifts beyond the ± 10 Hz per measurement seen at higher spinning frequencies. This decreased stability is shown in Figure 4.2a since the 1 kHz peaks results in side band peaks the merge into the main peak and decrease in intensity faster when compared to the higher frequency sideband peaks from Figures 4.2b-d. Even though instability in the rotational frequency is concerning, the practical concern is overstated since samples are ideally spun at the highest possible frequency to remove the sidebands from the region of interest.

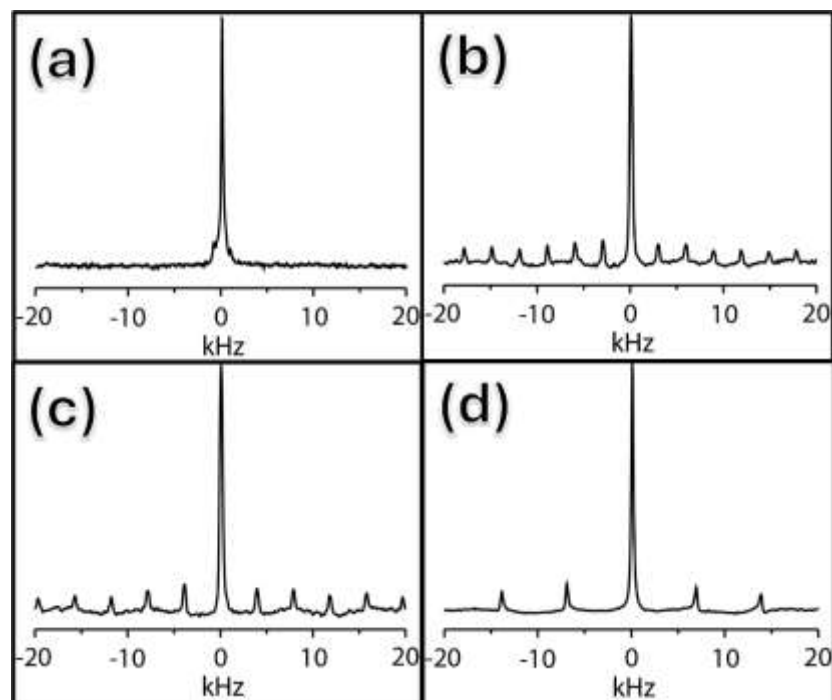


Figure 4.2: ^{79}Br spectra showing side bands at separation distances equal to the spinning speeds. The spectra (a-d) show spinning speeds of 1 kHz, 3 kHz, 4 kHz, and the maximum of 7 kHz, respectively.

The sideband peak heights can also be used to adjust the stator orientation to the magic angle. By turning the adjustment screw and taking a measurement for KBr at a fixed spinning frequency, an increase in the side band peak height was seen until reaching the minimum ratio shown in Figure 4.3a, corresponding to the magic angle. When the angle was set either below or above the magic angle, a noticeable decrease in sideband peak height in Figures 4.3b and d was seen when compared to the magic angle side band peaks in Figure 4.3c. When plotting the ratio of the first side band peak compared to the fundamental peak as shown in Figure 4.3a, the curve showed a local minimum which was used to determine the magic angle. The asymmetrical shape of the curve was likely due to contact point of the angle adjustment screw having changed. When flat or above the magic angle, the contact point was set by the arm and was located at the

adjustment screw center. Once past the magic angle, the screw contact point was changed from the center of the screw to the closest edge of the screw. This decreased the fulcrum length and thus slightly increased the rate of angle adjustment given an equivalent displacement of the screw. Once the results for a correctly angle adjusted sample were determined, future stators were directly attached to the probe body since the sideband ratios were equivalent to the adjustable stator set at the magic angle.

