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Advanced concepts in prompt gamma-ray imaging for ion-cancer verification

by

Justin Randolph Ellin

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Engineering – Nuclear Engineering

in the

Graduate Division

of the

University of California, Berkeley

Committee in charge:

Professor Kai Vetter, Chair

Professor Lee Bernstein

Professor Grant Gullberg

Professor David Attwood

Fall 2021

Advanced concepts in prompt gamma-ray imaging for ion-cancer verification

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Justin Randolph Ellin

Abstract

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Doctor of Philosophy in Engineering – Nuclear Engineering

University of California, Berkeley

Professor Kai Vetter, Chair

The major paradigm in the treatment of cancer has been to develop and improve methods for more focused targeting of cancerous cells while reducing the toxicity to healthy tissue. In radiation oncology, that effort has been focused recently on the use of proton beams. The dose kinematics of protons – namely the Bragg curve – allows for better conformity to tumors. However, as protons do not escape the patient, additional safety margins are added to treatment plans which undermine the theoretical therapeutic benefits of protons unless reliable *in vivo* range verification tools are found.

This dissertation describes advanced techniques and concepts as applied to a multi-knife edge slit collimator 2D imaging system. First, the physics of proton therapy is reviewed and a survey is given of current ongoing system designs for proton range verification. Next, an overview is given of the system as well as new improvements to the hardware and software of the data acquisition system. New measurements were then conducted using a 67.5 MeV proton beam at an order of magnitude higher beam current than has been done previously. Details of additional gain and crystal segmentation adaptation algorithms developed to correct for beam-induced effects on the photomultipliers are then described. The incorporation of a separate detector to provide timing information about the arrival of the beam is then discussed: both the potential benefits as well as limitations found in its use here that will inform future iterations of the design. Lastly, a physics kernel is introduced based on published angular excitation functions to further enhance image quality. The system was found to be able to determine the range of the proton beam to within 1 mm (2σ) with the delivery of 10^{10} protons across a 6 cm FOV. Future investigations utilizing the techniques proposed here should only enhance this sensitivity and contribute to efforts to better patient outcomes.

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Acknowledgments

“The correct analogy for the mind is not a vessel that needs filling, but wood that needs igniting — no more — and then it motivates one towards originality and instills the desire for truth” -Plutarch, On Listening to Lectures

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Chapter 1

Introduction

1.1 Proton Therapy History

The use of external radiation for cancer treatment, teletherapy, began almost immediately after Roentgen's discovery of x-rays in 1895 [1]. In 1946, Robert Wilson theorized that the dosimetric properties of proton beams would confer therapeutic benefits over the use of x-ray sources [2]. The first treatment of patients with protons subsequently took place at the Berkeley Radiation Laboratory in the 1950s with pituitary gland tumors [3] followed shortly afterward by the Harvard Cyclotron Laboratory [4]. And finally, in the 1990s, the first hospital based proton therapy center was built in Loma Linda University [5].

In the decades following Wilson, the sites treated by protons and the number of proton facilities has grown worldwide [6], with rapid growth since 2010 from 30 facilities [7] to 111 in 2021 with another 38 under construction. To date, more than 220,000 patients have been treated with protons with more than 20,000 treated in 2019 alone [8]. Less than 1% of radiation therapy patients receive protons, a number that has been steadily increasing [7], and a growing body of evidence supports proven efficacy in pediatrics [9]. But this rapid growth has met controversy, concerning the cost effectiveness and efficacy of treatment in clinical practice [10, 11]: compounded by the lack of proper phase 2 and 3 clinical evidence [12]. The next sections will outline the physics of proton therapy and some of the outstanding challenges that compromise its theoretical benefits to contextualize the motivation behind this current work.

1.2 Physics of Proton Therapy

The most important interactions of protons for proton therapy are from elastic and inelastic reactions of atomic electrons and nuclei. Inelastic scattering of atomic electrons slows the protons down, elastic scattering from atomic nuclei broadens the beam profile at depth, and inelastic nuclear collisions remove protons and energy from the treatment field [13]. Each will now be explained in more detail.

