Clinical Applications and Feasibility of Proton CT and Proton Radiography

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Proton therapy is a form of radiation treatment for cancer that utilizes the Bragg peak to create conformal high dose regions around the tumor volume. However, the use of x-ray computed tomography (CT) and x-ray radiography for treatment planning and pre-treatment quality assurance procedures improves the achievable effectiveness of proton treatment plans (using proton CT) and the pretreatment verification (using proton radiography). Errors in the conversion from x-ray Hounsfield units (HU) to proton relative stopping powers (RSP) leads to errors in the predicted proton range. To account for the errors, 3.5% margins are included in the treatment plan. This means that there are healthy tissues surrounding the tumor volume that receive high levels of dose and could potentially incur serious toxicities. Furthermore, after the patient initially receives a CT, there is no method of detecting anatomical changes that could lead to proton range errors. Proton CT and proton radiography are low dose alternatives for x-ray imaging that will lead to safer and more effective treatments. Proton CT removes the need for an error-prone conversion, allowing the treatment plan margins to be reduced to as low as 1%. Additionally, proton radiography can be used to detect anatomical changes that could lead to errors in the proton range prior to
the daily treatment. In this dissertation, we discuss two pre-clinical proton imaging systems and quantify the image quality using three metrics: spatial resolution, noise, and accuracy. We discuss the feasibility of clinical implementation by looking at the percent of patients that can be imaged with clinical proton beam energies. We also measure the ability to detect anatomical changes with proton radiography and compare the range accuracy of proton treatment plans created on x-ray CT and proton CT images.
CLINICAL APPLICATIONS AND FEASIBILITY OF PROTON CT AND PROTON RADIOGRAPHY

BY

CHRISTINA M. SAROSIEK
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A DISSERTATION SUBMITTED TO THE GRADUATE SCHOOL IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSICS

Dissertation Director:
George Coutrakon
ACKNOWLEDGEMENTS

First, I would like to thank my advisor, George Coutrakon. Your mentorship and guidance over the last five years has been invaluable to my growth as a physicist and as a person. Thank you for teaching me, supporting me, and fighting for me at every step. I appreciate what you’ve done for me more than words can say.

I would also like to thank my committee members, Nick Karonis, Jim Welsh, and Mike Syphers, for their time and effort spent correcting my dissertation. Thank you also to the NIU Physics Department faculty and administrative staff, especially Jane Pretkalis and Carlos Garcia.

Next I would like to acknowledge all my collaborators in the pCT and pRad collaborations. My conversations and collaboration with everyone I’ve worked with has taught me so much. A special thank you goes out to Reinhard Schulte at Loma Linda University for your invaluable insight into all things proton imaging and proton therapy. I am grateful for everything you’ve taught me and the opportunities that you have helped me obtain. Thank you to Nick Karonis, Caesar Ordoñez, John Winans, and Kirk Duffin from the NIU computer science department for your constant willingness to help me with the reconstruction codes and answer my questions. Thank you to Mark Pankuch, Brad Kreydick, and all the staff at the Northwestern Medicine Chicago Proton Center for allowing me to follow you around and for your constant support and encouragement. Thank you to Jim Welsh for your insight into the clinical aspect. Thank you to Fritz DeJongh, Ethan DeJongh, Victor Rykalin, and Igor Polnyi from ProtonVDA LLC for your help with the proton radiography detector and image reconstruction programs. Thank you to Robert Johnson at UCSC for teaching me how to operate the proton CT detector and for answering my late night questions during
beam runs. Thank you to Jacob Ricci and David Johnstone for their work on beam energy and film projects, respectively. Thank you to my peers in the NIU medical physics group, Andrew Best and Eli Brottman, for our thoughtful conversations and synchronous learning.

Lastly, I am so grateful for all my family and friends who have supported and encouraged me throughout this journey. Every “I’m proud of you” and “you can do it” has motivated me to continue to push forward.
DEDICATION

To my mom, Sheri Mastalish. Thank you for being my rock.
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CHAPTER 1

INTRODUCTION

1.1 Proton Radiation Therapy for Cancer Treatments

Proton therapy is a form of cancer treatment that uses the radiation produced by protons losing energy as they traverse a patient. Proton therapy was first proposed by Wilson in 1946 [2] due to the optimal dose-depth distribution, exploiting the high dose at the end of the range. Protons deliver dose proportional to the energy loss per unit length as shown in Equation 1.1. The energy of the proton beam is carefully chosen such that the so-called Bragg Peak falls inside the tumor volume. This means that the highest dose deposition occurs in the tumor volume with a significantly lower dose delivered in the entrance region and no dose past the distal fall-off. The proton dose-depth distribution offers a major advantage over conventional x-ray radiotherapy. X-rays deliver dose proportional to x-ray absorption through the patient. The dose distribution falls off exponentially with depth, offering the highest dose in the entrance region and a decreasing dose throughout the patient, as shown in Equation 1.2. The dose at depth $x$ in the patient from protons and x-rays are calculated as

$$D_{p^+}(x) = \Phi \frac{1}{\rho} \frac{dE}{dx}, \quad (1.1)$$

$$D_{\gamma}(x) = \frac{\Psi}{\rho} \mu_{en}(x), \quad (1.2)$$
where $\Psi$ is the photon energy fluence in units of ergs/cm\(^2\), $\rho$ is the mass density of the material, and $\mu_{en}(x)/\rho$ is the average mass-energy absorption coefficient in the medium at depth $x$ \cite{3,4}. $\Phi$ is the fluence which is defined as the number of protons per unit area, $\rho$ is the density of the stopping medium, and $\frac{dE}{dx}$ is the energy loss per unit depth of the proton, calculated using the Bethe-Bloch equation \cite{5},

$$- \frac{dE}{dx} = \frac{4\pi k_0^2 z^2 e^4 n}{mc^2 \beta^2} \left[ \ln \frac{2mc^2 \beta^2}{I(1-\beta^2)} - \beta^2 \right],$$

where $k_0 = 8.99 \times 10^9$ Nm\(^2\)C\(^{-2}\) is the Coulomb constant, $z$ is the atomic number of the traveling particle (for protons $z = 1$), $e$ is the charge of the electron, $n$ is the electron density of the medium, $m$ is the rest mass of the electron, $c$ is the speed of light in vacuum, $\beta = v/c$ is the speed of the particle relative to the speed of light, and $I$ is the mean excitation energy of the medium.

For cancer treatments, the goal is to target the tumor with high dose and minimize dose in the surrounding healthy tissues. The comparison of the dose-depth distributions with regards to a cancer treatment are shown in Figure 1.1. Because the proton Bragg peak is so narrow compared to the size of a tumor, a spread out Bragg peak (SOBP) is created by superimposing multiple proton pencil beams along a shared pathway with different energies, such that the Bragg peaks sum to create a plateau in the dose distribution that covers the entire planned tumor volume (PTV).

Photons deliver the maximum dose at 1 to 3 cm from the surface of skin. To get high levels of dose in a deeper tumor volume, intensity-modulated radiotherapy (IMRT) was developed to deliver photons at many angles to superimpose the dose in the tumor while lowering the dose outside the tumor. This allows the 180\% dose seen in Figure 1.1 to be spread out throughout the healthy tissues. However, this method creates a large low-dose bath surrounding the tumor volume. When the same technique is applied to protons
Figure 1.1: Comparison of dose-depth curve for x rays and protons [?]. The y-scale is the dose relative to the tumor dose where 100% is the dose prescribed to the tumor.

(called intensity-modulated proton therapy or IMPT), the same conformal tumor dose exists without the surrounding low dose bath. This reduces the dose to normal tissues even more. There have been many publications demonstrating the benefits of proton therapy over photon radiotherapy for many different tumor sites including: head and neck [7], pediatric [8], breast [9], and prostate [10]. Figure 1.2 shows an example from Yock, et. al. [11] demonstrating the difference between a photon and a proton plan for a pediatric orbital rhabdomyosarcoma. In both plans, the radiation comes in from the patient’s left (right side of the page). The protons stop in the tumor volume and show no dose downstream of the tumor. The photons do not stop in the tumor and therefore delivers a higher dose to the healthy tissues downstream of the tumor, specifically the patient’s right eye.
Figure 1.2: Example dose distributions of a pediatric orbital rhabdomyosarcoma treatment plan created by Yock, et. al. The left images show a 4-field photon plan using IMRT and the right shows a 3-field proton plan using IMPT, both with the radiation entering from the patient’s left side. The tumor volume in the patient’s left eye is outlined in red and healthy structures that are influenced by additional dose are outlined in blue. The transparent color spectrum represents the relative dose, where 100% (red) is the dose prescribed to the tumor and 0% (blue) is no dose. It is easy to see the extended low dose bath produced in the photon plan downstream of the tumor and missing in the proton plan.

1.2 Imaging in Proton Therapy

With a dose distribution that conforms so well to the tumor volume, it is imperative to know precisely where the protons will stop in the patient. This knowledge comes from having an accurate model of the patient in the form of a radiograph and a computed tomograph (xCT).
1.2.1 Radiography

Immediately prior to treatment, the patient is aligned to the treatment beam with two orthogonal x-ray radiographs. An x-ray radiograph is a planar image of the x-ray absorption through the patient. X-ray radiographs are useful for patient alignment because they produce spatially resolved, high contrast images of fixed bony landmarks in the patient. However, they have very low contrast for the low-density soft tissues and cannot distinguish many tumors from the surrounding healthy tissues. The total treatment is broken up into fractions that occur daily over the course of six to eight weeks. Between the fractions, it is possible for the soft tissue anatomy to change size or density, or move in a way that affects the range of the protons. Common anatomical changes can occur in the form of weight loss or gain, filling or emptying of the bladder or rectum, filling of the sinuses, or tumor shrinkage [12], [13]. Currently there is no method in proton therapy to detect anatomical changes of soft tissues in the patient. Because x-ray radiography has poor contrast for low density structures, it cannot be used to detect small changes in soft tissue composition along the beam path.

1.2.2 Computed Tomography

Currently, the initial image of the patient anatomy comes from an x-ray CT (xCT) of the patient. A CT is a 3-dimensional image showing the internal patient anatomy. Each 3-dimensional voxel in the x-ray CT contains the Hounsfield unit (HU), which is a measure of the x-ray linear attenuation coefficient relative to water and is calculated as

$$\text{HU} = \frac{\langle \mu_x \rangle - \langle \mu_{\text{water}} \rangle}{\langle \mu_{\text{water}} \rangle},$$

(1.4)
where \( \langle \mu_x \rangle \) and \( \langle \mu_{\text{water}} \rangle \) are the linear attenuation coefficients of the material and water, respectively, averaged over the x-ray energy spectrum.

The x-ray CT image acts as the 3D model of the patient for the treatment plan with the HU specified in each voxel of order 1 mm\(^3\) volume. To obtain an accurate 3D proton dose map in the patient, the water equivalent depth (WED) in the patient at each voxel that a proton pencil beam passes through must be calculated. From that WED, a dose can then be calculated for that voxel using a dose function (also called a kernel) that specifies the dose as a function of WED and the distance from the central axis of the pencil beam. It has been shown that WED is critically dependent on the ratio of \( \frac{dE}{dx}(\text{tissue}) \) to \( \frac{dE}{dx}(\text{water}) \) in each voxel and therefore this ratio, also called relative proton stopping power (denoted RSP), must be calculated from the HU (described below) in the x-ray CT voxels. Any systematic errors in the conversion from HU to RSP will translate into WED errors and therefore dose errors in the patient. This is especially important when the dose is being calculated near the end of the proton range (i.e., the stopping depth in the patient) where the dose drops from its maximum value to zero in a few millimeters. Any errors in calculating that range may result in damaging healthy tissue behind or in front of the tumor or under-dosing the deepest (distal) or nearest (proximal) regions of the tumor. The WED of a proton can be calculated from the RSP values using

\[
\text{WED} = \sum_{i=1}^{N} \text{RSP}(i) L_i
\]

where RSP\((i)\) is the RSP in the \(i\)th voxel from the skin surface along the proton path and \(L_i\) is the path length of the proton through the \(i\)th voxel. When \(N\) becomes sufficiently large,
the proton stops in the last voxel \((N_{\text{max}})\) that it crosses and then the dose drops to zero. The range \(R\) of the proton can be calculated from RSP values by

\[
R = \sum_{i=1}^{N_{\text{max}}} \text{RSP}(i) L_i. \tag{1.6}
\]

Data acquired for pCT imaging uses the residual proton energy from the energy detector. This is converted to water equivalent path length (WEPL) for a straight or curved trajectory through the patient as described in Section 2.1.2. This is similarly related to RSP by

\[
\text{WEPL} = \sum_{i=1}^{N} \text{RSP}(i) L_i \tag{1.7}
\]

where the summation is along the proton’s path.

Now we discuss the detailed definition of RSP using Equation 1.3 and how x-ray CT data is used to convert HU values to RSP values, albeit with certain inherent errors. Protons and photons interact with matter differently, so before the optimization occurs, the HU in each voxel needs to be converted to RSP, which is a measure of electron density relative to water and is calculated as

\[
\text{RSP} = \frac{\rho_{e,x}}{\rho_{e,\text{water}}} \times \frac{\ln \left( \frac{2m_e c^2 \beta^2}{I_x (1-\beta^2)} \right) - \beta^2}{\ln \left( \frac{2m_e c^2 \beta^2}{I_{\text{water}} (1-\beta^2)} \right) - \beta^2}, \tag{1.8}
\]

where \(\rho_{e,x}\) and \(\rho_{e,\text{water}}\) are the electron density of the medium and water, \(m_e\) is the mass of the electron, \(c\) is the speed of light, \(I_x\) and \(I_{\text{water}}\) are the mean ionization energy of the medium and water, respectively, and \(\beta\) is the velocity of the proton relative to the speed of light. The second multiplicative term in the Bethe-Bloch equation deviates from 1 by less than \(\pm 3\%\) over the range of \(I\) and \(\beta\) values encountered in proton therapy. So, to first order the RSP equals to relative electron density.
The typical method of conversion uses a stoichiometric calibration developed by Schneider, et. al. [14]. This method parameterizes the cross-sections for the photoelectric effect, coherent scattering, and Compton scattering [15] in terms of the effective atomic number of the materials as follows:

\[ \langle \mu_x \rangle = \rho_{e,x} \left( K_{ph} \tilde{Z}^{3.62} + K_{coh} \hat{Z}^{1.86} + K_{KN} \right), \]  
\[ \tilde{Z} = \left[ \sum \lambda_i Z_i^{3.62} \right]^{1/3.62}, \]  
\[ \hat{Z} = \left[ \sum \lambda_i Z_i^{1.86} \right]^{1/1.86}, \]  
\[ \lambda_i = \frac{\omega_i Z_i}{A_i}, \]

where \( K_{ph}, K_{coh}, \) and \( K_{KN} \) are constants for the photoelectric effect, coherent scattering, and Compton scattering, respectively, \( \tilde{Z} \) and \( \hat{Z} \) are the effective atomic numbers which are calculated using the atomic number \( Z_i \), the atomic weight \( A_i \) and the weight by fraction \( \omega_i \) of the \( i \)th element in the material composition. The HU-to-RSP conversion does not have a one-to-one mapping, as shown in Figure 1.3. This is especially true of soft tissues with densities similar to water.

![Figure 1.3: Plot of proton RSP to x-ray HU conversion from Moyers, et. al. [16].](image-url)
The lack of one-to-one correspondence between HU and RSP becomes apparent in the mathematical formulation. Equation 1.9 can be approximated as

$$\mu_x = \rho_{e,x} \left[ Z_{eff}^4 F(E, Z_{eff}) + G(E, Z_{eff}) \right],$$

(1.13)

where $F(E, Z_{eff})$ and $G(E, Z_{eff})$ are an approximation of the photoelectric effect and the combination of coherent scattering and Compton scattering, respectively [17]. The effective atomic number $Z_{eff}$ can be written as $Z_{eff}^4 = \sum \lambda_i Z_i^4$ and $E$ is the average energy of the diagnostic beam ($\sim$30-50 keV). Approximating Equation 1.4 in terms of Equation 1.13 gives

$$\text{HU} = \frac{\rho_{e,x}}{\rho_{e,\text{water}}} \frac{\left[ Z_{eff}^4 F(E, Z_{eff}) + G(E, Z_{eff}) \right]}{\left[ Z_{eff,\text{water}}^4 F(E, Z_{eff,\text{water}}) + G(E, Z_{eff,\text{water}}) \right]}.$$

(1.14)

The calculation of RSP in Equation 1.8 has a similar dependence on the electron density ratio to water $\rho_{e,x}/\rho_{e,\text{water}}$ but is also dependent on the natural log of the mean ionization potential of the medium $\ln I_x$. Using the Bragg Additivity rule, we can calculate the mean ionization number of the medium in terms of the properties of the elements that make up the medium [17]:

$$\ln I_x = \frac{\sum \lambda_i \ln I_i}{\sum \lambda_i}.$$

(1.15)

Yang, et. al. [17] calculated the effective atomic number and the mean ionization potential in several common tissue types using values of $I_i$ from Table 6 of Seltzer and Berger [18]. They then plotted the relationship as shown in Figure 1.4. The plot shows a distinction in the conversion between soft tissues and bone tissues, with the thyroid being an outlier due to the presence of iodine. It also shows some variance around the linear fits, especially in the soft tissue region.

For materials with a well-known elemental composition, we can calculate the effective atomic number and the mean ionization potentials and confirm the relationship between
Figure 1.4: Plot showing the relationship between the effective atomic number and the natural log of the mean ionization potential for many tissues [17].

HU and RSP experimentally. The uncertainty in the fits inherently produce errors in the conversion. These errors are amplified when the composition of the material is not well-known, such as in a human subject. The conversion is further complicated because each tissue type varies in elemental composition between patients of the same age and the compositions of a tissue type can vary in a single patient [19]. This requires interpolation of an already error-prone conversion curve.

The uncertainty in the conversion and RSP values propagates to cause uncertainties in the predicted proton range by up to ±3.5% [16],[20]. Underestimating or overestimating the proton range leaves portions of the tumor with minimal or no dose, leaving cancer cells in the body and lowering the efficacy of the treatment. To account for this error, current protocols include adding 3.5% margins on the proximal and distal edges of the tumor volume such that if the proton range is under- or overestimated, the full tumor volume still receives the
full prescription dose. For deep seated tumors, these margins can be as large as 8 or 9 mm. The margins force the high dose regions to extend outside of the tumor and into the healthy tissues. This may lead to harmful side effects, especially if near a critical organ such as the brain stem [21],[22].

1.3 Proton CT and Proton Radiography for Proton Imaging

Accurate therapy treatments rely heavily on the pre-treatment images. Since photons and protons interact with matter differently, using images created with photons for proton therapy leads to proton range errors as described above. Using the same radiation modality for both imaging and therapy can make treatments safer and more effective by removing the need for the HU-to-RSP conversion and allowing for proton range errors prior to irradiation. Proton radiography and proton CT can be implemented in the clinic to replace conventional x-ray imaging for treatment planning and pre-treatment patient setup.

One major benefit of proton imaging is that it delivers a lower dose to the patient for similar image quality provided by x-ray imaging [23]. Historically, the total amount of imaging dose delivered throughout the course of a radiotherapy treatment is significantly lower than that delivered by the therapeutic beam and therefore has not been a major concern. However, as adaptive radiotherapy and image-guided radiotherapy using daily CT scans becomes more commonplace, the total imaging dose would significantly increase and may become cause for concern. Therefore, an alternative low-dose imaging modality will be necessary. As described in Section 1.1, protons deposit the highest dose at the end of their range and x-rays deposit high dose at a shallow depth in the patient. Proton imaging requires the protons to stop behind the patient, meaning the patient only receives the relatively low
dose from the entrance region. The absorbed dose $D_c$ from $M$ projections at the center of a phantom can be estimated with the following equation from Schulte, et. al. [24]:

$$D_c = \frac{M \Phi_c}{\rho} \left( \frac{dE_c}{dx} + \kappa \gamma E_c \right),$$  \hspace{1cm} (1.16)

where $\Phi_c$ is the fluence at the center of the phantom, $\rho$ is the physical density of the object, $E_c$ is the mean proton energy at the center of the object. The $\frac{dE_c}{dx}$ term is calculated from the Bethe-Bloch equation in Equation 1.3 for the energy at the center of the object and the term with $\kappa \gamma E_c$ accounts for the dose from nuclear interactions, where $\kappa$ is the total nonelastic macroscopic cross section for protons in water and is approximately 0.01 cm$^{-1}$ for proton energies between 100 MeV and 300 MeV and $\gamma$ is the fraction of proton energy transferred to secondary charged particles in nuclear interactions and is approximately 0.65 in the proton energy range 100 MeV to 250 MeV [24],[25]. We calculate the fluence at the center of the phantom by:

$$\Phi_0 = \Phi_c e^{\kappa d/2},$$  \hspace{1cm} (1.17)

where $d$ is the diameter of the phantom. The circumference of an adult female head of height 172 cm is 56 cm at the 50th percentile [26]. The diameter, therefore, is approximately 18 cm. For ease of calculation, we will assume the head is composed of water with a density $\rho$ of $1 \times 10^{-3}$ kg/cm$^3$. The proton CT images discussed in this paper use an incident energy of 200 MeV and an incident fluence rate of 3,086 protons/cm$^2$/s. Each scan runs for 360 seconds, including all projection angles, for a total fluence of $1.11 \times 10^6$ protons/cm$^2$. From Equation 1.17, we calculated the fluence at the center of the head $\Phi_c$ to be $1.014 \times 10^6$ protons/cm$^2$. From interpolating the Janni tables for water [27], we have $E_c = 155$ MeV and $\frac{dE_c}{dx} = 5.2862$ MeV/cm. Using these values in Equation 1.16 with appropriate unit
conversions, we calculate the dose from a six minute proton CT scan to the center of a female adult head to be $D_c = 1.022 \text{ mGy}$, calculated as follows:

$$D_c = \frac{\Phi_c}{\rho} \left( \frac{dE_c}{dx} + \kappa \gamma E_c \right)$$

$$= \frac{1.014 \times 10^6 \text{ protons/cm}^2}{10^{-3} \text{ kg/cm}^3} (5.2862 \text{ MeV/cm} + 0.01 \text{ cm}^{-1} \times 0.65 \times 155 \text{ MeV})$$

$$= 6.381 \times 10^9 \text{ MeV/kg}$$

$$= 1.022 \text{ mGy}$$

The typical dose delivered to the brain in an x-ray CT of the head is on the order of 20 to 40 mGy [28] which is over ten times the amount of dose delivered for proton CT. This means that we could image patients more often throughout treatment while minimizing the potential side effects from delivering regular excess dose.