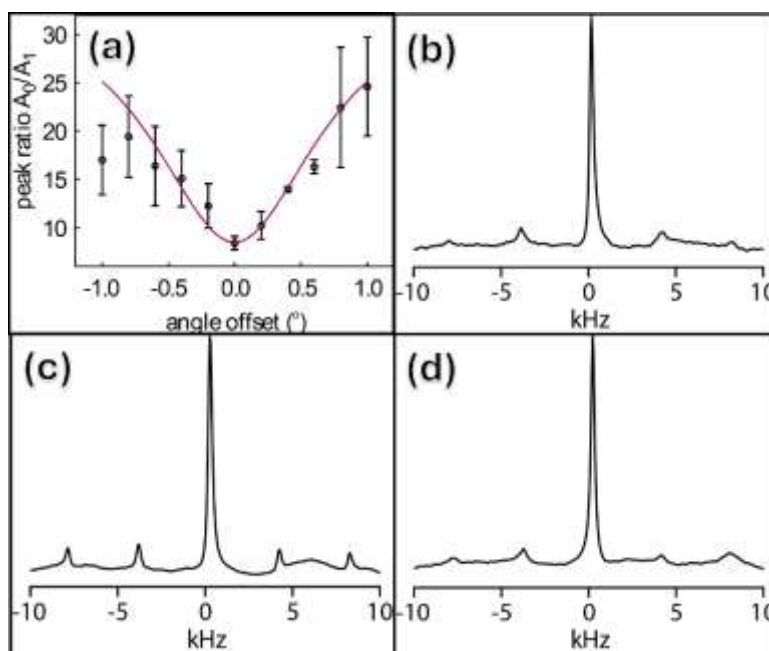


Figure 4.3: Side band peak plots used to adjust to the magic angle. The plot in (a) shows the peak height ratio with respect to the stator angle compared to the static magnetic field from the spectra of powdered KBr spinning at 4 kHz. The plots in (b-d) show the individual spectra for angle adjustments below, at, and past the magic angle, respectively.

After proving the capability of the single 3D printed rotor, significant doubts about the practical applications arose due to the small sample volume and the low signal to noise ratio. The low and small sample volume limited the sensitivity of the instrument and made it so that

measurements were only effective for the bromide salts tested and other narrow use cases. Although the amount of sample cannot be increased for the single rotor due to the size constraints of the AI-60 probe body, there is ample space adjacent to the MAS probe. With that in mind, a double rotor design doubles the sample volume and thus increases the signal. The double rotor resembles a duplicated stator assembly and allows for the simultaneous measurement of two samples.

The initial test for improving sensitivity was accomplished with two KBr samples which doubled the sample volume and therefore should increase the signal from the instrument proportionally. Since the signals are at the same frequency, signal from the two rotors combine to form signal which approximates the sum of the individual sample signals as shown in Figures 4.4a-c. With the samples capable of spinning at different frequencies being set by the regulator pressure, it is also possible to monitor the spinning speeds directly from the NMR using the spectrum. When measuring two samples simultaneously but at different speeds, the individual side band peak locations from Figures 4.4a and b both show up in the double sample spectra as shown in Figure 4.4c. Figures 4.4d-f show the same spectra for NaBr. Comparison of the KBr and NaBr spectra reveal about a 50 PPM chemical shift difference.