1.2.1 Inelastic (Coulombic) Scattering from Atomic Electrons

Protons primarily lose energy with a myriad of electromagnetic Coulomb inelastic interactions with atomic electrons (elastic scattering is negligible in comparison). The Bethe-Bloch formula [14] gives the mean energy loss per distance for charged particles traveling through media called the stopping power. One formulation of it is given below [15]:

$$-\left\langle \frac{dE}{dx} \right\rangle = \frac{4\pi}{m_e c^2} \cdot \frac{n z^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\epsilon_0} \right)^2 \cdot \left[\ln \left(\frac{2m_e c^2 \beta^2}{I \cdot (1 - \beta^2)} \right) - \beta^2 \right] \quad (1.1)$$

where:

- E = energy of incident particle
- x = path distance traveled
- n = electron density of the absorber media
- β = incident particle velocity relative to the speed of light
- I = mean excitation energy of the absorber material
- z = charge of the incident particle

while m_e and ϵ_0 are physical constants. For non-relativistic protons ($z=1$, $\beta \ll 1$) this gives the following simpler scaling:

$$S(E) \equiv -\frac{1}{\rho} \left\langle \frac{dE}{dx} \right\rangle \propto \frac{M_I}{E} \quad (1.2)$$

where:

- $S(E)$ is defined as the stopping power of the absorber
- ρ = the density of the absorber material
- M_I = the relative atomic mass of the incident ion

The inverse scaling with energy means physically that as the proton slows down it has more time to interact with nearby electrons and the energy loss keeps increasing as it slows down. As the kinetic energy nears the electron binding energy, the effective net charge of the particle declines to zero and further energy losses by coulombic interactions cease (see z in Equation 1.1) [16]. The large proton mass as compared to the electrons means that the proton range and travelled path are nearly identical, and that the depth of the proton is determined to first order by its initial energy. At larger depths, the probabilistic nature of interaction causes variability in the energy of the proton range and thus the range. This spread, range straggling, is about 4% of the total depth of the proton in tissue [13].

The resulting energy loss profile, the Bragg curve, offers distinct dose advantages for the treatment of cancer over traditional photon therapies (Figure 1.1a). The Bragg curve consists of a flat plateau region as well as a bump near the end of the range called the Bragg

peak. Compared to the photon dose profile (in black), the proton dose profile (in blue) has a smaller entrance dose and no dose distal to the treatment volume. To completely cover the tumor without rotating the gantry, multiple proton beams of different energies -either by tuning the energy of the accelerator or the use of a range modulator- are required to create a Spread Out Bragg Peak (SOBP, in red).

It is not just the physical quantity of delivered energy that is different with proton beams, but also its biological quality. Cell killing from radiation is mostly due to damage of the DNA that leads to programmed death or loss of reproductive function for the cell (Figure 1.1b). Protons lose energy, or equivalently deposit energy, more densely than photons. This higher linear energy transfer (LET) translates into a higher probability of creating damage on both sides of the DNA creating double strand breaks (DSBs) instead of single strand breaks (SSBs). Cells have far less effective mechanisms by which to repair DSBs, and so per unit dose the overall impact of higher LET radiation is more effective in destroying cells. This Relative Biological Effectiveness (RBE) is thus also much more pronounced near the end of the range while comparatively weaker at the entrance channel [17, 18]. Quantifying the RBE for proton beams has been an ongoing topic of research with no clear answer due to many confounding variables of biology. However, it is known that the RBE increases rapidly near the end of the Bragg Peak as a result of primary and secondary charged particles. But as a matter of practice, facilities generally assign an RBE of 1.1-1.2 to the entire proton beam path by recommendation of the International Committee for Radiological Units (ICRU) [19].