### 1.3.1 Proton Radiography

Proton radiography (pRad) is a 2-dimensional image of the water-equivalent thickness (WET), or integrated RSP, through the patient. The proton beam is delivered to the object from a single projection angle and the WET through the object is measured and plotted as a grey-scale image. The resulting images are ideal for proton therapy because they show high contrast for densities similar to water. Figure 1.5 shows a comparison of an x-ray radiograph and a proton radiograph.

Proton radiographic images can be used to detect dose errors in the treatment plan immediately prior to treatment. It can be used to detect anatomical changes in the patient, such as tumor shrinkage or bladder or sinus emptying or filling, that may occur interfraction. Figure 1.6 shows a schematic describing the intended range of the protons and the range of
the proton if the density of an anatomical structure increases. A proton radiograph taken
in situ immediately prior to the daily treatment gives an image in terms of proton range
through the patient. A proton digitally reconstructed radiograph (pDRR) can be created by
integrating the 3D RSP map from treatment planning along the beam path to get a 2D proton
radiographic image. Comparing this synthetic pDRR to the actual proton radiograph will
allow for verification of patient anatomy. A proton radiograph measures the WET through
the patient. If the WET changes along the beam’s path to the tumor, it could prompt a
rescan. If the anatomical change occurs downstream of the tumor, the proton range to the
tumor would not be affected, but the WET measured by the proton radiograph would still
change. In this case, it may be of use to take two orthogonal proton radiographs to check if
the anatomical change occurs upstream or downstream of the tumor.

The comparison may also detect errors from the conversion from x-ray HU to proton RSP.
If an error is detected in the WET that could lead to a change in the proton range to the
tumor, then the treatment would stop and the patient could be re-scanned and re-planned.
The errors from anatomical changes and the conversion may combine to show no errors and
Figure 1.6: Schematic displaying the range of the planned proton range (Right) and after an anatomical change (Left). The radiograph measures the WET through the phantom. The measured WET from the left image will be larger than the measured WET from the image on the right. This change in WET could prompt a rescan of the patient.

this method does not show if the errors are upstream or downstream of the PTV. In this case, clinicians may consider taking two orthogonal pRad images which could help isolate the location of the possible errors.

Proton radiography has also been studied to create a patient-specific HU-to-RSP conversion curve \[29\]. Using the measured WET from a few proton radiographs at different projection angles, the conversion curve is optimized so that the RSP values in various tissue types match the WET in the proton radiographs. This could reduce the necessary distal and proximal range margins in the xCT-based treatment plan.

Lastly, proton radiography can also be used for pre-treatment patient alignment \[30\], \[31\]. Though the spatial resolution of pRad images is lower than that of xRad images, Pankuch, et. al. has shown in silico that patient alignment can be performed with pRad to the same level of accuracy of xRad \[32\]. The study involved simulating positional and rotational offsets in DRR and pDRR images of a pediatric head phantom. Proton radiation therapists then aligned the offset DRRs and pDRRs to the DRR from the nominal head CT scan. The
mean and standard deviation of 30 translational offsets and 15 rotation offsets are shown in Table 1.1. The average errors in alignment using proton radiographs are less than 0.1 mm, approximately equivalent to the errors using x-ray-based DRRs. The standard deviations for the pDRR alignments are larger than for the DRR alignments. This could be due to the reduced spatial resolution of the proton radiographs. Additionally, since the radiation therapists do not clinically use proton based images for alignment, more practice may reduce the standard deviations.

Table 1.1: Alignment errors (mean ± standard deviation) from simulated patient alignment study by Pankuch, et. al. [32]

<table>
<thead>
<tr>
<th>Offset Direction</th>
<th>x-ray DRR</th>
<th>pDRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left/Right (mm)</td>
<td>−0.1 ± 0.3</td>
<td>0.0 ± 0.4</td>
</tr>
<tr>
<td>Anterior/Posterior (mm)</td>
<td>0.2 ± 0.3</td>
<td>0.0 ± 0.4</td>
</tr>
<tr>
<td>Superior/Inferior (mm)</td>
<td>0.0 ± 0.2</td>
<td>−0.1 ± 0.3</td>
</tr>
<tr>
<td>Yaw (deg)</td>
<td>0.0 ± 0.1</td>
<td>−0.1 ± 0.2</td>
</tr>
<tr>
<td>Pitch (deg)</td>
<td>0.1 ± 0.1</td>
<td>0.1 ± 0.2</td>
</tr>
<tr>
<td>Roll (deg)</td>
<td>0.1 ± 0.2</td>
<td>0.1 ± 0.5</td>
</tr>
</tbody>
</table>

### 1.3.2 Proton CT

Proton CT (pCT) produces a 3-dimensional image of RSP. Protons are delivered continuously to the object at many projection angles spanning 360°. The data from each projection angle is back-projected to form a 3D image. Because proton CT measures the RSP in each voxel directly, it removes the need for an HU-to-RSP conversion. This may reduce the proximal and distal treatment plan margins to as low as 1% [33]. The reduced margin only needs to account for proton range straggling. This reduction of margins is important because any excess dose outside of the clinical tumor volume (CTV) can cause harmful toxicities [21],[22].
In the presence of high density implants, such as gold crowns or titanium joints, x-ray CT images produce a “starburst” artifact. The high-density implant absorbs x-rays and the downstream detector measures little to no data in that region. In image reconstruction, the missing data results in the artifact. Protons do not get absorbed by high density materials, so this artifact is minimized or removed completely with proton CT. An example of this is shown in Figure 1.7. The reduction of artifacts is important to be able to visualize the organs at risk and to ensure the accuracy of the treatment plan.

![Figure 1.7: X-ray CT image and proton CT image of a pediatric head phantom with a gold crown. The artifacts seen in the x-ray image are nearly non-existent in the proton CT image. Note that the greyscales are set such that the brain material is approximately the same level of grey in both images.](image)

### 1.3.3 Challenges of Proton Imaging

While x-rays travel in straight line paths through matter, each proton traversing matter will take a slightly different path and have a slightly different range due to interactions with the atoms in the matter. Interactions with the atomic nuclei cause each proton to
change its path. Multiple Coulomb scattering (MCS) is characterized by small angle scatters caused by the Coulomb force as the traversing proton passes nearby an atomic nuclei. Most interactions with atomic nuclei are multiple Coulomb scatters since there are relatively large gaps between the atomic nuclei. Direct collisions of protons with nuclei can result in large angle scattering, large energy reduction, and/or inelastic scatters. The nuclear inelastic events remove about 1% of protons per centimeter of depth in a water equivalent patient [27]. In those cases, inelastic scattering usually results in emission of a secondary proton or neutron [34]. Additionally, the traversing protons give up discrete amounts of energy to electrons in the matter. Each proton will give up a different amount of energy to each electron based on its path and therefore each proton will have a slightly different range through the same thickness of material. This process is called range or energy straggling.

Without removing protons undergoing large-angle interactions, proton images have high levels of noise and poor spatial resolution [35]. However, the proton interactions with the material atoms are statistical processes that are well understood and characterized. Therefore, several methods have been developed to reduce the influence of proton interactions in the medium on the reconstructed image. Calibration techniques were developed to account for range straggling in the determination of the residual range, preprocessing software removes proton data with evidence of elastic and inelastic scatters, and most likely path (MLP) algorithms have been developed to account for the curved proton path due to MCS.

Additionally, the available clinical beam energy is limited at most proton therapy centers to 235 MeV or 250 MeV [36]. For proton imaging, the protons need high enough energy to completely traverse the patient and have sufficient residual energy to create a detectable signal in a detector. The limited beam energy will be sufficient to image small anatomical sites, such as the brain, but may not be sufficient to image larger sites, such as the pelvis. The inability to image some cancer sites in some patients with protons may limit its use in clinic.
Finally, before clinical implementation of proton imaging, consideration needs to be given to clinical work flow. Currently, multi-room proton facilities allow multiple patients to be aligned in one room with x-ray imaging while another room uses the proton beam for a treatment. With proton radiography replacing x-ray imaging for pre-treatment alignment and WET verification, there will be more demand for the proton beam which may decrease patient throughput in a facility. However, proton radiographs require less than 10 seconds of the beam-on time, so the excess beam time per patient should be minimal. Proton CTs require longer beam-on times, but only a few proton CT scans are performed in a facility each week. Additionally, clinical accelerators are designed to operate at a high intensity beam for treatment (i.e. $10^{10}$ protons per second). The operational prototype and pre-clinical proton detector systems require low-intensity beams (i.e. $10^6$ protons per second). Before proton imaging can be included in clinical use, the accelerators need to deliver a low intensity beam safely and effectively.

1.3.4 Proton Imaging Review

Particle imaging was first suggested by Cormack to better predict the necessary beam energy to accurately target the tumor in proton therapy [37], [38]. Proton imaging then became a reality when Kohler published his paper on proton radiography [39] and again when Cormack and Kohler published the first proton CT images [40]. Both publications noted the ability to see images of low contrast materials in a water-like background. Schneider, et. al. then published the first proton radiograph of an animal and proved the usefulness for detecting proton range discrepancies [41]. Since then, several collaborations have developed pre-clinical proton imaging systems for research purposes [42].
Currently, there are two main methods of proton imaging: single-particle tracking (sometimes called list mode) and integrated. The integrated proton imaging method utilizes proton pencil beams that pass through the object and measure the average residual energy for each pencil beam. The single-particle tracking proton imaging method requires tracker planes upstream and downstream of the object to track the position of individual protons and measure their residual energy. The integrated method requires less complexity in the detector and software. Several groups have used clinical dosimetry tools such as a multi-layered ion chamber (MLIC) to create a proton image [43], [44]. This may allow for quicker realization of clinical proton imaging. However, the integrated method produces images with lower spatial resolution and requires higher dose for similar image quality [42]. Single-particle tracking systems, such as the ones discussed in Chapters 2 and 3 of this dissertation, track the position and trajectory angle of each proton before and after the object. An energy detector then measures the residual energy of the proton downstream of the object. Several groups have investigated ways to reduce the complexity of particle-tracking systems by reducing the number of tracking planes and only tracking the position of the particle or only tracking on the downstream side of the object [45], [46].

### 1.3.5 Alternatives to Proton Imaging

Several other technologies have been proposed to improve the accuracy of proton range. Dual-energy CT (DECT) involves taking two xCT scans with different effective x-ray spectra. Because of the different contributions of photoelectric effect and incoherent/coherent scattering, the HU in each voxel in each scan can be decomposed to calculate the RSP in each voxel. This could reduce treatment plan margins by adding only $\sim 2\%$ of the mean proton range to the distal edge of the tumore volume instead of 3.5%. However, this method still
requires high dose and is still not a direct measurement of RSP. For a detailed description of DECT hardware and algorithms used for proton therapy, see the recent review paper by Wohlfahrt and Richter and the references therein [47].

Positron emission tomography (PET) and prompt $\gamma$ imaging measures the path of the protons in the patient either during the treatment or shortly thereafter. This allows for an \textit{in vivo} range/dose verification. As the protons traverse through the tissues, a small fraction of them create positron-emitting isotopes (e.g., $^{15}$O or $^{11}$C). When the positron recombines with a nearby electron, there are two photons produced, back to back. Only one of them is needed to reconstruct the point of origin in the patient if enough positron-electron emissions are detected. Prompt $\gamma$ imaging exploits the photons emitted from the irradiated nuclei as they de-excite. For both methods, the detected signals can be tracked back to the location of the original proton collision or irradiated nuclei. Comparing the reconstruction of the signals to a Monte Carlo calculation can determine if the proton range was accurate. For detailed descriptions of these technologies and methods, the reader is referred to review articles and the references within [48], [13], [49]. With PET and prompt $\gamma$ imaging, the range errors are detected while the patient is being irradiated. If the predicted proton range is wrong, the patient has already received the wrong dose before the error is detected. Proton radiography would allow the range errors to be detected \textit{before} the patient receives high-dose radiation from treatment.

1.4 What to Expect in this Dissertation

In this dissertation, we aim to show the usefulness of proton imaging for proton therapy. In Chapters 2 and 3 we present two proton imaging systems, the first for proton radiography and the second for proton CT. We will discuss each detector and the associated image
reconstruction software. We also present image quality metrics and guidelines for appropriate parameter choices in the reconstruction algorithms.

In Chapters 4 and 5, we present several studies determining the feasibility of clinical proton imaging. In Sections 4.1 and 5.1, we discuss the beam energy that would be necessary to image patients with protons in the clinic. We determine the percent of patients that could be imaged with current clinical beam energies and then look at the energy that would be necessary to image patients with protons. In Section 4.3, we determine the accuracy of detecting anatomic changes with proton radiography. In Section 5.2, we quantify the accuracy of the proton range predicted by treatment plans created on x-ray CT and proton CT images. We compare the predicted proton ranges to the dose delivered to a stack of radiochromic films in a pediatric head phantom.
A proton radiograph is a planar image of the integrated RSP, or WET, of the patient in beam’s eye view. In this chapter, we describe the proton radiography detector system developed by ProtonVDA, LLC and the accompanying software developed by NIU. We then discuss the image quality of the images.

2.1 Hardware

In this section, we will describe the proton radiography detector hardware developed by ProtonVDA. The detector, shown in Figure 2.1, tracks individual protons upstream and downstream of the object and into a single stage energy detector. The detector design includes considerations towards clinical implementation. It is compact, works with pencil beam scanned accelerator systems, and requires minimal electronics. Work in this section also appears in DeJongh, et. al. [46].

2.1.1 Tracking Planes

The proton radiography system includes one set of (X, Y) tracker planes in front of the object and one set after the object. The sensitive area of the tracker planes is 38.4 cm × 38.4 cm. Each X and Y tracker plane consists of two layers in beam’s eye view of 1 mm² square scintillating fibers (Saint-Gobain, model BCF12S-S1.00N). The layers are offset by one half
fiber width, as illustrated in Figure 2.2a. One fiber from each layer is connected into a fiber pair. Twelve bunches of 32 fiber pairs laid side-by-side creates one X or Y tracker plane. The number of electronics is reduced by feeding one fiber pair from each bunch into a single 6 mm × 6 mm solid state silicon photomultiplier (SiPM) (Hamamatsu, model S13360-6050VE), as illustrated in Figure 2.2b. There are a total of 128 SiPMs for the entire proton radiography system (32 X and 32 Y for front tracker, 32 X and 32 Y for rear tracker). An accelerator plan defines the location of each pencil beam at isocenter and helps to determine which of the 12 fiber bunches were hit. The fiber signals then determine the actual location of the proton hit on the tracker plane at a 0.5 mm pitch. We then calculate the entrance angle of the proton on the upstream tracker from the location of the proton hit and the vector distance from the steering magnets in the accelerator.
25

(a) Fiber layout

(b) Multi-plexing of fibers

Figure 2.2: Schmatic of the tracker hardware. (a) Cross-section of an X or Y tracker plane consisting of two layers in beam’s eye view of scintillating fibers each 1 mm × 1 mm by 40 cm active length. The fibers are grouped into 12 bunches of 32 fiber pairs where each pair includes one fiber from each layer. All fibers from every bunch with the same numerical label are attached to a single silicon photomultiplier (SiPM), which has an active area of 6 × 6 mm. (b) Top view of four adjacent fiber bunches. One fiber pair from each bunch is read out through a common SiPM. So, each SiPM reads out 12 fiber pairs regularly spaced across the plane.

2.1.2 Range Detector and Calibration

The energy detector contains a compact 40 cm × 40 cm-transverse size, 13 cm-thick scintillator block (Eljen Technology, model EJ230). The scintillating block has a sensitive thickness of 10 cm, and the radiographic image is acquired from several proton scans using different energies in different regions of the object. The use of several energies ensures that at every pixel some protons pass through the entire object and have a measurable residual water-equivalent range less than 10 cm. For example, the variations in WET in a pediatric head phantom require a minimum of three energies for a complete anterior-posterior (AP) proton radiograph. Sixteen 76 mm diameter vacuum photomultiplier tubes (PMTs) (Hamamatsu, model R6091) distributed in a 4 × 4 grid across the distal end of the scintillator. The 4 × 4 grid of PMTs located on the downstream face of the scintillating block collect the scintillating photons. The scintillator sides not covered by the PMTs are painted black to
absorb photons. This means that the PMTs only collect photons that have not scattered off
the walls, minimizing the collection time of photons.

The residual range of each proton is measured and converted to WEPL using the following
method. The 16 PMTs on the backend of the energy detector measure the light output
generated by the protons that passed through the object. The light collected in each PMT
depends on the residual energy and the position of the proton with respect to the energy
detector. The position dependence arises from the spacing of the PMTs, where a proton that
is directed at the center of a PMT will have a stronger signal than a proton directed between
two PMTs. An electronics board combines the 16 PMT signals into four weighted-sum
signals, named $E$, $U$, $V$, and $C$, minimizing the data volume output. The $E$ signal is the total
sum of all 16 PMT signals. For most positions, the $E$ signal increases approximately linearly
with the residual range of the proton but with a position-dependent slope. The position of
the proton entering the energy detector is known from the tracker planes. Therefore, the $E$
signal alone gives an accurate measure of the residual range for most protons entering the
detector. However, some positions have non-linear slopes in the $E$ signal at large residual
ranges, and many protons will undergo multiple Coulomb scattering throughout the energy
detector, confounding the linear $E$-signal dependence. For these cases, the $U$, $V$, and $C$
signals provide additional information to improve the residual range accuracy. The $U$ and
$V$ signals are weighted sums of the 16 PMT signals. The weight factor for each PMT is
shown in Figures 2.3a and 2.3b for $U$ and $V$, respectively. The $U$ and $V$ signals are designed
to give an approximation of the proton’s position entering the scintillator and correct for
multiple scattering inside the detector. Lastly, the $C$ signal is a weighted sum of the PMT
signals based on the two concentric squares in the $4 \times 4$ array, as shown in Figure 2.3c. The
$C$ signal helps determine the residual range of the proton in the areas where the $U$ and/or
$V$ signals are near zero. For example, the $C$ signal becomes more positive with depth for
events near the center, where the $U$ and $V$ signals have low absolute values.
A calibration procedure was developed to convert the $E$, $U$, $V$, and $C$ signals to residual proton range. Protons are delivered to a 30 cm × 40 cm field at 44 different residual ranges between 1.25 and 12 cm. Approximately 10,000 protons were delivered to each spot spaced 5 mm in the transverse direction and 0.25 cm in depth. The proton data is binned into a 3D calibration grid with points for each of the 384 X and Y fiber positions and the 44 residual ranges from the proton data in the calibration scans. The $E$, $U$, $V$, and $C$ signals for each proton are measured and the average $E$, $U$, $V$, and $C$ signals for each point in the calibration grid (denoted as $E$, $U$, $V$, $C$, respectively) are calculated. From these data, the EUVC covariance matrix $K_{EUVC}$ is calculated and collected into the calibration grid of (X, Y, Residual Range). The covariance matrix for each point in the grid is defined as

$$K_{EUVC} = \begin{pmatrix}
\text{Cov}(E, E) & \text{Cov}(E, U) & \text{Cov}(E, V) & \text{Cov}(E, C) \\
\text{Cov}(U, E) & \text{Cov}(U, U) & \text{Cov}(U, V) & \text{Cov}(U, C) \\
\text{Cov}(V, E) & \text{Cov}(V, U) & \text{Cov}(V, V) & \text{Cov}(V, C) \\
\text{Cov}(C, E) & \text{Cov}(C, U) & \text{Cov}(C, V) & \text{Cov}(C, C)
\end{pmatrix} \tag{2.1}$$

where the covariance between two variables $A$ and $B$ is $\text{Cov}(A, B) = \left(\frac{1}{N}\right) \sum_{i=1}^{N} (A_i - \bar{A})(B_i - \bar{B})$ and $N$ is the number of protons corresponding to a grid point [50, 51].
We now use the values in the calibration grid to determine the residual range of each proton in the imaging data set. For a single proton in the image data set, we calculate the $\chi^2$ versus residual range for all points in the calibration grid having the same (X, Y) position. Each point has a corresponding $\bar{E}$, $\bar{U}$, $\bar{V}$, $\bar{C}$ which are used in the $\chi^2$ calculations. We start with the $\chi^2$ definition:

$$\chi^2 = \Delta^T K_{EUV}^{-1} \Delta$$

and

$$\Delta = \begin{bmatrix} E - \bar{E} \\ U - \bar{U} \\ V - \bar{V} \\ C - \bar{C} \end{bmatrix}$$

(2.3)

where the averages and covariance matrix are taken from the calibration data and $E$, $U$, $V$, $C$ are the measurements from a single proton in the image data. The three lowest $\chi^2$ values versus range are fitted with a parabolic function, and the residual range of the proton is the location of the minimum of the fit. Lastly, the proton WEPL is calculated as the difference between the water-equivalent range of the incident proton and the residual range of the proton measured by the energy detector.