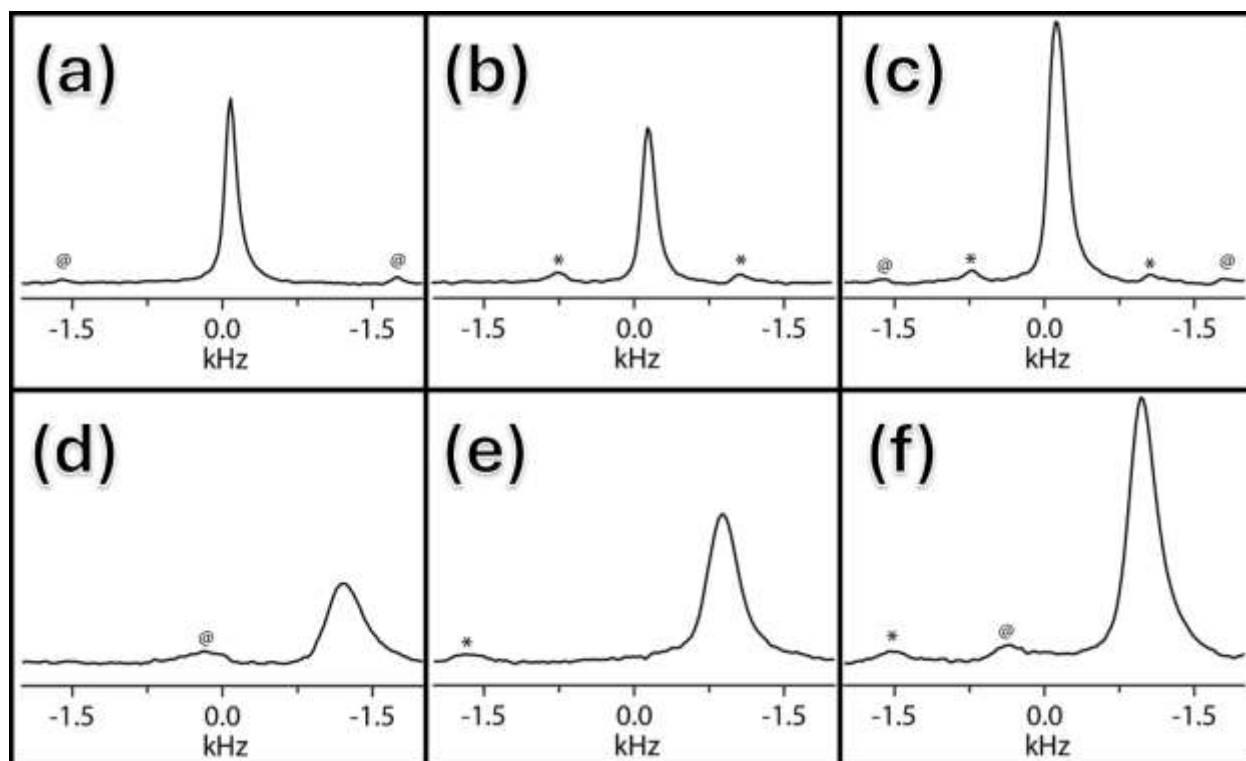


Figure 4.4: Double rotor measurements of pure KBr and NaBr samples. The spectra shown in (a-c) correspond to a sample of KBr in the left rotor, right rotor, and both rotors, respectively. The @ and * label the spinning sidebands. The plots in (d-f) show the spectra that correspond to the same sample loading configuration for NaBr.

After demonstrating that the double stator can run multiple samples simultaneously with signal proportional to sample mass, mixing and matching of the two types of samples was considered. The double sample rotors were tested with pure KBr, pure NaBr and a combined sample of 50:50 weight ratio of both KBr and NaBr. As previously stated, when placing the same sample in both coils, the peak height in Figures 4.4c and f corresponds to the sum of the individual rotor signals. When placing KBr in one coil and NaBr in the other coil, two distinct peaks form with a separation distance of approximately 800 Hz seen in Figures 4.5a and b corresponding to the expected separation for individual samples. The results in Figure 4.5d show similar signal

strength and peak separation when measuring two rotors containing 50:50 weight ratio NaBr and KBr. The combined sample rotors in Figure 4.5c continue to show similar results from having one pure sample in each rotor shown in Figure 4.5c. However, separating the samples into different rotors gives the added benefits of speed control for the individual samples. Regardless of sample type, individual rotors show no dependence on whether the sample is in the left or right coil for all three sample types when the magnet was shimmed prior to analysis.

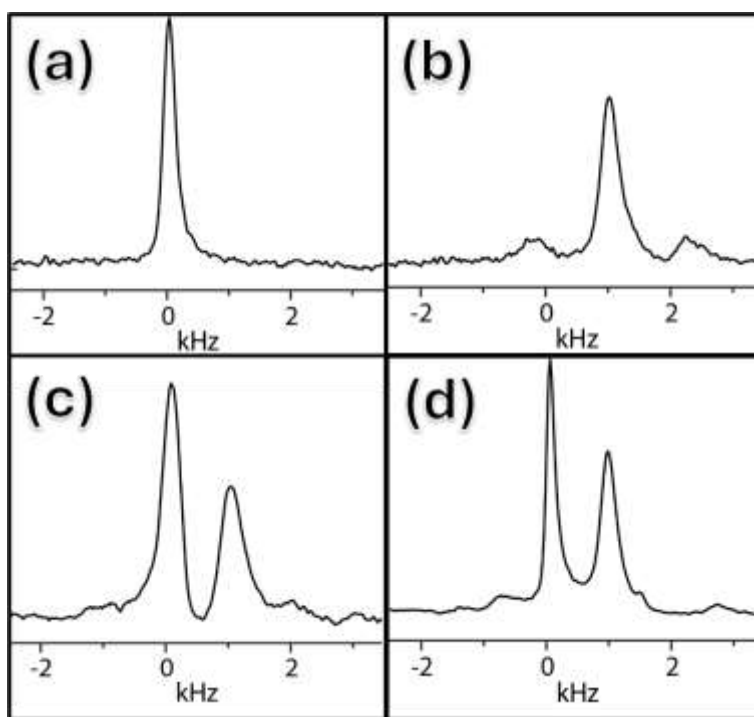


Figure 4.5: Multiple rotor spectra for combinations of KBr and NaBr using the double rotor setup. The multiple rotor spectra in (a-c) use a single rotor of KBr, a single rotor of NaBr, and a 50:50 mixture by weight of NaBr and KBr in two rotors, respectively. The plot in (d) shows one rotor containing KBr and a second rotor containing NaBr spun and measured simultaneously.