1.2.2 Elastic (Coulombic) Scattering from Atomic Nuclei

Although less frequent than electronic collisions, proton collisions with atomic nuclei do deflect the direction of the proton because of their comparable masses which allow larger momentum transfers. These slight deviations can accumulate over the course of many such collisions with depth. Given the statistical nature of these collisions, this results in an angular straggling of proton trajectories about the incident proton beam direction resulting in a lateral spread with depth.

The Molière theory of Multiple Coulomb Scattering [22] is well developed and comprehensive as a means to predict the lateral angular distribution of ions in matter at depth, further elaborated by Bethe [23]. It is found that nearly 98% of lateral spread can be modelled by far simpler and less computationally intensive Gaussian models which take only a few input parameters of the target material and compute a root-mean-squared (rms) spread; Highland's formulation [24] matches experimental results within 5% across several decades of material thicknesses and was later generalized for energies and energy spreads typical of proton beams [25].

Complete Monte Carlo simulations have found that the rms lateral spread of a 1 mm wide pencil beam (typical of proton therapy) to vary from 2-7 mm from 100 to 200 MeV. Further, that the ratio of the rms spread, $\langle r \rangle_{\text{rms}}$, to depth, z , is nearly a constant 3% across the radio-therapeutic energy range for protons [26]. The lateral uncertainty of the proton beam can as such be compensated for in treatment planning leaving much of the

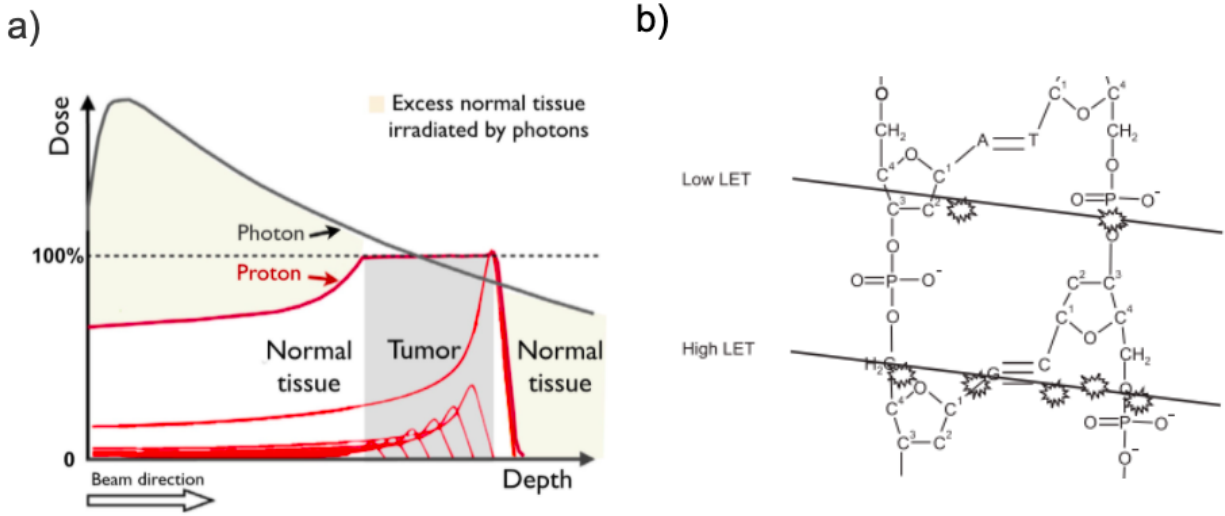


Figure 1.1: a) Dose-depth curve for proton vs. photon irradiation. The photon curve (grey) shows dose deposition with an initial build-up region followed by an exponential decrease as the beam goes deeper in tissue. The proton curve (burgundy) is the summation of several Bragg peaks (red curves) permitting dose deposition over a specific depth in tissue (e.g., the target). The beige-shaded regions demonstrate areas of excessive normal tissue irradiation by photons that could otherwise be spared by protons (adapted from [20]). b) Example interaction locations of low and high LET radiation. The greater concentration of direct and indirect reactions with high LET radiation increases the probability of double strand breaks (DSBs) which are correlated with more effective cell killing (adapted from [21])

concern instead focused on upstream absorbers to correct for angular deviations introduced by the beam optics [27].