### 2.2 Reconstruction Software

The image reconstruction software bins the WEPL values into pixels at the isocenter plane, which is the plane normal to the beam located at a defined distance from the accelerator scanning magnets, and usually corresponds to the center of the phantom. The water equivalent thickness (WET) is calculated as the most likely WEPL value in each pixel and
displayed as a grey-scale proton radiographic image. The image reconstruction methods are explained in Ordoñez, et. al. [52].

### 2.2.1 Most Likely Path-binned Reconstruction

As discussed in Chapter 1, protons undergoing MCS can cause the resulting reconstructed images to have limited spatial resolution. This is partially due to using reconstruction algorithms designed for x-ray CT with assumed straight-line trajectories. Introducing an algorithm which approximates the curved trajectory of the protons into consideration improves the spatial resolution and accuracy of the images. Several of these algorithms, so called most likely path (MLP) algorithms, have been developed [12], [53]. The algorithm we implemented in the proton radiography reconstruction code was developed by Schulte, et. al. [54] and modified for unknown exit angles. The method uses Bayesian statistics to estimate the most likely position and trajectory angle of the proton at any depth in the object given a priori knowledge of the position of the proton at the front and back of the object. The method assumes the upstream trajectory angle can be estimated from knowledge of the distance to the scanning magnets.

This MLP algorithm uses the Gaussian approximation of the generalized Fermi-Eyges theory of MCS [55] as the scattering model. The Gaussian approximation is sufficient because the tails on the range distribution caused by large angle nuclear scatters are removed with $3\sigma$ preprocessing cuts. The full derivation is available in Schulte, et. al. [54] with the main points discussed here.

We assume a coordinate system defined by the proton radiography detector where $z$ is the beam direction, $y$ is the vertical direction, and $x$ is the lateral direction. The trajectory angle relative to the $z$ axis in the $zy$ plane is $\theta$ and the trajectory angle relative to the $z$
axis in the $zx$ plane is $\phi$. The scattering in each plane can be considered as independent statistical processes. We parameterize the position and trajectory angle at depth $z_1$ as:

$$x_1' = \begin{pmatrix} x_1 \\ \phi_1 \end{pmatrix},$$

(2.4)

where the subscript 1 denotes some point within the object, as shown in Figure 2.4. A subscript of 0 denotes the entrance point at the front of the object and a subscript of 2 denotes the exit point at the back of the object.

Figure 2.4: Schematic illustrating the notation of the MLP algorithm. The red represents the true path of the protons and the blue represents the MLP. The entry position $x_0$ and angle $\theta_0$ and the exit position $x_2$ are known. We calculate the position $x_1$ and trajectory angle $\theta_1$ at each depth $z_1$.

The $x_{\text{mlp}}'$ when the entrance trajectory angle is assumed and the exit trajectory angle is unknown is calculated as:

$$x_{\text{mlp}}' = \left( \Sigma_1^{-1} + \frac{R_1}{\sigma_{x_2}^2} \right)^{-1} \left( \Sigma_1^{-1} R_0 y_0 + \frac{y_2}{\sigma_{x_2}^2} \right),$$

(2.5)
where \( R_0 \) and \( R_1 \) are defined as:

\[
R_0 = \begin{pmatrix} 1 & z_1 - z_0 \\ 0 & 1 \end{pmatrix}, \quad (2.6)
\]

\[
R_1 = \begin{pmatrix} 1 & z_2 - z_1 \\ z_2 - z_1 & (z_2 - z_1)^2 \end{pmatrix}, \quad (2.7)
\]

and \( \Sigma_1^{-1} \) is the inverse of the scattering matrix,

\[
\Sigma_1 = \begin{pmatrix} \sigma_{x_1}^2 & \sigma_{x_1 \phi_1}^2 \\ \sigma_{x_1 \phi_1}^2 & \sigma_{\phi_1}^2 \end{pmatrix} \quad (2.8)
\]

and

\[
\sigma_{x_1}^2(z_0, z_1) = E_0^2 \left( 1 + 0.038 \ln \frac{z_1 - z_0}{X_0} \right)^2 \int_{z_0}^{z_1} \frac{(z_1 - z)^2}{\beta^2(z)p^2(z)X_0} \, dz, \quad (2.9)
\]

\[
\sigma_{\phi_1}^2(z_0, z_1) = E_0^2 \left( 1 + 0.038 \ln \frac{z_1 - z_0}{X_0} \right)^2 \int_{z_0}^{z_1} \frac{1}{\beta^2(z)p^2(z)X_0} \, dz, \quad (2.10)
\]

\[
\sigma_{x_1}^2(z_0, z_1) = E_0^2 \left( 1 + 0.038 \ln \frac{z_1 - z_0}{X_0} \right)^2 \int_{z_0}^{z_1} \frac{(z_1 - z)}{\beta^2(z)p^2(z)X_0} \, dz, \quad (2.11)
\]

In these equations, \( \beta(z) \) is the velocity of the particle relative to the speed of light at depth \( z \) and \( p(z) \) is the particle’s momentum at depth \( z \). \( E_0 = 13.6 \) MeV/c and 0.038 are empirically-derived constants from Lynch and Dahl [56]. The radiation length \( X_0 \) is a material dependent property. We assume water which has a radiation length of \( X_0 = 36.1 \) cm. Substituting the \( \frac{1}{\beta^2(z)p^2(z)} \) with a polynomial allows for explicit evaluation of the integral form in Equations \(2.9 - 2.11\)

\[
\frac{1}{\beta^2(z)p^2(z)} = a_0 + a_1 z + a_2 z^2 + a_3 z^3 + a_4 z^4 + a_5 z^5. \quad (2.12)
\]
The coefficients for the polynomial are energy dependent and therefore need to be recalculated for each energy in the scan. As an example of the order of magnitude, the coefficients for a 200 MeV incident proton beam are $a_0 = 7.457 \times 10^{-6}$, $a_1 = 4.548 \times 10^{-7}$, $a_2 = -5.777 \times 10^{-8}$, $a_3 = 1.301 \times 10^{-8}$, $a_4 = -9.228 \times 10^{-10}$, $a_5 = 2.687 \times 10^{-11}$.

The final image formation uses the MLP calculation of the proton’s position at the isocenter plane, which is the plane normal to the beam and midway between the detectors. We bin the WEPL into pixels based on the position calculation and calculate the average WEPL (i.e., WET) in each pixel. We then display the pixels as a grey-scaled image of the WET.

### 2.2.2 Iterative Reconstruction

It is also possible to use more complex iterative algorithms, such as algebraic reconstruction techniques (ART) or component averaged row projections (CARP), that were initially developed for proton CT [57], [58]. The iterative algorithms refine the solution for large data sets when the initial solution is close to the real solution. A detailed description of iterative reconstruction techniques can be found in Section 3.2.3. The addition of iterative algorithms may further improve proton radiographic images. However, proton radiography requires approximately 2% of the number of protons required for a proton CT and the MLP-binning method of proton radiography image reconstruction accounts for the majority of the proton scattering. Therefore, using iterative algorithms may not have much benefit for proton radiography reconstructions. A comparison of images reconstructed with CARP and MLP-binned methods is presented in Section 2.3.4.
2.3 Image Analysis

Good image quality is vital to clinical implementation of proton radiography. We use three standard medical physics image quality metrics to determine image quality: WET accuracy, spatial resolution, and contrast-to-noise ratio (CNR) [59]. These are measured on three phantoms with known materials and geometry.

2.3.1 WET Accuracy

WET accuracy is important to be able to detect proton range errors before treatment. The phantom shown in Figure 2.5 has a blue bolus wax background and eight pegs of tissue-equivalent materials. The phantom is 4 cm thick with an 18 cm diameter. The pegs are also 4 cm thick and have a diameter of 1.8 cm. We verified the true WET of each insert by first calculating the RSP with a water-pullback measurement, then multiplying the RSP by the thickness of the inserts. The proton radiograph of the phantom, shown in Figure 2.5b, used three energies (100 MeV, 150 MeV, 180 MeV). We measure the accuracy by creating a region of interest (ROI) in the insert, away from the edges, and calculating the mean and standard deviation in the distribution. Table 2.1 compares the true and measured WET.

The measured WET in each insert is within 0.02 cm of the known WET and within 0.3%. For clinical implementation, the accuracy should be within 1% of the known WET. This level of accuracy would confirm that any range errors detected during pre-treatment range checks will lead to dose errors during treatment.
Figure 2.5: Photo and proton radiograph of the peg phantom. The radiograph was reconstructed using the MLP-binning method. Note that the photo in Figure 2.5a is rotated 45° with respect to the radiograph in Figure 2.5b.

Table 2.1: Table of WET accuracy of proton radiography system.

<table>
<thead>
<tr>
<th>Material</th>
<th>True WET (cm)</th>
<th>Measured WET (cm)</th>
<th>Physical Error (cm)</th>
<th>Percent Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolux Wax</td>
<td>3.88</td>
<td>3.89 ± 0.01</td>
<td>-0.01</td>
<td>-0.2</td>
</tr>
<tr>
<td>Sinus</td>
<td>0.80</td>
<td>0.80 ± 0.01</td>
<td>0.00</td>
<td>0.0</td>
</tr>
<tr>
<td>Brain</td>
<td>4.16</td>
<td>4.16 ± 0.01</td>
<td>0.00</td>
<td>0.0</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>4.16</td>
<td>4.17 ± 0.01</td>
<td>-0.01</td>
<td>-0.2</td>
</tr>
<tr>
<td>Spinal Disc</td>
<td>4.28</td>
<td>4.28 ± 0.01</td>
<td>0.00</td>
<td>0.0</td>
</tr>
<tr>
<td>Trabecular Bone</td>
<td>4.40</td>
<td>4.41 ± 0.01</td>
<td>0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>Cortical Bone</td>
<td>6.22</td>
<td>6.21 ± 0.01</td>
<td>-0.01</td>
<td>-0.2</td>
</tr>
<tr>
<td>Dental Dentin</td>
<td>5.98</td>
<td>5.96 ± 0.01</td>
<td>-0.02</td>
<td>-0.3</td>
</tr>
<tr>
<td>Dental Enamel</td>
<td>7.02</td>
<td>7.01 ± 0.01</td>
<td>-0.01</td>
<td>-0.1</td>
</tr>
</tbody>
</table>
2.3.2 Spatial Resolution

The spatial resolution of proton radiographic images is important for pre-treatment alignment. In the alignment procedures, sharp edges are aligned between the proton radiograph and a digitally-reconstructed radiograph (DRR) created from a CT image of the patient. The spatial resolution is measured with a modulation transfer function (MTF). The MTF is calculated by taking the Fourier transform of the line spread function, which is a line profile across the edge of an insert. If the edge is infinitely sharp, the derivative of the line profiles should be a Dirac delta function. Any blurriness of the edges in the images makes the derivative finite at the edge of the insert and is then used to quantify the spatial resolution. The Fourier transform gives the amplitudes for the spatial frequencies contributing to the function where frequency is the inverse of the wavelength. The spatial resolution is then quantified as the spatial frequency whose amplitude is 10% of the amplitude of the lowest frequency in the transform.

2.3.2.1 Edge Phantom

The edge phantom developed by Plautz, et. al. [60] and manufactured by Computerized Imaging Reference Systems, Inc. (CIRS) is a 6 cm thick, 20 cm diameter cylinder containing twelve inserts with straight edges as shown in Figure 2.6a. Each insert is 4.5 cm long with a square area of 1.5 cm × 1.5 cm. The compositions of the inserts are air (RSP = 0.007), lung (RSP = 0.217), adult cortical bone (RSP = 1.685), and enamel (RSP = 1.775). The surrounding phantom material is composed of water-equivalent plastic with RSP = 1.007. There are three inserts for each material set at three different radii to measure the effect of the inserts’ location on spatial resolution. The specifics are outlined in Figure 2.6a. The
pencil beam can cause more blurring when deflected further from the central axis of the beam (i.e., X=0, Y=0). This is due to a slightly longer path length through the phantom and the fact that straight line paths cross the edge of the inserts at an angle. This will affect the measurable spatial resolution. Additionally, the relative angle between the inserts and the pixel grid can affect the spatial resolution due to a voxel containing two materials and therefore giving an average WET.

Figure 2.6: Schematic and proton radiograph of the edge phantom. The radiograph was reconstructed with the MLP-binning method. Note that there is a 180° flip along the vertical axis between the schematic and the radiograph.

To measure the spatial resolution on the edge phantom, we calculate the MTF on each insert separately. Each MTF calculation starts by taking seven WET profiles (i.e. WET vs position s) parallel to the X or Y pixels across the edge of the insert closest to the center of the phantom, as demonstrated in Figure 2.7. The seven profiles can be aligned to a common coordinate s at the point where the WET is halfway between the WET of the insert and the WET of the background (WET-50%). We fit the aligned profile with a sigmoid curve and take the derivative of the function to obtain the line spread function. The MTF is the coefficients of Fourier transform of the resulting line spread function which peaks at
the WET-50% in the Edge Spread Function. The normalization of the MTF is unity at frequency $0 \text{ mm}^{-1}$. With this method, we calculate the spatial frequency in the Fourier domain rather than in real space such is the case with the line pair phantom. Figure 2.8 shows the MTF curves for each of the inserts. Table 2.2 summarizes the results. The results show a progressive decrease in MTF-10% (worsening resolution) as the inserts get further from the center. This is in part due to the geometry of the beam.

![Figure 2.7: Schematic showing the line profiles taken across the edge of an insert. If the teal rotated square is an insert in the Edge phantom, we take profiles (represented by the black dots) along several rows of pixels starting in the insert and ending in the background material. Each profile cross the boundary of the inserts at different positions $s$, so they must be aligned to a common value of the WET-50%.](image)
(a) MTF calculated on the Air inserts.

(b) MTF calculated on the Lung inserts.

(c) MTF calculated on the Cortical Bone inserts.

(d) MTF calculated on the Enamel inserts.

Figure 2.8: MTF calculated on the edges of each of the inserts. The MTF-10% is summarized in Table 2.2.
Table 2.2: Table with the MTF-10% of the edge phantom.

<table>
<thead>
<tr>
<th>Radius</th>
<th>MTF-10% (mm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Air</td>
</tr>
<tr>
<td>25 mm</td>
<td>1.07</td>
</tr>
<tr>
<td>55 mm</td>
<td>1.11</td>
</tr>
<tr>
<td>80 mm</td>
<td>0.73</td>
</tr>
</tbody>
</table>

2.3.2.2 Line Pair Phantom

We also calculated the MTF on a Catphan 528 Line Pair Phantom (The Phantom Laboratory, Salem, NY) with 20 cm of solid water behind the phantom. The line pair phantom, shown in Figure 2.9, is a 4 cm-thick cylinder with a diameter of 15 cm. There is a series of 21 aluminum line pairs that are 2 mm thick and 4 mm long set in an epoxy background. The WET through the background is 240 mm and the WET through each insert is 244 mm. The line pairs range in size from 1 lp/cm (line width equal to 0.5 cm) to 21 lp/cm (line width equal to 0.024 cm). The spacing between adjacent lines is equal to the width of the line. For this phantom, the MTF is measured by first taking several circular profiles through the inserts. Those profiles are averaged and the MTF per line pair is calculated by:

\[
MTF_{LP} = \frac{[WET_{\text{max}} - WET_{\text{min}}]_{LP}}{[WET_{\text{max}} - WET_{\text{min}}]_{LP=1lp/cm}}. \tag{2.13}
\]

The WET values in the numerator are the relative maximum and minimum WET values in the profile of each line pair. The denominator normalizes the MTF to be one for the first line pair (LP = 1 lp/cm) profile. Further increases in the line pair spacing will not increase the difference between the maximum and minimum value in the profile, making 1 lp/cm a sufficient spacing to use for normalization. The MTF-10% of the image is 0.6 lp/mm, as shown in Figure 2.10.
Figure 2.9: Line Pair phantom.

(a) Line pair phantom schematic.

(b) Line pair phantom radiograph.

Figure 2.10: Plot of MTF verses line pair spacing of the Line Pair phantom setup. The 10% value is near the frequency that two lines are barely resolvable to the human eye. In this case, 0.6 line pairs per mm or about 1.8 mm between aluminum inserts.
2.3.3 Contrast-to-Noise Ratio

Proton radiography image quality is susceptible to noise, or the pixel-to-pixel fluctuations, in the image. High levels of noise can make the detection of low contrast lesions difficult. The CNR gives a performance measure on the ability to detect low contrast lesions. The peg phantom shown in Figure 2.5 was also used to measure the CNR. The CNR is calculated by:

\[
\text{CNR} = \frac{|\text{WET}_{\text{insert}} - \text{WET}_{\text{background}}|}{\sqrt{\sigma^2_{\text{insert}} + \sigma^2_{\text{background}}}},
\]

where WET is the average WET in the ROI and \( \sigma \) is the standard deviation of the WET in the ROI. The background is the blue bolus wax material and the insert is one of the tissue-equivalent peg inserts in the phantom. Table 2.3 shows the CNR of the low-contrast inserts.

Table 2.3: Table with CNR measurements. The measured WET and \( \sigma \) values are the same as those in Table 2.1.

<table>
<thead>
<tr>
<th>Material</th>
<th>Measured WET (cm)</th>
<th>( \sigma ) (cm)</th>
<th>CNR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus Wax</td>
<td>3.89</td>
<td>0.01</td>
<td>–</td>
</tr>
<tr>
<td>Brain</td>
<td>4.16</td>
<td>0.01</td>
<td>19.0</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>4.17</td>
<td>0.01</td>
<td>19.8</td>
</tr>
<tr>
<td>Spinal Disc</td>
<td>4.28</td>
<td>0.01</td>
<td>27.6</td>
</tr>
<tr>
<td>Trabecular Bone</td>
<td>4.41</td>
<td>0.01</td>
<td>36.8</td>
</tr>
<tr>
<td>Dentin</td>
<td>5.96</td>
<td>0.01</td>
<td>144.9</td>
</tr>
<tr>
<td>Cortical Bone</td>
<td>6.21</td>
<td>0.01</td>
<td>162.6</td>
</tr>
<tr>
<td>Enamel</td>
<td>7.01</td>
<td>0.01</td>
<td>219.2</td>
</tr>
<tr>
<td>Sinus</td>
<td>0.80</td>
<td>0.01</td>
<td>219.9</td>
</tr>
</tbody>
</table>
2.3.4 CARP vs MLP-binned Reconstruction Method

The MLP-binned reconstructions show good image quality. Iterative reconstruction methods may be used to further refine the images. However, there may not be enough proton histories to make a large improvement upon the MLP-binned reconstructions. Figure 2.11 shows a visual comparison of the edge phantom reconstructed with the two methods and a difference map of the two. Table 2.5 shows the WET accuracy of the MLP-binned and the CARP reconstructions of the peg phantom. Table 2.4 shows a comparison of the spatial resolution as measured by the MTF-10% on the edge phantom. We do not gain spatial resolution or WET accuracy by using iterative reconstruction methods. The standard deviation of the WET in each ROI is also larger in the CARP reconstructions than in the MLP-binned reconstructions. CARP reconstructions are also computationally more expensive. As will be discussed in detail in Chapter 3, the iterative reconstruction algorithms can be dependent on parameter choice. It may be the case that the parameters used in this reconstruction are not optimal for this set of data. However, the MLP-binned method shows sufficient image quality for clinical use.

Table 2.4: Table comparing the MTF-10% of CARP and MLP-binning reconstructions. The average change in MTF-10% going from MLP-binning reconstructions to CARP reconstructions is 0.008 mm$^{-1}$.