Once the multiple rotor sensitivity improvements were verified, a triple sample stator was designed and tested using KBr for all seven possible configurations of samples. Single rotors show

the lowest signals and yield similar peak intensity when moving the same sample into different stator locations shown in Figures 4.6a-c. When two rotors are placed in the three possible configurations, peak signal again corresponds to the sum of the individual sample peaks shown in Figures 4.6d-f. These double rotor results show the same trends from Figures 4.6d-f as previously validated in Figure 4.4c.

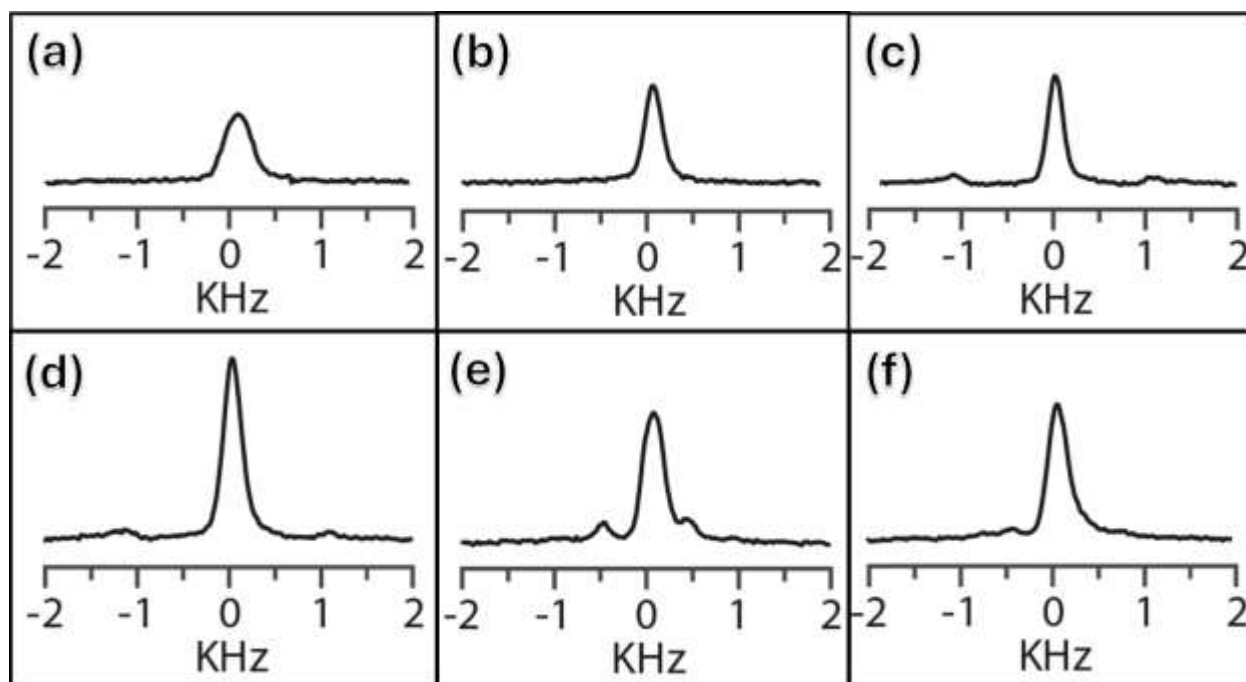


Figure 4.6: Triple rotor assembly results for one and two rotor inputs. The spectra in (a-c) show single rotor inputs in the left, center, and right rotor locations in the stator, respectively. The spectra in (d-e) show the combinations of two rotor inputs representing the left + right, center + right, and center + left rotor combinations in the stator, respectively.