<table>
<thead>
<tr>
<th>Radius</th>
<th>Air</th>
<th>Lung</th>
<th>Enamel</th>
<th>Cortical Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MLP</td>
<td>MLP</td>
<td>MLP</td>
<td>MLP</td>
</tr>
<tr>
<td>25 mm</td>
<td>1.07</td>
<td>1.25</td>
<td>0.79</td>
<td>0.96</td>
</tr>
<tr>
<td>55 mm</td>
<td>1.11</td>
<td>1.0</td>
<td>0.63</td>
<td>0.57</td>
</tr>
<tr>
<td>80 mm</td>
<td>0.73</td>
<td>0.69</td>
<td>0.67</td>
<td>0.75</td>
</tr>
</tbody>
</table>
2.4 Conclusion

The proton radiography system and accompanying reconstruction software shows good image quality. With the MLP-binning reconstruction method, we measured the spatial resolution with an MTF to be between 0.48 and 1.11 mm\(^{-1}\), depending on the insert and phantom type and we measured the WET within 0.3\% of the known WET. With the iterative reconstruction method, we measured the spatial resolution to be between 0.41 and 1.25 mm\(^{-1}\) and the WET within 0.7\% of the known values. To be clinically relevant, the images should show spatial resolution better than 0.5 lp/mm. During patient alignment, the proton radiographs are matched with DRRs from the treatment planning system using many high contrast edge boundaries. The errors in patient alignment are lower than the level of spatial resolution because of the many edges used when determining appropriate patient alignment. Additionally, we see a slight decrease in WET accuracy when reconstructing with CARP, but it is still within 1\% of the known WET value, which is sufficient for detecting possible proton range errors. CARP images also show higher levels of noise than MLP-binned images as evidenced by the standard deviation of the measured WET in the ROIs. The CNR measured on the CARP image was on average 30\% lower than the CNR measured on the MLP-binned image due to the larger amount of noise produced in the CARP images.
Figure 2.11: Comparison of proton radiographs reconstructed with MLP-binning and CARP. The MLP-binned radiograph is the same as in Figure 2.5b.
Table 2.5: Table comparing WET accuracy of CARP and MLP-binning reconstructions for each insert. The average absolute value of the errors for all inserts is 0.011 cm (0.3%) when reconstructed with CARP and 0.008 cm (0.1%) when reconstructed with MLP-binning. On average the CNR is reduced by 30% when reconstructing with CARP rather than MLP-binning.

<table>
<thead>
<tr>
<th>Insert</th>
<th>Truth</th>
<th>WET ± Std (cm)</th>
<th>Physical Error (cm)</th>
<th>Percent Error (%)</th>
<th>CNR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MLP</td>
<td>CARP</td>
<td>MLP</td>
<td>CARP</td>
</tr>
<tr>
<td>Bolus Wax</td>
<td>3.88</td>
<td>3.89± 0.01</td>
<td>3.90 ± 0.01</td>
<td>-0.01</td>
<td>-0.02</td>
</tr>
<tr>
<td>Brain</td>
<td>4.16</td>
<td>4.16 ± 0.01</td>
<td>4.16 ± 0.01</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Cortical Bone</td>
<td>6.22</td>
<td>6.21 ± 0.01</td>
<td>6.24 ± 0.03</td>
<td>0.01</td>
<td>-0.02</td>
</tr>
<tr>
<td>Dental Dentin</td>
<td>5.98</td>
<td>5.96 ± 0.01</td>
<td>5.98 ± 0.03</td>
<td>0.02</td>
<td>0.0</td>
</tr>
<tr>
<td>Dental Enamel</td>
<td>7.02</td>
<td>7.01 ± 0.01</td>
<td>7.04 ± 0.03</td>
<td>0.01</td>
<td>-0.02</td>
</tr>
<tr>
<td>Sinus</td>
<td>0.80</td>
<td>0.80 ± 0.01</td>
<td>0.80 ± 0.02</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>4.16</td>
<td>4.17 ± 0.01</td>
<td>4.18 ± 0.02</td>
<td>-0.01</td>
<td>-0.02</td>
</tr>
<tr>
<td>Spinal Disc</td>
<td>4.28</td>
<td>4.28 ± 0.01</td>
<td>4.29 ± 0.01</td>
<td>0.0</td>
<td>-0.01</td>
</tr>
<tr>
<td>Trabecular Bone</td>
<td>4.40</td>
<td>4.41 ± 0.01</td>
<td>4.43 ± 0.01</td>
<td>-0.01</td>
<td>-0.03</td>
</tr>
</tbody>
</table>
CHAPTER 3
PROTON COMPUTED TOMOGRAPHY

In this chapter, we discuss the LLU-UCSC proton CT detector system for proton CT and the images obtained of various phantoms. We present a comparison of iterative algorithms and discuss how to choose a relaxation parameter that optimizes the image quality for clinical use.

3.1 Detector Hardware

The pCT detector, shown in Figure 3.1, consists of a tracker system and an energy detector. The phantom sits on a rotation stage, centered on the z-axis of rotation, between the tracker planes and rotates at a constant rate of 1 RPM. Protons of 200 MeV are delivered to the pCT scanner with wobbling in the T and V direction with a total field size of 10 cm vertically by 30 cm horizontally. The intensity of the beam is reduced to 1 MHz by reducing the beam current and partially closing the energy selection system collimators.

3.1.1 Tracker Planes

The tracker planes measure the position and angle of each proton before and after the phantom. Each tracker module consists of two planes of silicon strip detectors, one measuring the V coordinate and one measuring the T coordinate. Two modules separated by 5 cm in the U direction create one tracker. There is one tracker on either side of the phantom and
Figure 3.1: Schematic of the US pCT Collaboration proton CT detector system [1]. The protons enter from the bottom right corner and travel in the $+U$ direction while the phantom, centered on the $Z$ axis, rotates with the $(X,Y,Z)$ coordinate system during each scan.

The center modules are separated by 30 cm. Each plane has an active area of 9 cm vertically by 36 cm horizontally.

### 3.1.2 Energy Detector

The residual energy of each proton is measured with a five-stage plastic scintillator detector. Each of the five stages has a WET of 52.9 mm along the beam’s direction. The light from each of the five stages is read out by PMTs and converted to WEPL with the following procedure. Reconstruction of the WEPL for each proton from the five-stage scintillator data relies on a calibration procedure to convert the scintillator pulse height to MeV and then MeV to WEPL [61]. A Monte Carlo simulation of the calorimeter with 200 MeV protons and no phantom provides the calculated proton energy loss in each stage. This is the first step of
the calibration. The second step of the calibration is to convert MeV to WEPL. A series of calibration runs are performed with a wedge phantom and polystyrene blocks to modulate where the protons stop in the calorimeter. The first run is an empty run which generates spatially-dependent correction factors to flatten the response profile across the \((T, V)\) plane. The second calibration run is of just the polystyrene wedge phantom. The thickest part of the wedge has a WET of 52.34 mm, slightly smaller than the WET of a single scintillator stage. We then take calibration runs of the wedge phantom adding on the polystyrene blocks one at a time. The wedge and wedge plus block runs modulate the residual energy such that the 200 MeV protons stop in each of the five scintillator stages. The wedge produces a continuous range of position- and angle-dependent WEPL values for the incident 200 MeV protons. The wedge with one polystyrene block is illustrated in Figure 3.2.

The WEPL through the phantom from each proton is calculated by projecting the straight-line trajectory from the tracker planes to the front and rear surfaces of the phantom.
The physical path length is then calculated as the distance between these points and multiplied by the RSP of polystyrene (1.030) to obtain the WEPL. The WEPL is then correlated to the MeV value of the last stage with a signal in the range detector.

### 3.2 Image Reconstruction Software

The pCT reconstruction code uses several algorithms, described in this section, to produce high quality images from proton data. Portions of this section are also found in Schultze, et. al. [1].

#### 3.2.1 FDK

The initial image is formed using the Feldkamp-Davis-Kress (FDK) algorithm. The FDK algorithm is a form of filtered backprojection algorithm adapted for conebeam CT. The general equations are adapted from the original FDK paper [62] and summarized here.

Because we acquire data with continuous rotation, the data is first segmented into 180 angular projection bins at 2° increments. The equation to calculate RSP(X, Y, Z) = RSP(r) from the projection data, WEPL(T', V', θ) in the FDK algorithm, is given by

\[
RSP(r) = \frac{1}{4\pi^2} \int_0^{2\pi} \frac{d^2}{(d + r \cdot \hat{x}')} \text{WEPL}'(T'(r), V'(r), \theta) d\theta
\]  

(3.1)
where \(d\) is the source to rotation axis distance (or SAD), \(\hat{x}'\) is the unit vector perpendicular to the \((T', V')\) plane and \(\text{WEPL}'\) is the Shepp-Logan filtering of \(\text{WEPL}(T', V', \theta)\). Also, \(T'\) and \(V'\) are parameterized in terms of the vector \(\mathbf{r}\), as follows:

\[
T'(\mathbf{r}) = \mathbf{r} \cdot \hat{n} \frac{d}{d + \mathbf{r} \cdot \hat{x}'} \\
V'(\mathbf{r}) = \mathbf{r} \cdot \hat{z} \frac{d}{d + \mathbf{r} \cdot \hat{x}'}
\] (3.2)

The equations for \(\text{WEPL}'\) are adapted from the FDK equations (31) - (33) \[62\], but are given here for completeness,

\[
\text{WEPL}'(T', V') = \int_{-\infty}^{+\infty} \int_{-\infty}^{+\infty} \text{WEPL}(T, V) g_1(T' - T) g_2(V' - V) \times \frac{d}{\sqrt{d^2 + T'^2 + V'^2}} dT dV
\] (3.4)

\[
g_1(Q) = \text{Re} \int_{0}^{\omega_{T_0}} \omega \exp(i\omega Q) d\omega
\] (3.5)

\[
g_2(P) = \frac{\sin(\omega_{V_0}P)}{P\pi}
\] (3.6)

The maximum spatial frequencies are given by \(\omega_{T_0}\) and \(\omega_{V_0}\). These are based on the finite spatial resolution determined by the pitch of the silicon strips, 0.228 mm, of the \(T\) and \(V\) tracker planes. With these values in the FDK equations, \(\omega_{T_0} = \omega_{V_0} = \frac{\pi}{0.228\text{mm}}\). The \(\text{RSP}(\mathbf{r})\) can then be calculated from Equation \[3.1\], which gives the initial reconstructed image for input to the subsequent iterative image reconstruction. An example FDK reconstruction of the peg phantom is shown in Figure \[3.3\]. The FDK image then acts as the initial iterate for the iterative reconstruction discussed in Section \[3.2.3\].
Figure 3.3: Example slice of FDK reconstruction of the CATPHAN 528 Line Pair Phantom and a custom peg phantom. The ring artifacts seen in the images are the edges of the reconstruction volume and are removed with the iterative solvers described in 3.2.3.

### 3.2.2 Most Likely Path Algorithm

The most likely path (MLP) algorithm was implemented to account for multiple Coulomb scattering in the phantom. It takes the position and trajectory angle of the proton at the entry and exit points of the object and estimates a curved path between the two. We then mark each of the voxels that the proton hits and calculate an approximate chord length in each voxel. This information is then used in the iterative reconstruction algorithm. Because the US pCT collaboration detector has two tracking planes upstream and downstream of the object, we measure the trajectory angle directly before and after the object. To find the entry and exit position at the surface of the object, we compute straight-line paths from the upstream and downstream tracker planes to the surface of the object.

We use the MLP algorithm developed by Schulte, et. al. [54] with scattering matrices derived by Erdelyi [63]. The general concept of the Schulte method is described in 2.2.1 for unknown exit angle. The equations shown here follow the same theory but are derived for
known exit trajectory angle. We also will use the \((T,U,V)\) coordinate system to match that of the pCT detector coordinates.

Assume the \(u\) axis is along the beam direction where \(u_0\) is the depth of the entry point of the proton, \(u_2\) is the depth of the exit point, and \(u_1\) is a depth in between. We parameterize the transverse position and trajectory angle of the proton at depth \(u_1\) as:

\[
y_1 = \begin{pmatrix} t_1 \\ \theta_1 \end{pmatrix}
\]

(3.7)

where \(\theta_1\) is the angle measured in the \(t-u\) plane relative to the \(u\)-axis. Recall that the scattering in each plane can be treated as independent statistical processes and therefore we only report the equations in one plane. In this notation, the \(y_{\text{mlp}}\) is calculated as:

\[
y_{\text{mlp}} = \left( \Sigma_1^{-1} + R_1^T \Sigma_2^{-1} R_1 \right)^{-1} \left( \Sigma_1^{-1} R_0 y_0 + R_1^T \Sigma_2^{-1} y_2 \right)
\]

(3.8)

where

\[
R_0 = \begin{pmatrix} 1 & u_1 - u_0 \\ 0 & 1 \end{pmatrix}
\]

(3.9)

\[
R_1 = \begin{pmatrix} 1 & u_2 - u_1 \\ 0 & 1 \end{pmatrix}
\]

(3.10)
The main difference between the Erdelyi and Schulte scattering matrices is the integration of the logarithmic term. The Schulte derivation assumes the logarithmic term is approximately constant with energy and therefore pulls it out of the integrand. The Erdelyi scattering matrices integrate the logarithmic term which requires numerical methods.

\[
\sigma^2_{t_1}(u_0, u_1) = \int_{u_0}^{u_1} \frac{1}{(\beta(u)p(u))^2} \frac{E_0^2}{X_0} \left( 1 + 0.038 \ln \frac{u}{X_0} \right) \left( 1.076 + 0.038 \ln \frac{u}{X_0} \right) (u_1 - u) \, du \tag{3.13}
\]

\[
\sigma^2_{t_1 \theta_1}(u_0, u_1) = \int_{u_0}^{u_1} \frac{1}{(\beta(u)p(u))^2} \frac{E_0^2}{X_0} \left( 1 + 0.038 \ln \frac{u}{X_0} \right) \left( 1.076 + 0.038 \ln \frac{u}{X_0} \right) (u_1 - u) \, du \tag{3.14}
\]

\[
\sigma^2_{t_2}(u_0, u_1) = \int_{u_0}^{u_1} \frac{1}{(\beta(u)p(u))^2} \frac{E_0^2}{X_0} \left( 1 + 0.038 \ln \frac{u}{X_0} \right) \left( 1.076 + 0.038 \ln \frac{u}{X_0} \right) (u_1 - u)^2 \, du \tag{3.15}
\]
\[ \sigma^2_{\theta_2}(u_1, u_2) = \int_{u_1}^{u_2} \frac{1}{(\beta(E)p(E))^2 X_0} \left( 1 + 0.038 \ln \frac{u}{X_0} \right) \left( 1.076 + 0.038 \ln \frac{u}{X_0} \right) du \]  

(3.16)

\[ \sigma^2_{t_2\theta_2}(u_1, u_2) = \int_{u_1}^{u_2} \frac{1}{(\beta(E)p(E))^2 X_0} \left( 1 + 0.038 \ln \frac{u}{X_0} \right) \left( 1.076 + 0.038 \ln \frac{u}{X_0} \right) (u_1 - u) du \]  

(3.17)

\[ \sigma^2_{t_2}(u_1, u_2) = \int_{u_1}^{u_2} \frac{1}{(\beta(E)p(E))^2 \frac{E_0}{X_0}} \left( 1 + 0.038 \ln \frac{u}{X_0} \right) \left( 1.076 + 0.038 \ln \frac{u}{X_0} \right) (u_1 - u)^2 du \]  

(3.18)

where \( \beta(u) \) and \( p(u) \) are the relativistic velocity and momentum of the particle at depth \( u \), \( X_0 = 36.1 \) cm is the radiation length of water, and \( E_0 = 13.6 \) MeV/c. The \( \frac{1}{(\beta(u)p(u))^2} \) term is again approximated as a fifth order polynomial (see Equation 2.12 and surrounding discussion).

The MLP for each proton is calculated at each depth \( u_1 \). Each voxel that the proton touched in the reconstruction volume is recorded and will be used during the iterative reconstruction described in the next section.

### 3.2.3 Iterative Reconstruction Algorithms

Iterative reconstruction techniques were introduced to the pCT reconstruction code to minimize imaging artifacts and find most accurate RSP maps which include curved (MLP) paths through the patient following FDK solutions of \( \text{RSP}(X,Y,Z) \) as a starting point. Figure 3.4 shows an FDK image side-by-side with an image reconstructed with an iterative algorithm. Iterative reconstruction takes a linear set of equations, \( \text{WEPL} = \sum_{i=1}^{n} \text{RSP}_i d\ell_i \) which is generated for each proton trajectory and is represented by a hyperplane in an \( M \)-dimensional space as defined below. \( \text{WEPL} \) is determined from the calorimeter data and \( d\ell_i \).
Figure 3.4: Side-by-side comparison of an image reconstructed with just FDK and an image reconstructed with an iterative method (CARP).

is an approximate chord length for each proton track that crossed the \( i \)th voxel. The chord length is determined with the mean chord length approximation developed by Penfold [64]. The 3D RSP values are linearized into a one dimensional array. Typically only a couple hundred voxels out of several million are crossed by a single track. We define a matrix equation

\[
A_{ij} \text{RSP}_j = \text{WEPL}_i \quad \text{for} \quad i = 1..M \quad \text{proton tracks crossing the object and} \quad j = 1..N \quad \text{voxels in the image.}
\]

From here forward, we redefine \( \vec{\text{RSP}} \) as \( \vec{x} \) and \( \vec{\text{WEPL}} \) as \( \vec{b} \). The equation is then written as:

\[
A \vec{x} = \vec{b} \tag{3.19}
\]

The iterative reconstruction seeks to find the intersection of the \( M \) hyperplanes with a solution for the RSP value in each of the \( N \) voxels. Hence the matrix \( A \) is \( M \times N \) with \( M \gg N \). Typically, \( M \) is of order \( 100 \times N \). A unique solution is not guaranteed but generally finds good agreement for phantoms with known RSP values, such as the peg phantom.

The implementation of the projection steps change with different algorithms. The projections onto each hyperplane can be done sequentially or simultaneously, or the hyperplanes
can be partitioned for parallelization and a combination of simultaneous and sequential projections can be used. The two algorithms implemented into the reconstruction software are described below.

### 3.2.4 Component-Averaged Row Projections

Component Averaged Row Projections (CARP) is a form of a string averaged projection (SAP) method which partitions the hyperplanes into strings and projects the solution on to each hyperplane in the string sequentially. The algorithm is parallelized by completing each string simultaneously. Figure 3.5 shows the projection scheme for CARP.

![Figure 3.5: Schematic of the first iteration of the CARP algorithm.](image)
The algorithm can be described mathematically as follows. For a given string \( s \) where \( 0 \leq s \leq S - 1 \) and the total number of strings is \( S \), the projections onto each hyperplane sequentially follows:

\[
\vec{x}^{(k_s,p+1)}(k_s,p) = \vec{x}^{(k_s,p)} + \lambda \frac{b_i - \langle \vec{a}_i, \vec{x}^{(k_s,p)} \rangle}{\|\vec{a}_i\|^2} \vec{a}_i^T \tag{3.20}
\]

\[0 \leq p \leq P_s - 1\]

where \( \vec{x}^{(k_s,p+1)} \) is the \( p \)th partial iterate of string \( s \) within the \( k \)th full iteration, \( \vec{a}_i \) is the \( i \)th row vector of matrix \( A \), representing the \( i \)th proton history, \( b_i \) is the WEPL value of the \( i \)th proton, and \( \lambda \) is the relaxation parameter. The relaxation parameter defines the fractional length of the projection onto each hyperplane with \( \lambda = 1 \) projecting exactly onto each hyperplane, \( \lambda < 1 \) projecting short of each hyperplane, and \( \lambda > 1 \) projecting past each hyperplane. The term \( \langle \vec{a}_i, \vec{x}^{(k_s,p)} \rangle \) is the inner product of the two vectors and \( \|\vec{a}_i\|^2 \) is the norm of the vector. The typical range of \( \lambda \) between zero and two. Each projection within a string is considered a partial iterate. To calculate the next full iteration, we combine the endpoints from each string in the following manner:

\[
\vec{x}^{(k+1)} = \vec{x}^{(k)} + C \sum_{s=0}^{S-1} \vec{x}^{(k_s,P_s)} \tag{3.21}
\]

\[
C = \text{diag} \left\{ \frac{1}{c_j} \right\}_{1 \leq j \leq n} \tag{3.22}
\]

The weighting factor \( C \) is a \( n \times n \) diagonal matrix where the components are related to \( c_j \) which is equal to the number of strings containing at least one proton history whose path intersected the \( j \)th voxel.
3.2.5 Diagonally-Relaxed Orthogonal Projections

The diagonally-relaxed orthogonal projection (DROP) method is a form of block-iterative projection (BIP) methods which partitions the hyperplanes into blocks [65]. The initial solution is projected onto each hyperplane in a block simultaneously. The large size of each block, typically containing a few million hyperplanes, indicates that a high degree of parallelization occurs in DROP as well. A partial iteration occurs when we create a convex combination of each of those projections in a block. The partial iteration from the first block is then used as the initial solution for the next block. A full iteration occurs after the full sequence of blocks is completed. Figure 3.6 shows how DROP proceeds for two blocks.

Figure 3.6: Schematic of the first iteration of the DROP algorithm.
Mathematically, for a given block \( p \) the simultaneous projections can be described as:

\[
\bar{x}^{(p_{p+1})} = \bar{x}^{(p_p)} + \lambda D \sum_{i=1}^{S_p} \frac{b_i - \langle a_i, \bar{x}^{(p_p)} \rangle}{\|a_i\|^2} a_i^T
\]

(3.23)

\[
0 \leq p \leq P - 1
\]

(3.24)

\[
D = \text{diag} \left( \min \left( 1, \frac{1}{d_j^p} \right) \right)
\]

(3.25)

where \( D \) is a diagonal \( n \times n \) matrix where the elements are related to \( d_j^p \) which is equal to the number of proton paths in block \( p \) intersecting the \( j \)th voxel, \( S_p \) is the size of block \( p \), and \( P \) is the number of blocks.

3.2.6 Total Variation Superiorization

The iterative algorithms assume that all hyperplanes intersect at a single point. However, noise in the proton data causes the data to be inconsistent and therefore a range of feasible solutions exists. The Total Variation Superiorization (TVS) algorithm is a feasibility-seeking algorithm which helps to reduce the noise in the image without compromising spatial resolution \cite{66}. When using CARP as the iterative solver, TVS must be executed at the end of each full iteration (TVSi). When using DROP as the iterative solver, TVS can be executed after each block (TVSb) or each iteration (TVSi). For each slice in the current iterate of the pCT, we calculate four image gradients, labeled in Figure 3.7 \( \Delta(X,Y) \) as follows:

\[
\Delta_x(X,Y) = \text{RSP}(X+1,Y) - \text{RSP}(X,Y)
\]

(3.26)

\[
\Delta_y(X,Y) = \text{RSP}(X,Y+1) - \text{RSP}(X,Y)
\]

(3.27)

We then normalize the gradients in the X and Y direction as:
Figure 3.7: Illustration of $\Delta RSP$ for a given pixel in the TVS slice.

\[
\delta_x(X,Y) = \frac{\Delta_x(X,Y)}{\sqrt{\Delta_x^2(X,Y) + \Delta_y^2(X,Y)}} \tag{3.28}
\]

\[
\delta_y(X,Y) = \frac{\Delta_y(X,Y)}{\sqrt{\Delta_x^2(X,Y) + \Delta_y^2(X,Y)}} \tag{3.29}
\]

The pixel variation $V(X,Y)$ is then calculated as:

\[
V(X,Y) = \delta_x(X-1,Y) + \delta_y(X,Y-1) - (\delta_x(X,Y) + \delta_y(X,Y)) \tag{3.30}
\]

Each of the $V(X,Y)$ in every slice are linearized into a vector $\mathbf{V}^{(kp)}$, similar to the RSP vector $\mathbf{x}^{(kp)}$. This vector is then normalized:

\[
\hat{\mathbf{V}}^{(kp)} = \frac{\mathbf{V}^{(kp)}}{\|\mathbf{V}^{(kp)}\|} \tag{3.31}
\]
The perturbation is then calculated by multiplying the perturbation vector $\vec{V}(k_p)$ by a scalar multiplier $\beta^{(k_p,r)}$ that determines the magnitude of each perturbation. The scheme proceeds as follows:

$$\bar{x}^{(k_p,r+1)} = x^{(k_p,r)} + \beta^{(k_p,r)}\vec{V}(k_p)$$  \hspace{1cm} (3.32)

where $\beta^{(k_p,r)} = \alpha^{(k_p,r)}$  \hspace{1cm} (3.33)

$$\ell^{(k_p,r+1)} = \ell^{(k_p,r)} + 1$$  \hspace{1cm} (3.34)

where $\alpha$ is the perturbation kernel and set to a constant of $\frac{1}{2}$, and the initial exponent $\ell^{(0,0)} = 1$. After each $r$ perturbation, the total variation (TV) of the image is calculated:

$$TV^{(k_p)} = \sum_{j=1}^{n} V_j^{(k_p)}$$  \hspace{1cm} (3.35)

The perturbations are repeated, increasing $\ell$ by 1 each time, until the total variation in the image is decreased.

### 3.3 Relaxation Parameter Optimization

The resulting quality of images created with iterative reconstruction techniques is highly dependent on the choice of parameters in the iterative algorithm. These parameters are interdependent and changing one parameter can greatly change the image quality of the final solution. We choose some parameters for practical reasons, then use those to help us determine the remaining parameters. The number of hyperplanes depends on the length of the pCT scan (typically 6 minutes). This leads to about 120 million protons in the iterative solvers. We choose 40 blocks (DROP) or strings (CARP), yielding about 3 million hyperplanes per block or per string, to take full advantage of parallel processing on the
compute cluster at NIU. The remaining parameters are chosen to optimize the image. The relaxation parameter $\lambda$ is particularly dependent on the rest of the parameter space. The typical range of $\lambda$ in literature is between 0 and 2. However, for our datasets, we found that $\lambda < 1$ gives the best convergence to true RSP values. The goal of this section is to empirically understand how the relaxation parameter affects the resultant image quality.

### 3.3.1 Image Quality Metrics

Judgment of image quality must focus on the main clinical uses of the images. Proton CT, once accepted, will be used for proton therapy treatment planning. The images must have accurate reconstructed RSP values for accurate proton range predictions, high spatial resolution for accurate patient alignment and anatomical contouring, and sufficiently low noise to differentiate low contrast objects. The metrics we will use for “sufficient” image quality are 1% for RSP accuracy, 1 mm spatial resolution, and 1% noise, as suggested by Schulte, et. al. [24].

The image quality metrics are similar to those presented in Chapter 2 but modified for proton CT. We measured the noise and accuracy of each image on the custom peg phantom and the spatial resolution on the CATPHAN Line Pair Phantom. We determine the RSP accuracy by calculating the average RSP in a $7 \times 7$-pixel ROI in each insert, avoiding the voxels near the edges that may see partial volume effects. We then calculate mean absolute percent error (MAPE) by calculating the percent error for each insert and averaging the absolute values. To ensure that the errors for each insert are systematic (rather than one insert with a high percent error and another with a very low percent error), we also calculate the standard deviation of the percent errors of the inserts.
We add one additional metric to judge the noise for pCT. The signal-to-noise ratio (SNR) is defined as $SNR = \frac{RSP}{\sigma}$, where the RSP and $\sigma$ are the mean RSP and standard deviation in a given ROI. For our analysis, the noise in the image is calculated with the SNR in the background and the CNR between the brain insert and the background. To have a noise level less than 1% of the signal, the SNR in the background material needs to be greater than 100. The target CNR can be calculated by assuming the $\sigma$ in the background and brain are 1% of their respective signals. This means that $CNR \geq \frac{|1.04 - 0.98|}{\sqrt{0.0104^2 + 0.0098^2}} = 4.2$ is the target value.

We define the spatial resolution of the image by calculating the MTF-10% on the line pair phantom. We calculate the MTF for each line pair by:

$$MTF = \frac{RSP_{\text{MAX}} - RSP_{\text{MIN}}}{RSP_{\text{MAX}_{LP=1}} - RSP_{\text{MIN}_{LP=1}}}$$

(3.36)

where the $RSP_{\text{MAX}}$ and $RSP_{\text{MIN}}$ are the average of the peaks and valleys, respectively, in the profile through the given line pair. The denominator normalizes the MTF to 1 by dividing by the RSP difference in the largest line pair (LP = 1). The MTF-10% is the smallest line pair that shows an MTF greater than 10% or 0.1.

These metrics can work against one another, so optimizing for one image quality metric can cause deficiencies in the other two metrics. For example, over-smoothing of the image will allow for a high SNR, but will also smooth edge and reduce spatial resolution. Therefore, we built a cost function that combines the metrics into a single value that can be minimized. The generalized formula of the function is:

$$C = \min \left( \sum_i w_i c_i \right)$$

(3.37)
where we have a weighted sum of costlets $c_i$ which are target functions used for each of the metrics. A “good” result of a target function should be smaller and a “bad” result of a target function should be higher. The weights $w_i$ are user chosen and will be discussed later. The first step is to develop the costlets for our three metrics.

For spatial resolution, we want to maximize the MTF-10% value. We therefore write our costlet $c_{sr}$ as the inverse of the MTF-10%, converted to units of lp/mm, as follows:

$$f_{sr} \text{(MTF-10%)} = \min \left( \frac{1}{\text{MTF-10%}} \right)$$

A higher MTF-10% will then give a smaller $c_{sr}$. The minimum quality metric for spatial resolution is 1 mm. This corresponds to an MTF-10% of 5 lp/cm = 0.5 lp/mm. That means our maximum target is 0.02. Therefore, the costlet becomes:

$$c_{sr} = \begin{cases} 
  f_{sr}^2 & f_{sr} \leq 0.02 \\
  f_{sr} & f_{sr} > 0.02 
\end{cases}$$

By squaring the function $f$ when it is less than the target value, we are able to more heavily punish images that do not meet the target value for sufficient image quality.

The noise costlet follows in a similar fashion. We want to maximize the SNR in the background (BG) material of custom peg phantom. Therefore, we again take the inverse of the metric:

$$f_{\text{noise}} \text{(SNR)} = \frac{1}{\text{SNR}_{\text{BG}}} = \frac{\sigma_{\text{BG}}}{\text{RSP}_{\text{BG}}}$$

The minimum quality metric is the noise is 1% of the signal value. Therefore, the costlet becomes:

$$c_{\text{noise}} = \begin{cases} 
  f_{\text{noise}}^2 & f_{\text{noise}} \leq 0.01 \\
  f_{\text{noise}} & f_{\text{noise}} > 0.01 
\end{cases}$$
Lastly, we can create the costlet for RSP accuracy. As mentioned earlier, we want to minimize the MAPE, but also ensure that materials have a small spread in errors. Therefore, we add the MAPE and the standard deviation of the percent errors in the inserts $\sigma_{\text{MAPE}}$ as follows:

$$f_{\text{Accuracy}}(\text{MAPE}) = \text{MAPE} + \sigma_{\text{MAPE}}$$ \hfill (3.42)

The minimum quality metric for the RSP accuracy is 1% and we want $\sigma_{\text{MAPE}}$ to remain less than 0.005. Therefore, the maximum target is $0.01 + 0.005 = 0.015$ and the costlet becomes:

$$c_{\text{Accuracy}} = \begin{cases} 
  f_{\text{Accuracy}}^2 & f_{\text{Accuracy}} \leq 0.015 \\
  f_{\text{Accuracy}} & f_{\text{Accuracy}} > 0.015 
\end{cases}$$ \hfill (3.43)

The total cost function $C_{\text{Total}}$ can then be written as:

$$C_{\text{Total}} = w_{\text{sr}} c_{\text{sr}} + w_{\text{Accuracy}} c_{\text{Accuracy}} + w_{\text{noise}} c_{\text{noise}}$$ \hfill (3.44)

where the weights are: $w_{\text{sr}} = 30$, $w_{\text{Accuracy}} = 40$, $w_{\text{noise}} = 30$. The RSP accuracy is given the highest weighting to ensure that proton ranges can be accurately predicted in treatment planning. The spatial resolution and noise tend to act in contradiction to one another, so it is important to use equal weightings to balance one another.

### 3.3.2 Results

We tested 26 relaxation parameters ranging from $0.002 \leq \lambda \leq 1.8$ for five algorithm combinations: CARP, CARP+TVSi (sometimes referred to as CARP+TVS), DROP, DROP+TVSi, DROP+TVSb. For each relaxation parameter and algorithm, we reconstructed the line pair phantom and the peg phantom using the same initial datasets and identical image recon-
struction parameters. The number of proton histories that survived preprocessing and pre-
conditioning data cuts \[1\] was about 121 million for the line pair phantom and about 130
million for the peg phantom. The rest of the image reconstruction parameters are listed in
Table 3.1. We chose the pixel size and slice thickness to match typical x-ray CT scans.

Table 3.1: pCT reconstruction parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pixel Size</td>
<td>0.8 mm</td>
</tr>
<tr>
<td>Number of Subsets</td>
<td>40</td>
</tr>
<tr>
<td>Slice Thickness</td>
<td>1.25 mm</td>
</tr>
<tr>
<td>Number of FDK Projections</td>
<td>180</td>
</tr>
<tr>
<td>Maximum Iterations</td>
<td>20</td>
</tr>
<tr>
<td>Reconstruction diameter</td>
<td>24 cm</td>
</tr>
</tbody>
</table>

Each of the images were reconstructed on the NIU Gaea hybrid compute cluster \[67, 68\].
The final image solutions following FDK and iterative linear solvers were analyzed with
Python code written in-house to calculate the MTF-10% on the line pair phantom and the
RSP accuracy and noise levels on the peg phantom. Using the MTF-10%, MAPE, and SNR,
we then calculated the cost function for each image solution. The image that produced the
lowest value of the cost function for each of the five algorithms is considered the “Overall”
optimal image. Figures 3.8 and 3.9 show the overall optimal images of the peg and line
pair phantoms, respectively, for each of the five algorithms. The optimal images in terms
of spatial resolution, noise, and RSP accuracy can be found in Appendix B. The quantitative
results for the optimal images overall, and in terms of the three metrics are shown in Table
3.2. For each algorithm, the table shows the quantitative image quality results for the
relaxation parameter $\lambda$ and iteration number (IN) that optimizes the given metric listed:
spatial resolution (SR), RSP accuracy (Accuracy), Noise, and overall. The RSP accuracy
is quantified in the table by the MAPE, the insert with the highest percent error, and the
insert with the lowest percent error. The spatial resolution is quantified in the table by the
MTF-10%. The noise is quantified in the table the SNR and CNR. The value of the cost
function is also listed for each of the images.
Figure 3.8: pCT reconstructions of the optimal peg phantom reconstructions.
Figure 3.9: pCT reconstructions of the optimal line pair phantom reconstructions.
Table 3.2: Image quality results for the 6 minute datasets. Optimal relaxation parameter $\lambda$ and iteration number (IN) for five pCT reconstruction options, optimized for Spatial Resolution (SR), Noise, and RSP Accuracy. The three metrics are combined into a cost function to determine an “overall” optimum. For each image, we report the mean average percent error (MAPE), the insert with the highest (max) and lowest (min) percent error, the MTF-10%, the SNR in the background, the CNR between the brain insert and background, and the result of the cost function.

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Metric</th>
<th>$\lambda$</th>
<th>IN</th>
<th>MAPE</th>
<th>Max % Err</th>
<th>Min % Err</th>
<th>MTF-10%</th>
<th>SNR</th>
<th>CNR</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARP</td>
<td>SR</td>
<td>1.2</td>
<td>13</td>
<td>7.75</td>
<td>26.4 (Sinus)</td>
<td>0.203 (BG)</td>
<td>7</td>
<td>5.46</td>
<td>0.305</td>
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<td>173.2</td>
<td>7.84</td>
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<td>5</td>
<td>0.307</td>
<td>0.64 (TB)</td>
<td>0.005 (Sinus)</td>
<td>2</td>
<td>1737.6</td>
<td>72.2</td>
<td>0.015</td>
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From the results in Table 3.2 and summarizing the trends that appeared while searching for the optimal images, we outline several main conclusions to keep in mind when choosing which algorithm to use.

- Referring to Table 3.2, the cost function values for the overall optimal images do not show significant improvement by using TVSi for either CARP or DROP. However, the SNR is a factor of two better for DROP+TVSi than for DROP and the SNR is a factor of two worse for CARP+TVSi than for CARP.

- Looking at Figures 3.8 and 3.9, which show the best overall image quality of the five algorithms, there is a slight but noticeable improvement in spatial resolution and noticeably improved contrast when using CARP+TVSi compared to the other images. These images would favor CARP+TVSi as a superior algorithm choice for these two phantoms. Considering the CARP+TVSi image shows a reduced SNR value with a higher MTF-10% value, this may suggest that an SNR target value of 100 is too high and that it would be acceptable to relax the constraint on the noise and instead emphasize higher spatial resolution.

- Noise and Spatial resolution are in direct competition with each other. The images with high spatial resolution also show high noise. Figure 3.10 shows two images of the line pair phantom reconstructed with CARP+TVSi at the 10th iteration. Figure 3.10a uses a relaxation parameter of $\lambda = 0.002$ and shows a high SNR and a low MTF-10%. Figure 3.10b uses a relaxation parameter of $\lambda = 0.16$ and shows a low SNR but a high MTF-10%.

- Optimizing for spatial resolution alone yields a large decrease in SNR and CNR for all algorithms and is therefore not recommended.
(a) CARP+TVSi, $\lambda = 0.002$, SNR = 4366.7, MTF-10% = 2 lp/cm  
(b) CARP+TVSi, $\lambda = 0.16$, SNR = 14.19, MTF-10% = 6 lp/cm

Figure 3.10: CARP+TVSi reconstructions of the line pair phantom with two different relaxation parameters, both at the 10th iteration, to demonstrate the competition of noise and spatial resolution.

- DROP+TVSb significantly lowers the spatial resolution but with a 17 times increase in SNR and CNR. This may be important for cases where contrast is more important than spatial resolution.

- Empirically we found that the image noise increased as the relaxation parameter increases, as seen in Figure 3.11a. Also, in many cases, the image noise also increased as the number of iterations increased. In those cases, TVS was not able to keep the SNR from rising as the number of iterations increased beyond 9 or 10. The one exception was DROP+TVSb, but that came with marked decrease in spatial resolution; a trade off that does not bode well for overall image quality.

- After about six iterations, the accuracy for all images is most dependent on the relaxation parameter for all values of $\lambda$. Inappropriate choice of the relaxation parameter may reconstruct certain density inserts more accurately than others. When judging
Figure 3.11: (a) Demonstration of how the noise increases (SNR decreases) with relaxation parameter. Additionally, for the same relaxation parameter, CARP reconstructs more noise than DROP. (b) Optimal relaxation parameters for the SNR. Note, the log scale.
accuracy, it is therefore important to account for both the MAPE and the accuracy of each individual material. Figure 3.12 shows an example of an image where the MAPE is below 1% but the low density insert (Sinus) shows a percent error 3.5% compared with the optimal accuracy image where MAPE and all inserts show errors less than 1%. Although many of the inserts show lower percent errors with the first image, the high percent error in the sinus insert makes this image less ideal. Additionally, it is important to choose a phantom that has inserts that cover the range of RSP values typically seen in patients (RSP = 0 to RSP = 2).

Figure 3.12: Plot showing the percent error of each insert and the MAPE for two CARP+TVSi reconstructions with different relaxation parameters. Although the MAPEs for the two reconstructions are both under 1% and only 0.3% different, we see a very high error in the sinus insert for one of the images and not for the other.

Overall, we can achieve high levels of image quality with any of the five algorithms. Each algorithm, however, presents different image quality trends which could be better or worse for a particular clinical use case.
3.4 Image Quality as a Function of Dose

In this section, we understand how the image quality changes if we change the imaging dose. Note that the dose is directly proportional to the length of the pCT scan, and therefore the number of proton histories in the image reconstruction. To double the dose, we scanned the peg phantom 12 minutes and to half the dose, we scanned the peg phantom for 3 minutes. We expect that the image quality will be better with more dose, but ultimately we prefer to deliver the least amount of dose possible to each patient while still maintaining sufficient image quality.

The image quality metrics used in Section 3.3 were used in this section as well. We did not have access to 3 minute and 12 minute datasets of the line pair phantom, so the spatial resolution was instead measured with the peg phantom with the edge method described in Section 2.3.2.1.

Figures 3.13-3.17 compare the image quality metrics for the three dose levels. Figure 3.13 plots the MAPE versus the relaxation parameter for the 10th iteration of CARP and DROP reconstructions. For CARP reconstructions, it seems that there is little advantage for scanning for 6 minutes over 3 minutes. For low relaxation parameters ($\lambda < 0.1$) the MAPE is approximately equal for all three dose levels. However, for larger relaxation parameters, the 12 minute scan produces worse MAPE. For the DROP reconstruction, there is no difference between the dose levels in terms of MAPE.

Figure 3.14 plots the background SNR against relaxation parameter for the 10th iteration of DROP and CARP reconstructions of the 3, 6, and 12 minute scans. Opposite to MAPE, the CARP reconstructions show little preference to dose. However, the SNR shows better SNR with more dose. We expect that more dose will result in higher SNR, but after
Figure 3.13: MAPE versus relaxation parameter for CARP and DROP reconstructions at the 10th iteration of 3 minute, 6 minute, and 12 minute datasets. The dark grey band represents 0.5% error and the lighter grey band represents 1% error.

10 iterations, it is likely that iterative solutions overcome the reduction in the number of histories.

Figure 3.15 shows the MTF-10% for the 10th iteration of CARP and DROP reconstructions for the 3, 6, and 12 minute scans. The CARP reconstructions show varied MTF-10% and shows a weak preference for a 6 minute scan. The DROP reconstructions show equal MTF-10% for all dose levels and relaxation parameters.

Figures 3.16 and 3.17 show the MAPE and SNR for the overall optimal relaxation parameters for CARP, CARP+TVSi, DROP, and DROP+TVSi reconstructions of 3, 6, and 12 minutes scans. Figure 3.16 shows that after the first three to five iterations, the MAPE is approximately equal regardless of dose, assuming the appropriate relaxation parameter is chosen. The dose, however, has a much greater impact on the SNR, as shown in Figure 3.17.
Figure 3.14: SNR versus relaxation parameter for CARP and DROP reconstructions at the 10th iteration of 3 minute, 6 minute, and 12 minute datasets. The black dashed line is at SNR = 100, which is the clinical goal for image quality.

Figure 3.15: MTF-10% versus relaxation parameter for CARP and DROP reconstructions at the 10th iteration of 3 minute, 6 minute, and 12 minute datasets.
Figure 3.16: The MAPE versus iteration number for the optimal lambdas for each of the 12 categories (4 algorithms, 3 dose levels).
Figure 3.17: The SNR versus iteration number for the optimal lambdas for each of the 12 categories (4 algorithms, 3 dose levels).
Table 3.3 summarizes the optimal relaxation parameters and number of iterations of each of the iterative solvers for spatial resolution, noise, accuracy, and overall. The overall optimal images of the 3 minute scan of the peg phantom are shown in Figure 3.18. Table 3.4 shows the image quality results for the 12 minute scans. The overall optimal images of the 12 minute scan of the peg phantom are shown in Figure 3.19. As expected, the SNR tends to be lower on the 3 minute dataset and higher on the 12 minute dataset than what we measured on the 6 minute data set in Table 3.2. The accuracy and spatial resolution on the 3 and 12 minute images are about equal to those on the 6 minute image. The images optimized for spatial resolution, noise, and RSP accuracy for the 3 and 12 minute scans can be seen in Appendix B.