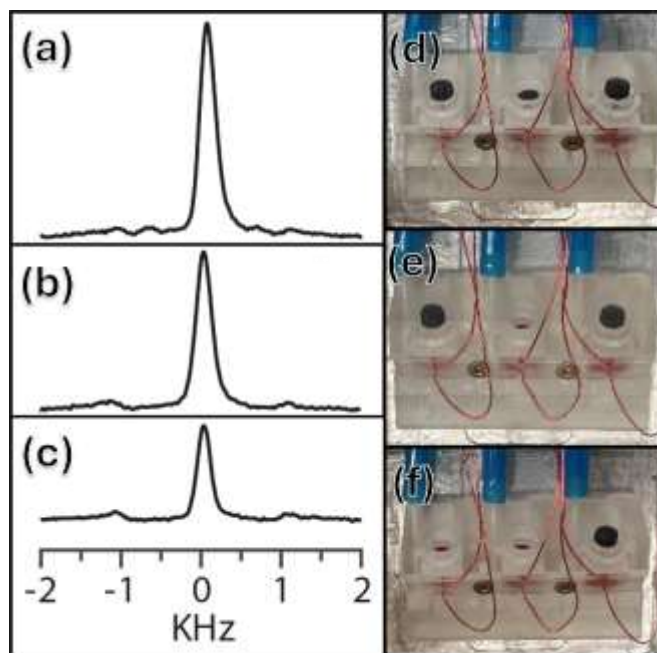


Figure 4.7: Multiple rotor spectra results for the triple rotor configuration. The spectra in (a-c) show rotors containing KBr in the triple, double, and single configurations, respectively. The images of the triple spinner configurations in (d-f) depict the sample locations for three rotors, two rotors, and a single rotor, respectively. Triple and double rotor signals corresponded to the approximate sum of individual rotor signals.

The final analysis needed was to confirm that three samples continued to follow the same proportional increase in signal. Figure 4.7a shows the increase in the number of samples is directly proportional to the peak signal even for three rotors. Given the available space inside the AI-60 probe, further designs were made with the proportional signal principle in mind. With a stator unit cell width of 13.5 mm, up to 4 stators fit across the length of the 54 mm wide probe. Since the magic angle is in reference to the field coming through the flat side of the probe, a total of 8 rotors can be packed in the available space by mirroring the stator as shown in Figure 4.8a.