Overall, good image quality can be obtained with any level of dose with appropriate choice of algorithm and relaxation parameter. The dose is most influential on the level of noise in the image, with higher dose leading to higher SNR. Optimization of the relaxation parameter is necessary no matter how many proton histories are used in the reconstruction.
Table 3.3: Image quality metrics for 3 minute dataset. Optimal relaxation parameter $\lambda$ and iteration number (IN) for five pCT reconstruction options, optimized for Spatial Resolution (SR), Noise, and RSP Accuracy. The three metrics are combined into a cost function to determine an “overall” optimum. For each image, we report the mean average percent error (MAPE), the insert with the highest (max) and lowest (min) percent error, the MTF-10%, the SNR in the background, the CNR between the brain insert and background, and the result of the cost function.

<table>
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<tr>
<th>Algorithm</th>
<th>Metric</th>
<th>$\lambda$</th>
<th>IN</th>
<th>MAPE</th>
<th>Max % Err</th>
<th>Min % Err</th>
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<th>SNR</th>
<th>CNR</th>
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(a) CARP, $\lambda = 0.01$, IN=4
(b) CARP+TVS, $\lambda = 0.04$, IN=16
(c) DROP, $\lambda = 0.24$, IN=3
(d) DROP+TVSi, $\lambda = 0.05$, IN=17
(e) DROP+TVSb, $\lambda = 0.9$, IN=14

Figure 3.18: Optimal reconstructed images of the 3 minute dataset with each of the five iterative algorithms.
Table 3.4: 12 minute scan results. Optimal relaxation parameter $\lambda$ and iteration number (IN) for five pCT reconstruction options, optimized for Spatial Resolution (SR), Noise, and RSP Accuracy. The three metrics are combined into a cost function to determine an “overall” optimum. For each image, we report the mean average percent error (MAPE), the insert with the highest (max) and lowest (min) percent error, the MTF-10%, the SNR in the background, the CNR between the brain insert and background, and the result of the cost function.

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<td>7.1</td>
<td>0.2033</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>0.005</td>
<td>2</td>
<td>0.661</td>
<td>1.84 (Sinus)</td>
<td>0.018 (Enamel)</td>
<td>3</td>
<td>144.4</td>
<td>6.97</td>
<td>0.0101</td>
</tr>
<tr>
<td>CARP+TVSi</td>
<td>SR</td>
<td>1.4</td>
<td>15</td>
<td>17.86</td>
<td>56.61 (Sinus)</td>
<td>5.99 (Brain)</td>
<td>10</td>
<td>4.893</td>
<td>0.252</td>
<td>0.1945</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
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<td>1</td>
<td>0.519</td>
<td>1.18 (Sinus)</td>
<td>0.004 (Dentin)</td>
<td>3</td>
<td>517.0</td>
<td>28.1</td>
<td>0.0100</td>
</tr>
<tr>
<td></td>
<td>Noise</td>
<td>0.002</td>
<td>5</td>
<td>0.545</td>
<td>1.46 (Sinus)</td>
<td>0.014 (Dentin)</td>
<td>3</td>
<td>2272</td>
<td>83.8</td>
<td>0.0100</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>0.01</td>
<td>1</td>
<td>0.519</td>
<td>1.84 (Sinus)</td>
<td>0.004 (Dentin)</td>
<td>3</td>
<td>517.0</td>
<td>28.1</td>
<td>0.0100</td>
</tr>
<tr>
<td>DROP</td>
<td>SR</td>
<td>1.8</td>
<td>8</td>
<td>1.72</td>
<td>6.63 (Sinus)</td>
<td>0.065 (CB)</td>
<td>8</td>
<td>24.18</td>
<td>0.990</td>
<td>0.0269</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
<td>0.6</td>
<td>1</td>
<td>0.337</td>
<td>0.668 (Disc)</td>
<td>0.106 (Dentin)</td>
<td>3</td>
<td>155.2</td>
<td>7.34</td>
<td>0.0100</td>
</tr>
<tr>
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<td>17</td>
<td>12.37</td>
<td>105.1 (Sinus)</td>
<td>0.272 (Enamel)</td>
<td>2</td>
<td>167.7</td>
<td>7.13</td>
<td>0.2037</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
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<td>1</td>
<td>0.337</td>
<td>0.668 (Disc)</td>
<td>0.106 (Dentin)</td>
<td>3</td>
<td>155.2</td>
<td>7.34</td>
<td>0.0100</td>
</tr>
<tr>
<td>DROP+TVSi</td>
<td>SR</td>
<td>1.8</td>
<td>8</td>
<td>1.72</td>
<td>6.63 (Sinus)</td>
<td>0.006 (CB)</td>
<td>8</td>
<td>25.33</td>
<td>1.03</td>
<td>0.0263</td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
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<td>0.337</td>
<td>0.668 (Disc)</td>
<td>0.098 (Dentin)</td>
<td>3</td>
<td>168.3</td>
<td>7.94</td>
<td>0.0100</td>
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<tr>
<td></td>
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<td>20</td>
<td>10.53</td>
<td>88.7 (Sinus)</td>
<td>0.204 (Enamel)</td>
<td>2</td>
<td>468.1</td>
<td>18.1</td>
<td>0.1745</td>
</tr>
<tr>
<td></td>
<td>Overall</td>
<td>0.05</td>
<td>16</td>
<td>0.426</td>
<td>0.863 (Disc)</td>
<td>0.069 (Enamel)</td>
<td>3</td>
<td>351.9</td>
<td>17.9</td>
<td>0.0100</td>
</tr>
</tbody>
</table>
Figure 3.19: Optimal reconstructed images of the 12 minute dataset with each of the five iterative algorithms.

(a) CARP, $\lambda = 0.005$, IN=2

(b) CARP+TVS, $\lambda = 0.01$, IN=1

(c) DROP, $\lambda = 0.60$, IN=1

(d) DROP+TVSi, $\lambda = 0.05$, IN=16
3.5 Streak Artifacts

X-ray CT images produce streak artifacts in the presence of high density artifacts. Proton CT images do not show these same artifacts. Figure 3.20 compares an x-ray CT and a proton CT of a customized CIRS pediatric head phantom with a gold crown. The xCT image (Figure 3.20a) shows large variations in HU emanating from the gold crown. This is not seen in the pCT image (Figure 3.20b). The grey scale of the two images are comparable. Figure 3.21 shows a comparison of the profiles through the center of the image along the vertical axis. The variation in HU from the streak artifacts are visible between the black dashed lines. The same section in the RSP profile shows no variation and evidences the lack of streaking in the pCT image. The variation in this region of the xCT HU profile after converting to RSP is ±45.2% from the median value. The variation in the same section of the pCT profile is ±1.9% from the median value.
Figure 3.20: X-ray CT image and proton CT image of a pediatric head phantom with a gold crown. The artifacts seen in the x-ray image are nearly non-existent in the proton CT image. Note that the greyscales are set such that the brain material is approximately the same level of grey in both images.

Figure 3.21: HU and RSP profile of the xCT and pCT through the center of the phantom along the vertical axis. The region between the black lines shows the variation in the HU and the consistency in the RSP.
As discussed in Section 1.3.1, proton radiography can be used for pre-treatment patient alignment and detection of anatomical changes and proton range errors immediately prior to treatment. In this chapter we look at the feasibility of translating proton radiography into clinical use by determining the minimum beam energy necessary to image patients and the application of detecting proton range errors with proton radiographic images. Looking forward to clinical applications, proton radiographic images will be taken in beam’s eye view (BEV). This will allow for patient alignment in the transverse direction and for range errors to be detected.

4.1 Minimum Beam Energy Requirements for Clinical Proton Imaging

Most current clinical proton accelerators have a maximum proton beam energy of 235 MeV or 250 MeV, with only one site having a higher maximum beam energy of 330 MeV [36]. These energies have a maximum range in water of 34 cm, 37 cm, and 60 cm, respectively. In order for proton radiography to be clinically feasible, we need to determine if the clinical proton beam energies are sufficient to image the majority of patients undergoing proton therapy.
4.1.1 Methods

We wrote an algorithm in Python 3 [69] to calculate the WET of a set of straight-line proton trajectories in a divergent beam geometry passing through a patient along the proton treatment beam axis. The algorithm reads in DICOM files of a patient’s planning CT and treatment plan. From these files, the algorithm uses the CT data, treatment isocenter position, treatment beam gantry angle, patient support angle, and aperture or pencil-beam spot pattern data. We use this information, along with a user-defined source-to-isocenter distance (SAD), to determine the geometry of the set of proton trajectories and to calculate the WET of the individual ray.

4.1.1.1 Setup

Before we can calculate the WET of the set of trajectories, we need to determine the path of each trajectory in the set in relation to the patient CT data. The treatment isocenter has a defined location relative to the CT data set and the gantry and patient support angles rotate relative to CT data set about the treatment isocenter, as shown in Figure 4.1. We choose the coordinate system, \((X,Y,Z)\), in reference to the CT with the treatment isocenter located at \((0,0,0)\), the axes aligned with the pixels and the CT slices stacked along the \(Z\) axis. The central proton trajectory, passing from the source point through the treatment isocenter, rotates relative to the CT coordinate system according to the gantry and patient support angles. Divergent trajectories in a cone beam geometry surround the central proton trajectory.

Figure 4.2 shows a schematic of the CT slice containing the isocenter and the protons traversing a patient slice for visualization of the trajectories calculated by the algorithm.
Assume the large blue oval is a patient contour and the embedded green oval is the planning target volume (PTV). The dashed lines represent the trajectories of protons in an AP field initiating at the source point and traversing the patient in a divergent beam. The horizontal line represents the isocenter plane which is defined as the plane normal to the central beam axis and crosses through the treatment isocenter. The stars on that plane represent points in the PTV through which the calculated trajectories pass. The segment of the proton trajectories included in the calculation of patient WET are the solid line segments extending past the patient contour by 2 cm on each end. In practice, we calculate the trajectories in 3 dimensions. The details of the calculations are described in the following paragraphs.

**Isocenter Grid.** The first step is to determine where each proton trajectory passes through the isocenter plane. These points are represented by the stars in Figure 4.2. We chose to only calculate trajectories passing through the PTV as those trajectories are the most important for pre-treatment range accuracy checks. We estimate the PTV from the
Figure 4.2: Transverse view of the trajectories that are calculated for this study. Straight-line paths in a cone-beam geometry are assumed for the proton trajectories. The divergent rays fall on trajectories that emanate from the effective source point and pass through a point in a 1 cm-spaced grid that lies on the isocenter plane within the PTV.

aperture shape for a uniformly scanned treatment or the pencil beam scanned (PBS) spot pattern for a PBS treatment which are read in from the DICOM RTPLAN files. From either the aperture shape or the PBS spot pattern, we create a grid with points spaced 1 cm apart on the isocenter plane. This grid, herein called the isocenter grid, is contained within the extents of the PTV and is usually centered on the treatment isocenter. Each proton trajectory that is calculated by the program passes through one of these points in the isocenter grid.

**Imaging Axis and Divergence Angles.** The central imaging axis is the central proton trajectory in the cone beam geometry that passes from the source point through the
treatment isocenter. The direction of the trajectory is defined by the treatment gantry angle \(\theta_g\) and patient support angle \(\theta_k\) known from the DICOM RTPLAN file. The Euler matrices in Equations 4.1 and 4.2 rotate the set of trajectories according to the imaging axis.

\[
R_g = \begin{pmatrix}
\cos(-\theta_g) & -\sin(-\theta_g) & 0 \\
-\sin(-\theta_g) & \cos(-\theta_g) & 0 \\
0 & 0 & 1
\end{pmatrix} \tag{4.1}
\]

\[
R_k = \begin{pmatrix}
\cos(\theta_k) & 0 & \sin(\theta_k) \\
0 & 1 & 0 \\
-\sin(\theta_k) & 0 & \cos(\theta_k)
\end{pmatrix} \tag{4.2}
\]

The diverging trajectories initiate at the source point and pass through one of the points in the isocenter grid \(P(P_x, P_z)\), as shown in Figure 4.3. \(P_x\) and \(P_z\) are the distances between the isocenter point and the projection of point \(P\) onto the X and Z axes, respectively. The proton beam at NMCPC has a cone beam geometry with an effective point source 206 cm upstream of the treatment isocenter. The two divergence angles, \(\theta_{Dz}\) and \(\theta_{Dx}\), are then calculated from the SAD and \(P_z\) or \(P_x\), respectively, with simple trigonometric formulas as follows:

\[
\theta_{Dz} = \tan^{-1} \frac{P_z}{\text{SAD}} \tag{4.3}
\]

\[
\theta_{Dx} = \tan^{-1} \frac{P_x}{\text{SAD}} \tag{4.4}
\]

The divergent trajectories are then rotated from the central axis about the source point.
Figure 4.3: The divergence angles of each ray are calculated using basic trigonometry of the source-to-isocenter distance SAD and the distance from the isocenter to the point \( P(P_x, P_z) \) on the isocenter plane that the trajectory ray passes through.
according to the two divergence angles using the following Euler rotation matrices:

\[
R_{dz} = \begin{pmatrix}
1 & 0 & 0 \\
0 & \cos(\theta_{Dz}) & -\sin(\theta_{Dz}) \\
0 & \sin(\theta_{Dz}) & \cos(\theta_{Dz})
\end{pmatrix}
\]  \hspace{1cm} (4.5)

\[
R_{dx} = \begin{pmatrix}
\cos(-\theta_{Dx}) & -\sin(-\theta_{Dx}) & 0 \\
\sin(-\theta_{Dx}) & \cos(-\theta_{Dx}) & 0 \\
0 & 0 & 1
\end{pmatrix}
\]  \hspace{1cm} (4.6)

After the trajectory is rotated according to the four Euler matrices, we can then calculate the WET as described in the next section.

4.1.1.2 Calculation of WET

The trajectory of each ray is discretized into a set of equally spaced points. Each of these points falls in a voxel in the patient CT. The HU in that voxel is assigned to the point to be used in the calculation of the WET. For consistency, 2 cm worth of air on both sides of the patient are included in the WET. We find the contour of the patient by looking for the set of points where all of the HU are below -1000, which correspond to the HU of air. The HU for each point is then converted to RSP by extrapolating the points in the HU-to-RSP conversion curve used at NMCPC shown in Figure 4.4. The WET for the trajectory is calculated from the HU for each point and the spacing \( \ell \) between the points according to Equation 4.7

\[
\text{WET} = \ell \cdot \sum_{n} \text{RSP}_n
\]  \hspace{1cm} (4.7)
where $\ell$ is calculated by

$$\ell = 0.2 \times \text{pixel} \sqrt{\cos^2(-\theta_g) \cos^2(\theta_k) + \sin^2(-\theta_g) + \cos^2(-\theta_g) \sin^2(\theta_k)}.$$  

(4.8)

where the point spacing is one-fifth of the CT pixel size (0.2 x pixel) and adjusted for the rotation of the trajectory. This spacing was chosen to ensure minimal errors due to smearing across pixel boundaries or skipping pixels that are crossed at an angle. Examples of these are shown in Figure 4.5.

4.1.1.3 Incorporating Uncertainties

The calculation of WET directly from the x-ray CT, assumes a perfect calibration from HU to RSP. However, as discussed in Section 1.3.3, the calibration used in the clinic causes errors in proton range by $\pm 3.5\%$. Therefore, we add a $+3.5\%$ margin on all the WET
Figure 4.5: Schematic showing possible errors from the chosen spacing. Figure (a) shows an example where the pixel boundary falls between two points. Figure (b) shows an example where the path clipped a corner. This corner does not get included in the WET calculation because the point doesn’t fall within the pixel. The smaller the pixel size, the less effect either of these scenarios have on the WET calculations.
values. This then becomes the WET through the patient. We do not care about the -3.5% WET value because protons that have sufficient energy to go through +3.5% will also have sufficient energy to traverse the smaller WET value.

We then add 20 mm of WET to account for additional detector material that the protons would need to pass through to get a detectable signal for imaging. We chose 20 mm based on the design of the ProtonVDA system discussed in Chapter 2. Each of the tracker planes are about 5 mm of WET, leaving 10 mm of residual range in the residual energy detector. As we will show in Section 4.2, 10 mm is sufficient to collect all protons out to 1.5σ of the range straggling. It may be useful to note, other proton imaging systems may require more or less additional WET.

At this point, the total WET that the protons need to pass through is the WET through the patient plus 3.5% plus 20 mm. We convert this total WET to energy using the Janni tables for water [27]. The Janni table also tells us the range straggling at one sigma. This is how we ensure that the 10 mm residual range in the energy detector is sufficient to collect over 95% of the protons.

4.1.2 Results and Discussion

The set of patients used for this study consisted of 548 patients treated at NMCPC during 2018 that were enrolled in the Proton Collaborative Group registry study. The patient set consists of pediatrics and adults of both genders and includes a variety of anatomical sites. To further analyze results, the set of patients were separated into three categories by anatomical region: head/neck/brain, torso/abdomen/breast, and pelvis.

The proton trajectory with the largest WET and, therefore, the largest required energy in a patient defines the minimum energy required to image the patient. Histograms of the
minimum energy for each anatomical site are shown in Figure 4.6. Table 4.1 shows the percent of patients that can be imaged with 235 MeV, 250 MeV, and 330 MeV, as well as the minimum energy necessary to image all patients.

Many of the head/neck/brain patients who were deemed to have WET too large for proton radiography had at least one treatment field (i.e., vertex field) that would require a collision between the detector and the patient as shown in Figure 4.7. In these cases, proton imaging would not be feasible regardless of available proton energy. If we remove all the fields with $60^\circ \leq \theta_g \leq 120^\circ$ and $240^\circ \leq \theta_k \leq 300^\circ$ or $240^\circ \leq \theta_g \leq 300^\circ$ and $60^\circ \leq \theta_k \leq 120^\circ$ (i.e., within 30° of a superior beam), we can image 97% of patients with 235 MeV and 99% patients with 250 MeV protons. The minimum energy necessary to image all patients is reduced to 250.47 MeV.
Table 4.1: Percent of patients that can have a proton radiograph taken along the treatment field.

<table>
<thead>
<tr>
<th></th>
<th>Num Patients</th>
<th>235 MeV</th>
<th>250 MeV</th>
<th>330 MeV</th>
<th>Min Energy (MeV)</th>
<th>% Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>548</td>
<td>59.12%</td>
<td>63.14%</td>
<td>100.00%</td>
<td>324.34</td>
<td>95%</td>
</tr>
<tr>
<td>Head/Neck/Brain</td>
<td>221</td>
<td>93.21%</td>
<td>96.83%</td>
<td>100.00%</td>
<td>260.56</td>
<td>99%</td>
</tr>
<tr>
<td>Torso/Abdomen/Breast</td>
<td>118</td>
<td>92.37%</td>
<td>98.31%</td>
<td>100.00%</td>
<td>251.64</td>
<td>99%</td>
</tr>
<tr>
<td>Pelvis</td>
<td>209</td>
<td>4.31%</td>
<td>7.66%</td>
<td>100.00%</td>
<td>324.34</td>
<td>95%</td>
</tr>
</tbody>
</table>

Figure 4.7: Schematic showing an example of a treatment field with $\theta_g = 75^\circ$ and $\theta_k = 270^\circ$ causing a collision between the patient and the imaging system.
The high percentage of torso, abdomen, and breast patients that can receive a proton radiograph is likely due to the large amount of low-density tissues in the region, such as lung and fat. In a similar vein, the low percentage of pelvic cases that can be imaged with proton radiography may be due to the high-density bony anatomy, such as the femurs, that the protons must pass through and the common use of lateral fields in the pelvic region.

4.1.2.1 Multiple Coulomb Scattering

For each of our proton trajectories, we assumed straight line paths. As discussed in Section 1.3.3, this is not an accurate picture of the path of protons. Protons traversing matter undergo multiple Coulomb scattering which causes each proton to take a slightly different path. Each proton is just as likely to scatter left as it is to scatter right. This means that for many protons, the average scattering angle is zero [70]. Additionally, compared to range straggling, the difference in path length between a straight-line path and the scattered trajectory is relatively small. We accounted for range straggling, which creates much more variability on the WET than multiple Coulomb scattering. Because we are not working in homogeneous material, some protons may scatter into higher or lower density features, which may cause larger variability in the WET. To get a full measure of the energy required for all protons, a full Monte Carlo simulation could be performed.

4.2 Conclusions

Over 90% of patients with tumor volumes in the head/neck/brain or abdomen/torso/breast regions can be imaged with proton radiography in BEV using clinical proton beams. Conversely, over 90% of patients with tumor volumes in the pelvic region require proton beam
energies larger than 250 MeV to image with proton radiography in BEV. To image all patients in BEV with proton radiography, a proton beam energy of at least 325 MeV is required.

### 4.3 Detection of Anatomical Changes

As discussed in Section 1.3.1, proton radiography has been proposed as a method to detect anatomical changes between fractions. A proton radiograph taken immediately prior to treatment can be compared to either a pDRR created from the treatment planning CT or a proton radiograph taken at the same time as the treatment planning CT. The proton radiograph measures the proton range through the patient. If there is a change in anatomy or errors from the HU-to-RSP conversion, the WET through the patient will be different than the what was measured in the planning CT and produced in the pDRR.

#### 4.3.1 Methods

To detect changes, we take two radiographs of the same phantom with a change of WET between the radiographs. We then create difference maps between the two images by subtracting the corresponding pixels. To demonstrate the method, we started by imaging phantoms with simple geometry. The first set up was a block of polystyrene with a wedge of the same material placed in front as shown in Figure 4.8. The block was first imaged individually, then imaged again with the wedge placed in front. The two proton radiographs and the corresponding difference map are shown in Figure 4.9.

To determine the clinical usefulness, we then tested the method with different materials in a more realistic geometry. A customized pediatric head phantom (CIRS, Norfolk, Virginia) has a 4 cm × 4 cm × 4 cm cavity in the posterior fossa. This cavity was filled with 2 cm
Figure 4.8: Polystyrene block with polystyrene wedge placed in front. The block was first imaged individually. The wedge was then placed in front of the block and the setup was imaged in the geometry shown in the picture.

× 4 cm × 4 cm inserts of varying tissue equivalent materials and two 1 cm-thick spacers on either side of the insert, as shown in Figure 4.10. We first took a proton radiograph of the phantom with an insert made of brain-equivalent plastic. This radiograph was considered as our baseline. We then interchanged the inserts with six other tissue-equivalent plastic materials and radiographed the phantom in the same location to avoid mixing alignment and anatomical errors. We took radiographs in the anterior-posterior (AP) and lateral directions. Radiographs of several of the inserts in the AP and lateral direction are shown in Figure 4.11.

4.3.2 Results

Difference maps, such as those shown in Figure 4.12, are created by subtracting corresponding pixels between two radiographs. The proton radiograph of the brain insert is considered the baseline image and all other radiographs are subtracted from that image. We calculated the mean and standard deviation in a 1200 pixel ROI located in the lateral center of the insert just below the air gap between the superior and inferior portions of the
Figure 4.9: Proton radiograph of polystyrene block, proton radiograph of the polystyrene block and wedge, difference map of the two images.

In both the AP and the lateral directions, the mean WET difference is calculated to be within 0.3 mm of truth with a standard error of less than 0.05 mm. The percent difference of the measured value in terms of the total range through the phantom is less than 0.2%. The standard error in the AP measurements is slightly higher overall than those in the lateral measurements. This can be attributed to more heterogeneous structures in the path of the
Figure 4.10: Pediatric head phantom with tissue-equivalent insert and spacers in place. Higher density inserts will appear brighter and lower density inserts will appear darker.

protons, creating more noise in the proton radiographic images, and therefore more noise in the difference maps.

4.3.3 Discussion

Proton treatment plans currently include a 3.5% proximal and distal range margin on the target volume due to the conversion errors between HU and RSP [71]. The errors we measured were well within the 3.5% margin and therefore would be useful for detecting anatomical changes. Proton CT has been predicted to reduce the range margins down to 1% [24]. If proton radiography were to be used in conjunction with proton CT, we are still under the 1% level and therefore could be useful to detect anatomical changes that could cause range errors.

In practice, it is possible that anatomical changes, HU-to-RSP errors, and patient alignment errors compound to net zero and a proton range error is not detected. Additionally, because the proton radiograph measures the WET through the entire patient, an error could
be detected that is downstream of the tumor volume and therefore would not cause an error in the range to the tumor. To avoid these possibilities and to disentangle the different errors, we propose taking two orthogonal proton radiographs by rotating the patient or gantry 90° relative to one another. This would give the additional information necessary to determine if there are errors affecting the proton range.
Figure 4.12: Difference maps corresponding to the radiographs in Figure 4.11. The proton radiograph with the brain insert is used as the base image and the radiographs with the other inserts are subtracted from the base. The black outline represents the ROI used to measure the WET differences shown in Tables 4.2 and 4.3.

Table 4.2: WET differences between the phantom with the brain insert and another tissue-equivalent insert for the AP orientation. The percent difference of total range in the last column is calculated as \( \frac{\text{Measurement Error}}{\text{Total Range} + \text{True WET Difference}} \times 100 \), where the total range is 16.32 cm.

<table>
<thead>
<tr>
<th>Insert</th>
<th>True WET Difference (cm)</th>
<th>Measured WET Difference, mean ± standard error (cm)</th>
<th>Measurement Error (cm)</th>
<th>Percent Difference of Total Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>-2.080</td>
<td>-2.073 ± 0.003</td>
<td>0.007</td>
<td>0.05</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>0.000</td>
<td>0.009 ± 0.002</td>
<td>0.009</td>
<td>0.06</td>
</tr>
<tr>
<td>Spinal Disc</td>
<td>0.060</td>
<td>0.065 ± 0.002</td>
<td>0.005</td>
<td>0.03</td>
</tr>
<tr>
<td>Trabecular Bone</td>
<td>0.120</td>
<td>0.130 ± 0.003</td>
<td>0.010</td>
<td>0.06</td>
</tr>
<tr>
<td>Dentin</td>
<td>0.910</td>
<td>0.936 ± 0.003</td>
<td>0.026</td>
<td>0.15</td>
</tr>
<tr>
<td>Cortical Bone</td>
<td>1.030</td>
<td>1.052 ± 0.002</td>
<td>0.022</td>
<td>0.13</td>
</tr>
<tr>
<td>Dental Enamel</td>
<td>1.430</td>
<td>1.453 ± 0.003</td>
<td>0.023</td>
<td>0.13</td>
</tr>
</tbody>
</table>
Table 4.3: WET differences between the phantom with the brain insert and another tissue-equivalent insert for the lateral orientation. The percent difference of total range in the last column is calculated as \( \frac{\text{Measurement Error}}{\text{Total Range} + \text{True WET Difference}} \times 100 \), where the total range is 12.04 cm.

<table>
<thead>
<tr>
<th>Insert</th>
<th>True WET Difference (cm)</th>
<th>Measured WET Difference, mean ± standard error (cm)</th>
<th>Measurement Error (cm)</th>
<th>Percent Difference of Total range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>-2.080</td>
<td>-2.073 ± 0.002</td>
<td>0.007</td>
<td>0.07</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>0.000</td>
<td>0.005 ± 0.001</td>
<td>0.005</td>
<td>0.04</td>
</tr>
<tr>
<td>Spinal Disc</td>
<td>0.060</td>
<td>0.054 ± 0.001</td>
<td>-0.006</td>
<td>-0.05</td>
</tr>
<tr>
<td>Trabecular Bone</td>
<td>0.120</td>
<td>0.118 ± 0.002</td>
<td>-0.002</td>
<td>-0.02</td>
</tr>
<tr>
<td>Dentin</td>
<td>0.910</td>
<td>0.900 ± 0.001</td>
<td>-0.010</td>
<td>-0.08</td>
</tr>
<tr>
<td>Cortical Bone</td>
<td>1.030</td>
<td>1.020 ± 0.001</td>
<td>-0.010</td>
<td>-0.08</td>
</tr>
<tr>
<td>Dental Enamel</td>
<td>1.430</td>
<td>1.423 ± 0.002</td>
<td>-0.013</td>
<td>-0.05</td>
</tr>
</tbody>
</table>
CHAPTER 5
CLINICAL APPLICATIONS AND FEASIBILITY OF PROTON CT

As discussed in Section 1.3.2, proton CT can replace x-ray CT in proton treatment planning. The advantages of proton CT include the direct measurement of RSP and reduced artifacts in the presence of high density implants. In this chapter, we discuss the minimum proton beam energy necessary to image typical proton therapy patients with proton CT and compare the accuracy of treatment plans created on proton CT images with those created on x-ray CT images.

5.1 Minimum Beam Energy Requirements for Clinical Proton Imaging

In order to feasibly implement proton CT into clinical use, it is necessary to determine the minimum beam energy necessary to image a majority of patients. The program developed in Section 4.1 was also used to calculate the WET of patients at several projection angles used for tomography. A proton CT can be approximated as many radiographs at various gantry angles with a patient support angle equal to 0°. For this study, we chose to calculate the WET for gantry angles at 10° increments between 0° and 180°. Because the protons pass through the entire patient, we can assume symmetry past 180°. For patients with large PTVs, it is possible that the WET of the trajectories from directly opposing angles are not
equal due to the divergence of the beam. However, this is only the case for a relatively few number of patients with large PTVs and would not greatly alter the final results.

5.1.1 Results

Figure 5.1 shows the percent of patients that can be imaged at each gantry angle for 235 MeV, 250 MeV, or 330 MeV protons, separated by anatomical site. Note that all head patients can be imaged with all three clinical proton beam energies. Figure 5.2 shows the minimum beam energy required to image each angle for the three anatomical sites.

Figure 5.1: Percent of patients that can be imaged with clinical protons by CT angle, separated by anatomical site. Note that in (b) all patients can be imaged at all gantry angles with all three beam energies.

Unlike proton radiography, there are no beam angles that would cause a collision of the detector and the patient. Therefore, the percent of head/neck/brain patients that can be
imaged with 235 MeV is much higher than the percent of patients that can be imaged with proton radiography. Proton centers would need proton beam energies of at least 330 MeV to image all patients at all angles. However, both the torso/abdomen/breast and pelvic data show a high angular dependence for the percent of patients that can be imaged with a beam energy of 235 MeV or 250 MeV. Many more patients can be imaged with angles corresponding to anterior-posterior beam directions (gantry angles $\sim 0^\circ$ or $\sim 180^\circ$) than patients that can be imaged with lateral and oblique beam angles. These results make a strong case for developing partial-angle proton CT or using proton radiography to create a patient-specific HU-to-RSP calibration curve [72].

5.2 Quantification of Predicted Proton Range Errors

As discussed in Chapter [1] proton treatment plans created on x-ray CT images have additional 3.5% distal and proximal error margins around the tumor volume. Creating treatment plans on proton CT images have been suggested to be able to reduce those margins to as low as 1% [24]. Additionally, proton CT has fewer artifacts from high-density implants,
which may also improve the treatment plans near the implants. The goal of this work is to quantify the accuracy of the proton range predicted in treatment planning.

5.2.1 Materials

The same pediatric head phantom used in Section 4.3 was used for this project. In addition to the cavity, this phantom was also modified with a gold crown and amalgam dental filling. We filled the cavity with a film holder made of brain-equivalent material. The film holder fits into the cavity and has a cylindrical piece which allows the film to be rotated to any beam direction. The holder fits a stack of 36 Gafchronic™ EBT3 radiochromic film (Gafchromic, Bridgewater, NJ). This stack of films act as planar dosimeters that allows us to measure the dose distribution in a 3D volume. Each film is 1.5 cm $\times$ 3 cm transverse size and 0.27 mm thick with an RSP value of 1.33 and a WET of 0.36 mm. The total stack as a physical thickness of about 1 cm.

EBT3 films have a central layer of blue polymer that is activated when exposed to radiation. The result is a darkened film where the opacity of the film is proportional to the

![Pediatric head phantom](image1.png)  ![Cavity in pediatric head phantom](image2.png)

Figure 5.3: Pictures of custom CIRS 715HN head phantom.
deposited dose. On either side of the active layer is a matte-polyester substrate. The films are optimal to measure doses between 0.2 and 10 Gy with near energy independence [73].

### 5.2.2 Treatment Planning and Irradiation

First, we scanned the phantom with the film stack in place with x-ray CT and proton CT. We then imported both of the CT images into RayStation Treatment Planning System (RaySearch, Stockholm, Sweden), a Monte Carlo-based treatment planning system used for clinical IMPT treatment plans. RayStation takes a CT in terms of HU and converts each pixel to stoichiometric composition then to RSP. To import the proton CT, we created an artificial one-to-one calibration to keep the RSP in each pixel.

Next, we created and optimized the treatment plan on the x-ray CT, then transferred the beam parameters and fluence pattern to the proton CT image and calculated the corresponding dose distribution. The treatment plan was created such that the spread-out Bragg peak (SOBP) was located just upstream of the film stack and overlapped with the first few films in the stack, as shown in Figure 5.4. The distal falloff of the SOBP then extends through the film stack. The maximum dose in the SOBP is 300 cGy. Finally, we delivered the treatment plan to the phantom with the film in place.

We tested two treatment fields: one vertex and one AP. The vertex field traverses relatively homogeneous materials and is used to test the methods. The AP field traverses heterogeneous materials, including high-, mid-, and low-density materials (bone, brain, sinus, respectively). A heterogeneous region causes higher amounts of proton scattering than homogeneous regions. This can lead to higher uncertainties in the proton range prediction. Figure 5.5 shows a schematic with the three fields and a comparison of one cross-section of the dose distribution for the AP field.
Figure 5.4: Top view schematic illustrating the setup of the treatment plan. The large oval is the head phantom, the tan square is the film cube and the dark green rectangle is the stack of films. The colorful overlay represents the dose where blue is low dose and red is high dose. The protons enter the phantom from the left and travel towards the film stack. The SOBP (dark red) is located upstream of the film stack and on the first few films in the stack. The dose from the distal fall-off then is recorded throughout the rest of the films.

5.2.3 Film Scans and Calibration

After the phantom has been irradiated with the treatment plan, the films are removed from the phantom and scanned using an Epson Perfection V700 Photo Scanner. Each film is scanned individually in the center of the scanning bed in a portrait orientation such that the long sides (3 cm) of the film are parallel with the long sides of the scanning bed. The scans are 48-bit using the red channel and have a resolution of 150 dpi. The scanned images are imported into OmniPro I’mRT (Ion Beam Applications, Louvain-La-Neuve, Belgium) analysis software where the film scans are cropped and calibrated from ADC to Dose.

A calibration curve is created by irradiating several films size 5 cm × 5 cm to known doses. After scanning the films, we import them to OmniPro where we calculate the mean ADC in a 49-pixel ROI in the center of the films. We correlate the ADC on each film to the
Figure 5.5: One slice of the AP treatment plan created on the xCT (left) and pCT (right). The color map represents the predicted dose on the slice where the maximum dose is the light purple in the center and the lowest dose is the dark blue on the edges. The overlaid large blue square is the film cube and the smaller rectangle is the film stack.

known dose and fit with a curve. To validate the calibration, we irradiated several films to the same doses as in the calibration and used the calibration to reproduce the dose. Due to interpolation and variations in film response, we saw up to an 8% error in the film dose with an average film dose error of 3%. These results are shown in Figure 5.6. A separate test utilized two films irradiated to 225 cGy, which was not one of the calibration points. We measured the dose on the two films to be 236 cGy and 235 cGy, showing a percent error of 5% and 4%, respectively.

After calibration, the film scans are cropped such that there is 0.5 mm padding around the film, then the pixels are rebinned into 1 mm² pixels to match the RTDOSE files exported from RayStation. The ROI is made to be smaller than the size of the film to avoid edge effects from scattering of the protons during treatment or the light rays from the scanner on the film. Finally, the film scans are then “stacked” and registered to the RTDOSE files with the treatment plan dose.
Figure 5.6: Variation of film dose after calibration. We irradiated two sets of films to the same dose as the calibration films. After the two sets were calibrated, we measured the percent error in the dose. The dose of all films showed a maximum percent error of 8% with a mean of 3%.

5.2.4 Determination of Range Error

The RTDOSE files from treatment planning are imported into OmniPro as 1 mm-thick dose planes to compare with the film stack. A two-dimensional gamma analysis of 3% in 3 mm is used to compare the dose plane-to-plane between the two distributions. A gamma score for each pixel is calculated by

\[ \Gamma = \sqrt{\left( \frac{\text{DTA}}{3 \text{ mm}} \right)^2 + \left( \frac{\% \text{Diff}}{3\%} \right)^2}, \]

where DTA is the distance to the pixel with the closest dose agreement and % Diff is percent difference between the dose in those two pixels. 3 mm and 3% are the target values for agreement. These values are common clinical standards. The percent of pixels with \( \Gamma < 1 \) is
the gamma pass rate. If the gamma pass rate equals 100% then every pixel in the plan has a corresponding pixel on the film within a 3 mm circumference that has a dose within 3%.

The range error is determined by calculating a gamma pass rate for every combination of exported planes from RayStation and films in the stack as illustrated in Figure 5.5. The depth of the film with the highest gamma pass rate is taken to be the true range of the protons. The range error for the stack is the average difference in the predicted stopping depth of the protons from the treatment plan and the true stopping depth of the protons from film. The average range error for all planes from the treatment plan is taken to be the range error for the stack.

5.2.5 A Note about LET

Protons are a form of high linear energy transfer (LET) radiation. LET is the amount of energy that an ionizing particle delivers to the material traversed per unit distance. At the very end of the proton range, i.e. in the distal falloff, the attenuation of the protons get higher and the dose produced on the EBT3 film is suppressed. We measured the effects
of LET on the film dose with the following procedure. EBT3 films of size 5 cm × 5 cm were used to measure the dose at six points along the distal falloff of an SOBP. The dose was also measured with an ion chamber at the same water equivalent depths. The dose difference was compared and a LET correction factor was created for each of the six depths. This correction factor was interpolated through into points with spacing equal to the film thickness. To test the effects of the LET dose suppression on the range determination, the dose distribution on the distal edge of an SOBP in for a vertex field in the pediatric head phantom was planned in RayStation and measured with film. The film dose was adjusted using the LET correction curve and compared with the uncorrected dose, as shown in Figure 5.8. The range of the protons, in this case defined at the point where the dose hits 80% of the maximum dose, shifted distally by one to two film thicknesses, or 0.27 - 0.54 mm. This is well within our measurement errors, and therefore, for our purposes, ignored in the range error determination described in the previous section.

![Figure 5.8: LET-corrected and uncorrected dose-depth curve of the distal falloff of an SOBP for the vertex field in the pediatric head phantom. The 80% dose falloff shifts by 0.27 mm with LET correction.](image)
5.2.6 Results

5.2.6.1 Vertex Field

We started with the vertex field because of the homogeneity of the field. The protons will scatter less in this field and we should see a high accuracy in the range predictions created on both the xCT and pCT images. Figure 5.9 shows a heat map of the gamma scores (from 0% to 100%) matching each plane in the TPS dose cloud to each film. The bottom left corner of the plot corresponds to the front of the film stack and the top right corner is the bottom of the film stack. The strong yellow band in each of the gamma score maps shows that we are able to confidently compare the dose planes from the TPS to the films. From this data, we extract the depth of the film that shows the highest gamma score for each TPS plane, as shown in Figure 5.10. We then fit the maximum gamma scores with a linear function of slope equal to one and record the y-intercept. We force the slope to be equal to one because the depth offset should be the same throughout the entire film stack. The range error is the y-intercept of the fit divided by a factor of $\sqrt{2}$. Table 5.1 summarizes the results of the three trials of the vertex field. Both the xCT and pCT show minimal range errors (within 0.5 mm) and gamma scores above 95%.

<table>
<thead>
<tr>
<th></th>
<th>Range Error (mm)</th>
<th>Ave Max $\Gamma$ Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>xCT</td>
<td>pCT</td>
</tr>
<tr>
<td>Trial A</td>
<td>0.33±0.09</td>
<td>0.42±0.13</td>
</tr>
<tr>
<td>Trial B</td>
<td>0.22±0.08</td>
<td>0.36±0.10</td>
</tr>
<tr>
<td>Trial C</td>
<td>0.39±0.08</td>
<td>0.50±0.13</td>
</tr>
<tr>
<td>Average</td>
<td>0.31±0.05</td>
<td>0.41±0.07</td>
</tr>
</tbody>
</table>
Figure 5.9: Vertex field $\Gamma$ scores for each combination of film and TPS dose plane.
Figure 5.10: Vertex field TPS dose plane depth vs film depth for the maximum $\Gamma$ scores. The blue points are the location of the maximum $\Gamma$ scores for each film. The black line represents where the data would be if the TPS accurately predicted the range of the proton and the light blue line is a linear fit of the data with slope forced equal to one. The offset is the y-intercept of the linear fit divided by $\sqrt{2}$.
5.2.6.2 AP Field

The AP field has to the heterogeneous anatomy and the high contrast boundaries in the sinus region. Figure 5.11 shows the \( \Gamma \) scores for each TPS dose plane matched to each film. Figure 5.12 shows the depths of the maximum gamma scores in each row and the linear fit. Table 5.2 summarizes the results of the three trials. The range error for the xCT is marginally higher than the range error for the pCT. However, the average gamma score is almost 20\% lower for the pCT than for the xCT.

Table 5.2: AP results

<table>
<thead>
<tr>
<th></th>
<th>Range Error (mm)</th>
<th>Ave Max ( \Gamma ) Score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>xCT</td>
<td>pCT</td>
</tr>
<tr>
<td>Trial A</td>
<td>0.31±0.19</td>
<td>-0.22±0.12</td>
</tr>
<tr>
<td>Trial B</td>
<td>0.24±0.21</td>
<td>-0.24±0.12</td>
</tr>
<tr>
<td>Trial C</td>
<td>0.13±0.19</td>
<td>0.05±0.10</td>
</tr>
<tr>
<td>Average</td>
<td>0.23±0.11</td>
<td>-0.11±0.06</td>
</tr>
</tbody>
</table>
Figure 5.11: AP field $\Gamma$ scores for each combination of film and TPS dose plane.
Figure 5.12: AP field TPS dose plane depth vs film depth for the maximum $\Gamma$ scores. The blue points are the location of the maximum $\Gamma$ scores for each film. The black line represents where the data would be if the TPS accurately predicted the range of the proton and the light blue line is a linear fit of the data with slope forced equal to one. The offset is the $y$-intercept of the linear fit divided by $\sqrt{2}$. 
5.2.7 Discussion and Conclusions

In both fields, we measured range errors of less than $\pm0.5\text{ mm}$ on both the pCT and xCT image. The vertex field produced high $\Gamma$ scores ($>95\%$) on both the pCT and xCT plans. The AP field showed lower $\Gamma$ scores for the pCT ($77.6\%$ to $82.7\%$) than for the xCT ($88.0\%$ to $99.9\%$).