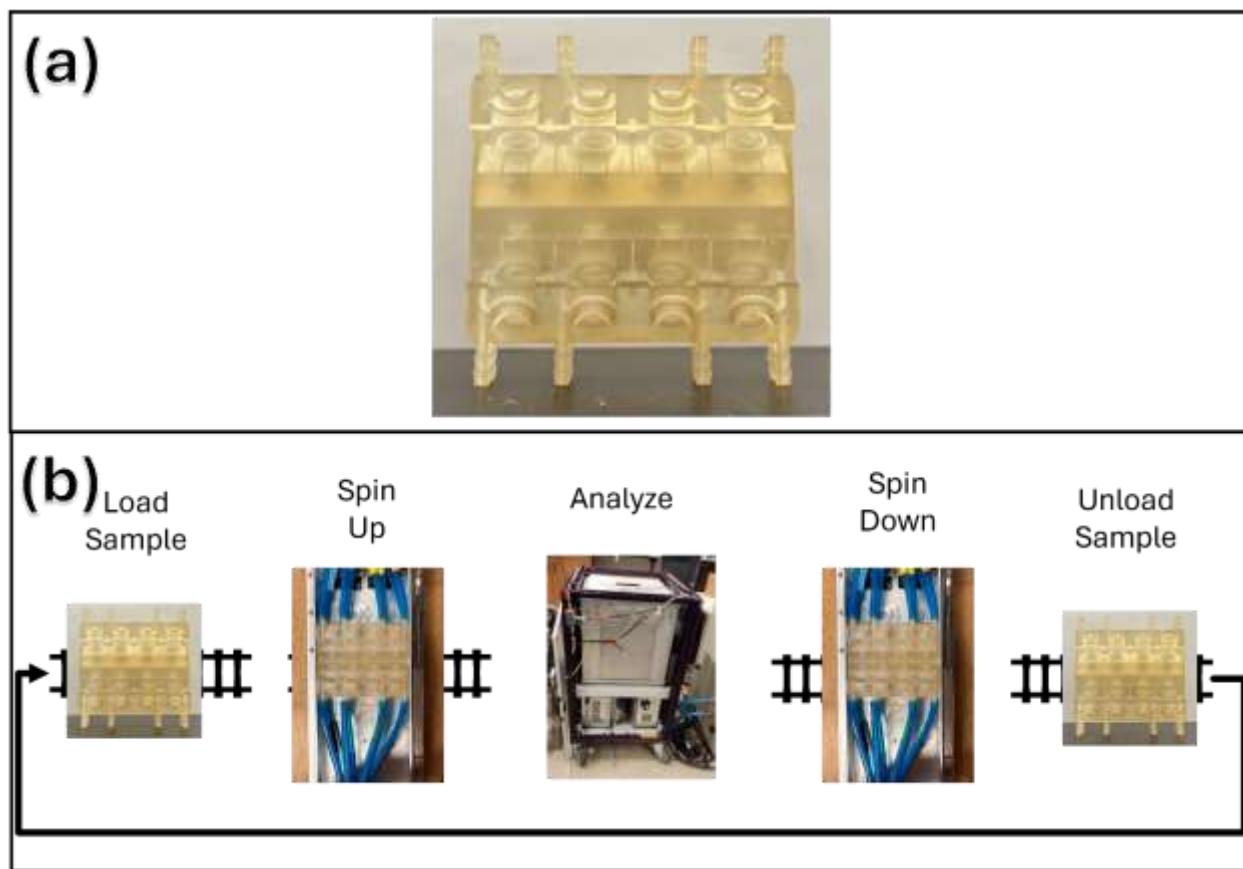


Figure 4.8: Schematic for incipient analysis workflow using an 8-spinner stator assembly. The image in (a) shows the stator capable of holding up to 8 rotors at a time. The workflow shown in (b) shows a possible way to automate the creation and detection of signals from multiple samples in a real process environment. The first step uses an autosampler to deposit prepared samples into the individual stator cells. Next, the samples are spun to the working speed of multiple kHz. Once the desired spinning speed is reached, the stator is transferred into the NMR instrument for signal detection. After signal acquisition, the samples are removed from the NMR instrument and sent into a controlled spin down configuration. Finally, the samples can be removed from the stator using an autosampler and the process is repeated for the next set of samples.

Table 4.1: Input costs for a complete single rotor MAS probe assembly. Prices are based on the actual costs incurred during the research and development of the device. The cost increase for multiple rotor stators is only due to an increase in resin volume needed with an approximate increase in cost of \$0.10 per added rotor to the stator.

Product	Cost (USD)	100 Unit Cost (USD)	Price Per Unit (USD)
99% Isopropyl	\$17.5 per 4 L	\$17.5	\$0.18
Rinsing Bucket	\$5.59	\$5.59	\$0.06
Resin	\$17.5 per kg	\$29.58	\$0.30
Anycubic Photon SQ	\$180	\$180	\$1.80
Electricity	\$0.53 / kWh	\$1.27	\$0.01
Total		\$233.94	\$2.34

With such an improvement in sensitivity, inspection of price to performance was conducted. The upfront costs of 3D printing have significantly gone down in recent years with entry level resin printers costing less than \$200. Given the availability and adequate specifications when using the Anycubic Photon or comparable printers, high quality parts can be made due to the low startup cost. While a single part may take an initial investment in a printer and cleaning supplies, these fixed costs quickly become irrelevant when designing on the order of hundreds of prototypes or during a production run. With individual parts taking only grams of resin to print, it becomes possible to iterate many multiple design parameters simultaneously for only a few dollars. For the single sample stator design, Table 4.1 shows that a production run cost of 100 stators reached a price per unit of \$2.34 which is a price unmatched by conventional machining.

The fact that these parts were printed at such a low cost for the commendable sensitivity previously discussed, shows a price to performance that is exemplary.

4.4 Conclusion:

We have demonstrated simultaneous measurement of solid bromide salts at low field using 3D printed MAS stators and rotors. Although only a 3-stator assembly was tested, the probe body for an AI-60 has the capability to fit at least 8 MAS stator unit cells. This aids in incipient analysis through simultaneous measurement of a standard and a set of unknowns using missing or extraneous peaks. This creates a lower cost alternative for pharmaceutical quality control testing and could be automated to drive costs down even further [159].

By exploring unprotonated resins or 3D printable ceramics, further use cases for ^1H can be validated. These more durable materials also open the door for further testing on increased rotational frequencies and longer lasting rotors. While 7 kHz is sufficient for resolving the two bromide peaks, having higher speeds would allow for resolution of more complex powder patterns. Given the size and portability of a low field system like the AI-60, further uses could be applied for solid state analysis for diffusion of fluids inside sedimentary rocks [160].

Finally, this design allows for the alteration for uses in other benchtop systems. By creating a simple unit cell design, others can alter the design for different rotor sizes and probe bodies. Due to the low cost and exceptional price to performance, design modifications increase accessibility for underprivileged institutions unable to afford high field magnets.

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