The potential uncertainties in the $\Gamma$ pass rate come from the registration of the two CTs in RayStation and also the registration between the film stack and treatment plan dose distribution. There is up to $0.5\text{ mm}$ offset in the registration of the two CT images relative to each other in the treatment planning system due to the orientation of the isocenter. Then the dose distribution from the treatment planning system needs to be registered in the transverse plane. The registration in OmniPro has the potential to introduce large errors. However, the $\Gamma$ score criteria is $3\text{ mm}$ which can encompass errors up to $1\text{ mm}$. Uncertainties in the final range error can also be attributed to the finite thickness of the films and the larger finite thickness of the exported planes from RayStation. The averaging on each could give false positives and lower the $\Gamma$ scores overall.

Additionally, our methods will likely produce artificially good results for the treatment plans created on the xCT. The treatment planning system is designed for proton therapy treatment planning on x-ray CT. The HU-to-RSP conversion curves in RayStation are calibrated using tissue-equivalent plastics, similar to the ones used in the pediatric head phantom. Therefore, the treatment plans created on xCT images will not see the same levels of proton range uncertainty as what is likely in a patient. For conclusive results, this experiment should be repeated using animal tissues.
CHAPTER 6
CONCLUSION

6.1 Proton Radiography

We quantified the image quality of proton radiographic images produced by the Proton-VDA system. We compared the use of the MLP-binning reconstruction method with the use of iterative solvers. The MLP-binning reconstruction shows an average WET error of 0.1% and the CARP reconstruction shows an average WET error of 0.3%. On average, we measured the CNR to be 30% lower on the CARP images than the MLP-binning images. Reconstructing with CARP marginally increases the spatial resolution by 0.008 mm$^{-1}$ on average. Both reconstruction methods produce sufficient image quality for clinical use. As we saw with proton CT, the image quality in iterative reconstructions is highly dependent on the parameter choice. A more careful parameter selection could continue to improve image quality. Additionally, the noise levels in the CARP images could be improved by the addition of a smoothing filter, such as the TVS algorithm discussed for proton CT in Section 3.2.6.

The MLP-binning reconstruction requires less time and reconstruction power. For many of the use cases of proton radiography, the patient will be on the table. Therefore, the speed of reconstruction could outweigh any improvement that could be seen with CARP images.

Clinically, patient alignment with proton radiography has already been validated using synthetic proton radiographic images from real patient data with accuracy better than 0.5 mm [32]. In this dissertation, we showed that the MLP-binning method is sufficient for detecting anatomical changes in a pediatric head phantom that could affect the proton
range to the tumor. We were able to detect range changes as small as 0.06 cm to within 0.05% in both homogeneous and heterogeneous fields. These results give evidence that proton radiography could replace x-ray radiography for patient alignment while having the additional benefit of detecting anatomical changes that could affect the range of the proton. However, before clinical use more realistic range changes should be studied. This includes detecting changes in WET produces by smaller inserts or spherical inserts where a change in range may not be as visually obvious. Additionally, real tissues have less homogeneity in a single tissue type and therefore may be harder to detect small range errors.

6.2 Proton CT

We empirically studied the relationship between image quality, imaging dose, and relaxation parameter on proton CT images. We measured the spatial resolution with MTF, the noise levels with SNR and CNR, and the RSP accuracy of proton CT reconstructions using known RSP values of tissue substitutes. We observed that noise and spatial resolution work in opposition of each other, where an image with high spatial resolution also tends towards high noise and vice versa. The accuracy is also worse when optimizing for only spatial resolution or only noise. Additionally, it is important to optimize not only the MAPE in the image, but also the individual RSP errors for a wide range of densities and RSP values. The iterative reconstruction methods assume a system with no noise. When noise is added to the system, such as is the case for pCT, the algorithm may find local minima that do not necessarily optimize all image quality metrics simultaneously. This means that all three image quality metrics need to be optimized simultaneously. This led to the development of our weighted cost function which combines the three metrics of image quality. The weighted cost function includes target values for each of the metric, allowing the user to optimize the
image specifically for clinical use. We optimized for general use, but if a particular use case does not require high spatial resolution or high accuracy, the cost function is easily adjusted.

Appropriate selection of relaxation parameter and iteration number is necessary to achieve high image quality. However, regardless of dose or algorithm-type, with appropriate choice of relaxation parameter and iteration number, the images can always be optimized for good image quality. Using the cost function to define the best overall image quality, TVSi shows little influence on the cost function value and overall RSP accuracy compared to CARP or DROP images without TVS. CARP+TVSi shows a reduction of SNR and CNR with an increase in spatial resolution compared to CARP. DROP+TVSi shows an increase in SNR and CNR with no affect on the spatial resolution when compared to DROP. Visually, the higher spatial resolution and lower noise of the CARP+TVSi images seem to be a favorable tradeoff. However, a clinical use case where spatial resolution is less important than noise may favor one of the DROP algorithms. DROP+TVSb shows a large increase in SNR and CNR but a decrease in spatial resolution when compared to DROP and DROP+TVSi. Additionally, we saw that the streak artifacts caused variations in the x-ray CT images to be $\sim 45\%$. These streak artifacts were all but missing in the proton CT image where the variations in the same profile are $\sim 2\%$.

Clinically, we presented proof that proton CT does at least as well as x-ray CT for predicting the proton range in a head phantom with realistic tissue and bone substitutes. We created treatment plans on an x-ray CT and a proton CT of a pediatric head phantom and compared the predicted dose distribution on the distal edge to the dose measured on radiochromic films. The dose distribution on the distal edge from the x-ray CT treatment plan and the proton CT treatment plan showed range errors less than 0.5 mm. These errors are well within 1% of the total range meaning that there is evidence to reduce the distal and proximal treatment planning margins. The tissue-equivalent plastics in the phantom, however, is historically easy to predict proton range since similar materials are used for
system calibration. Our work did act as a proof of concept for the method and the project should be repeated with animal tissues. Post-mortem animal tissues would create a more realistic set up and may give sufficient evidence as to whether or not proton CT images can reduce the treatment planning margins. The concern with the animal tissue set up may be that since the animal tissues decay over time, the CTs, treatment plans, and irradiations must be executed in a timely manner. Any decay in the tissues could result in poor results.

6.3 Clinical Feasibility

We calculated the percent of patients that could be imaged with clinical proton beam energies and the minimum proton beam energy that is required to image all patients. Most proton centers currently have 235 MeV beams available. We showed that 235 MeV protons are sufficient for imaging over 90% of head, neck, and brain patients and torso, breast, and abdomen patients with proton radiography. Only 4% of pelvic patients can be imaged with proton radiography with 235 MeV beams. The high percentage of patients that can be imaged immediately with proton radiography makes it feasible for clinical implementation. Proton centers with 250 MeV protons would be able to image even more patients with proton radiography.

Over 90% of head, neck, and brain patients can be imaged with proton CT with 235 MeV protons. However, only 40% of torso, breast, and abdomen patients can be imaged with proton CT and only 2% of pelvic patients can be imaged with proton CT with 235 MeV protons. More developments may be necessary before proton CT may be feasible for clinical implementation. The development of partial-angle proton CT would raise the number of patients who could be imaged with proton CT and therefore improve the feasibility of immediate clinical implementation. Alternatively, a beam energy of 330 MeV, such as what
is available at the ProTom center in Flint, Michigan [36], would be sufficient for proton radiography or CT of all treatment sites.

Overall, all testing to date indicates that the proton imaging hardware and software are of sufficient quality for clinical implementation. However, low intensity beam controls for clinical accelerators need to be developed for safe proton imaging. Results from the clinical applications work show promise that proton images can improve proton therapy. We have shown that proton imaging can provide accurate treatment plans and that it can be used to detect range errors on plastic phantoms. However, more study is required before clinical implementation should occur. Further comprehensive studies with animal tissues are necessary to provide irrefutable evidence that proton imaging will provide safer and more effective treatments.
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APPENDIX A

RSP CALCULATION OF TISSUE-EQUIVALENT PLASTICS
Tissue-equivalent plastics are materials with well-known compositions that interact with radiation similar to human-equivalent tissues. They meet standards set by the International Commission on Radiation Units and Measurements (ICRU) in Report 44 [19]. When imaged with medical systems, the resulting image appears as if it were human tissues. These plastics are used in a variety of ways in both clinical and research settings. For our purposes, we use quality assurance phantoms, such as the custom peg phantom, to quantify the accuracy of imaging systems and we use anthropomorphic phantoms to mock a patient setup.

From the composition, we can calculate the RSP values for each of the eight inserts in the custom peg phantoms and the pediatric head phantom. Because the manufacturers have some batch-to-batch variation in the composition, we always verify these calculations with water pullback measurements.

For a compound material, we first calculate the log of the mean ionization energy $\ln I$ for the compound with the Bragg-Additivity rule:

$$\ln I = \frac{\sum w_j \frac{Z_j}{A_j} \ln I_j}{\sum w_j \frac{Z_j}{A_j}}$$  \hspace{1cm} (A.1)

where $w_j$ is the fraction by weight of the $j$th element in the compound with atomic number $Z_j$, mass number $A_j$, and mean excitation energy $I_j$. Equation (A.2) gives an approximate empirically-derived formula can be used to estimate $I_j$ with atomic number $Z_j$ [74]. Since the value of $I$ is only used in the logarithmic function, the values obtained with this formula is accurate enough.
\[
I_j = \begin{cases} 
19 \text{ eV} & Z_j = 1 \\
11.2 + 11.7Z_j \text{ eV} & 2 \leq Z_j \leq 13 \\
52.8 + 8.71Z_j \text{ eV} & Z_j > 13 
\end{cases} 
\]
(A.2)

Accurately measured values of \( I_j \) can be found in sources such as the National Institute of Standards and Technology (NIST) [75], the International Commission on Radiation Units and Measurements (ICRU) [76], and the International Commission on Radiation Protection (ICRP) [77].

The electron density of the compound \( \rho_m \) is calculated:

\[
\rho_{e,\text{med}} = \rho_{\text{med}}N_A \sum_j \left[ w_j \frac{Z_j}{A_j} \right] 
\]
(A.3)

where \( N_A \) is Avogadro’s number and \( \rho_{\text{med}} \) is the material density.

Finally, the relative stopping power of the material \( \text{RSP}_{\text{med}} \) is calculated:

\[
\text{RSP}_{\text{med}} = \frac{\rho_{e,\text{med}}}{\rho_{e,\text{water}}} \ln \left( \frac{2m_ec^2}{I_{\text{med}}} \frac{\beta^2}{1-\beta^2} \right) - \beta^2 
\]
(A.4)

where \( \beta^2 \) is a function of the particle’s kinetic energy \( E \) and the proton rest mass \( m_pc^2 = 938.295 \text{ MeV} \):

\[
\beta^2(E) = 1 - \left( \frac{m_pc^2}{E + m_pc^2} \right)^2 
\]
(A.5)

We will first calculate the RSP of water (H\(_2\)O). Table A.1 shows the important values for calculation for all eight materials in the custom peg phantom and pediatric head phantom.
The constants for Hydrogen and Oxygen in water are:

\[ A_H = 1.009 \text{ amu}, \quad Z_H = 1, \quad w_H = 0.112 \]  \hspace{1cm} (A.6)

\[ A_O = 15.999 \text{ amu}, \quad Z_O = 8, \quad w_O = 0.888 \]  \hspace{1cm} (A.7)

The weight by fraction for each element follows as:

\[ w_H = \frac{n_H A_H}{n_H A_H + n_O A_O} = \frac{2 \times 1.009}{2 \times 1.009 + 1 \times 15.999} = 0.112 \]  \hspace{1cm} (A.8)

\[ w_O = \frac{n_O A_O}{n_H A_H + n_O A_O} = \frac{1 \times 15.999}{2 \times 1.009 + 1 \times 15.999} = 0.888 \]  \hspace{1cm} (A.9)

Then using Equation [A.2] we see that \( I_H = 19 \text{ eV} \) and \( I_O = 11.2 + 11.7 \times 8 = 104.8 \text{ eV} \).

These values are used in Equation [A.1]

\[ \ln I_{\text{water}} = \frac{w_H Z_H}{A_H} \ln I_H + w_O Z_O}{A_O} \ln I_O}{w_H A_H + w_O A_O} \]

\[ = \frac{0.112 \times \frac{1}{1.009} \ln 19 + 0.888 \times \frac{8}{15.999} \ln 104.80}{0.112 \times \frac{1}{1.009} + 0.888 \times \frac{8}{15.999}} \]

\[ = 4.31 \]  \hspace{1cm} (A.11)

\[ I_{\text{water}} = 74.48 \text{ eV} \]  \hspace{1cm} (A.12)

Next we can calculate the electron density of water, assuming the material density of water is \( \rho_{\text{water}} = 1 \text{ g/cc} \) and \( N_A = 6.022 \times 10^{23} \text{ atoms/mol} \).

\[ \rho_{e,\text{water}} = \rho_{\text{water}} N_A \times \left( w_H \frac{Z_H}{A_H} + w_O \frac{Z_O}{A_O} \right) \]

\[ = 1 \times 6.022 \times 10^{23} \times \left( 0.112 \times \frac{1}{1.009} + 0.888 \times \frac{8}{15.999} \right) \]

\[ = 3.343 \times 10^{23} \text{ e/cm}^3 \]
Calculating the RSP for water is trivial as the numerator and the denominator are the same, so \( RSP_{\text{water}} = 1 \). The value of the RSP is not sensitive to the choice of \( \beta \). The range of clinical proton beam energies gives a typical range of \( \beta \) between 0.4 and 0.6. For the calculations of RSP listed here, we chose to use \( \beta = 0.4 \).

Table A.1: Weight by fraction of CIRS tissue-equivalent plastics.

<table>
<thead>
<tr>
<th>Weight by fraction</th>
<th>Z</th>
<th>A</th>
<th>Sinus</th>
<th>Brain</th>
<th>Cord</th>
<th>Disc</th>
<th>Trabecular</th>
<th>Cortical</th>
<th>Dentin</th>
<th>Enamel</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1</td>
<td>1.009</td>
<td>0.086</td>
<td>0.082</td>
<td>0.074</td>
<td>0.071</td>
<td>0.084</td>
<td>0.0413</td>
<td>0.045</td>
<td>0.0277</td>
</tr>
<tr>
<td>C</td>
<td>6</td>
<td>12.011</td>
<td>0.659</td>
<td>0.536</td>
<td>0.543</td>
<td>0.525</td>
<td>0.597</td>
<td>0.2969</td>
<td>0.354</td>
<td>0.2181</td>
</tr>
<tr>
<td>N</td>
<td>7</td>
<td>14.007</td>
<td>0.035</td>
<td>0.015</td>
<td>0.022</td>
<td>0.021</td>
<td>0.016</td>
<td>0.0085</td>
<td>0.012</td>
<td>0.0082</td>
</tr>
<tr>
<td>O</td>
<td>8</td>
<td>15.999</td>
<td>0.193</td>
<td>0.265</td>
<td>0.266</td>
<td>0.276</td>
<td>0.214</td>
<td>0.3411</td>
<td>0.294</td>
<td>0.3402</td>
</tr>
<tr>
<td>Na</td>
<td>11</td>
<td>22.990</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Mg</td>
<td>12</td>
<td>24.305</td>
<td>0.000</td>
<td>0.100</td>
<td>0.094</td>
<td>0.096</td>
<td>0.015</td>
<td>0.0311</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>P</td>
<td>15</td>
<td>30.974</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.023</td>
<td>0.0757</td>
<td>0.092</td>
<td>0.1233</td>
</tr>
<tr>
<td>S</td>
<td>16</td>
<td>32.060</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.001</td>
<td>0.0031</td>
</tr>
<tr>
<td>Cl</td>
<td>17</td>
<td>35.450</td>
<td>0.017</td>
<td>0.019</td>
<td>0.002</td>
<td>0.002</td>
<td>0.001</td>
<td>0.0004</td>
<td>0.000</td>
<td>0.0003</td>
</tr>
<tr>
<td>K</td>
<td>19</td>
<td>39.098</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Ca</td>
<td>20</td>
<td>40.078</td>
<td>0.010</td>
<td>0.000</td>
<td>0.000</td>
<td>0.010</td>
<td>0.050</td>
<td>0.2048</td>
<td>0.198</td>
<td>0.2660</td>
</tr>
<tr>
<td>Ba</td>
<td>56</td>
<td>137.33</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.0033</td>
<td>0.0131</td>
<td>0.0131</td>
</tr>
</tbody>
</table>

| \( \rho_{\text{med}} \) (g/cm\(^3\)) | 0.205 | 1.070 | 1.070 | 1.100 | 1.130 | 1.750 | 1.660 | 2.040 |
| \( \rho_{e,\text{med}} \) (10\(^{24}\) e/cm\(^3\)) | 0.6683 | 3.473 | 3.448 | 3.537 | 3.676 | 5.464 | 5.198 | 6.266 |
| \( I_{\text{med}} \) (eV) | 69.61 | 73.95 | 75.35 | 76.85 | 73.80 | 104.28 | 101.31 | 120.43 |
| Ratio of ln terms | 1.009 | 1.001 | 0.999 | 0.996 | 1.001 | 0.957 | 0.961 | 0.939 |
| RSP (calculated) | 0.202 | 1.040 | 1.030 | 1.054 | 1.101 | 1.565 | 1.494 | 1.760 |
| RSP (measured) | 0.200 | 1.040 | 1.040 | 1.070 | 1.100 | 1.555 | 1.495 | 1.755 |

As mentioned, the calculated RSP values are not too sensitive to the chosen value of \( \beta \). We recalculated the RSP for each material with three values of \( \beta \), as shown in Figure A.1. The low- and mid-density materials show variations of less than 2%. The high density materials show larger sensitivities of up to 7%. Our chosen value of \( \beta = 0.4 \) shows closest agreement with the measurements for all materials.
Figure A.1: Difference of calculated RSP values from measure RSP values with different values of $\beta$. 

![Diagram showing percent error between measured and calculated RSP values for different tissues and values of $\beta$.]
Here we show the pCT reconstructions optimized for spatial resolution, accuracy, and noise at all three dose levels. Figures B.1 - B.5 show the optimized images for the six minute scans. Figures B.6 - B.10 show the optimized image for the three minute scans. Figures B.11 - B.14 show the optimized images for the twelve minute scans.
Figure B.1: Optimal CARP reconstructions for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
(a) CARP+TVSi, SR, $\lambda = 1.0$, IN = 15

(b) CARP+TVSi, Accuracy, $\lambda = 0.08$, IN = 1

(c) CARP+TVSi, Noise, $\lambda = 0.002$, IN = 6

Figure B.2: Optimal CARP+TVSi reconstructions for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
Figure B.3: Optimal DROP reconstructions for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
(a) DROP+TVSi, SR, $\lambda = 1.4$, IN = 11

(b) DROP+TVSi, Accuracy, $\lambda = 0.05$, IN = 15

(c) DROP+TVSi, Noise, $\lambda = 0.01$, IN = 20

Figure B.4: Optimal DROP+TVSi reconstructions for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
Figure B.5: Optimal DROP+TVSb reconstructions for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
Figure B.6: Optimal CARP reconstructions of the 3 minute dataset for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
Figure B.7: Optimal CARP+TVSi reconstructions of the 3 minute dataset for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
(a) DROP, SR, $\lambda = 0.6$, IN = 19  
(b) DROP, Accuracy, $\lambda = 0.6$, IN = 1  
(c) DROP, Noise, $\lambda = 0.01$, IN = 20

Figure B.8: Optimal DROP reconstructions of 3 minute scan for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
(a) DROP+TVSi, SR, $\lambda = 0.9$, IN = 14

(b) DROP+TVSi, Accuracy, $\lambda = 0.6$, IN = 1

(c) DROP+TVSi, Noise, $\lambda = 0.01$, IN = 20

Figure B.9: Optimal DROP+TVSi reconstructions of 3 minute scan for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
(a) DROP+TVSb, SR, $\lambda = 1.8$, IN = 17

(b) DROP+TVSb, Accuracy, $\lambda = 0.1$, IN = 8

(c) DROP+TVSb, Noise, $\lambda = 0.002$, IN = 17

Figure B.10: Optimal DROP+TVSb reconstructions of 3 minute dataset for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
Figure B.11: Optimal CARP reconstructions of the 12 minute dataset for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
Figure B.12: Optimal CARP+TVSi reconstructions of the 12 minute dataset for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
(a) DROP, SR, $\lambda = 1.8$, IN = 8  
(b) DROP, Accuracy, $\lambda = 0.6$, IN = 1

(c) DROP, Noise, $\lambda = 0.01$, IN = 17

Figure B.13: Optimal DROP reconstructions of 12 minute scan for (a) spatial resolution, (b) RSP accuracy, and (c) noise.
(a) DROP+TVSi, SR, $\lambda = 1.8$, IN = 8  
(b) DROP+TVSi, Accuracy, $\lambda = 0.6$, IN = 1  
(c) DROP+TVSi, Noise, $\lambda = 0.01$, IN = 20

Figure B.14: Optimal DROP+TVSi reconstructions of 12 minute scan for (a) spatial resolution, (b) RSP accuracy, and (c) noise.