1.2.3 Nuclear (Inelastic) Reactions with Atomic Nuclei

Nuclear reactions of protons with tissue can redistribute the energy of the beam to locations outside the prescribed treatment volume. The rest of this section will briefly overview the possible secondary particles produced during proton irradiation with an eye toward their impact on both dosimetry and monitoring. Discussion of nuclear reactions resulting in the production of gamma rays (prompt, delayed, and annihilation photons) will be deferred to Chapter 2.

First and foremost, inelastic scattering has the effect of removing primary protons from the beam. Figure 1.2 shows both the total inelastic cross section of protons on oxygen, carbon, and nitrogen as well as the fluence profile of a proton beam as a function of depth. The total inelastic cross section is largely constant at energies greater than 100 MeV representing the physical size of the target nuclei that increases with mass number and density. Below this energy, the cross section rises as the proton spends more time near each target nucleus

and then turns over back towards zero at still lower energies from coulombic repulsion. The resulting total proton fluence is then a combination of nuclear reactions in the plateau region and the Bragg peak from electronic stopping mentioned earlier. A general guideline for the plateau region is that about 1% of the primary proton beam is lost per centimeter of tissue [28].

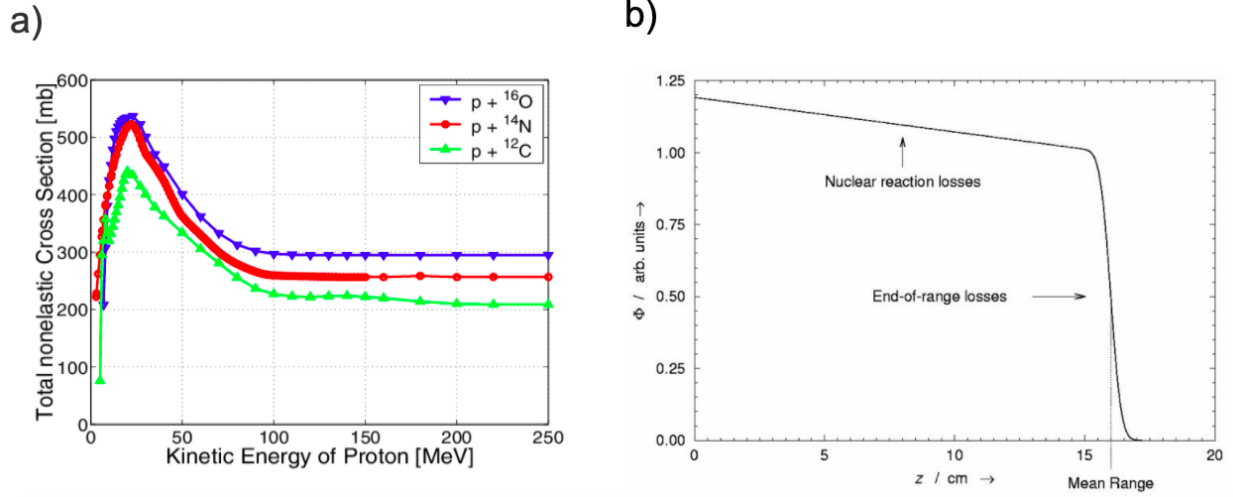


Figure 1.2: a) Total non-elastic cross sections as a function of energy on common tissue isotopes (¹⁶O, ¹⁴N, ¹²C) from ENDF [29]. b) Relative proton fluence as a function of depth for a proton beam. Inelastic collisions cause a gradual loss of protons until a rapid sigmoidal fall off as a result of range straggling [30].

The production of secondary charged particles (SCPs) - p, ²H, ³H, α , heavier charged fragments and their recoils - have been a subject of study because of their high ionization density and local dose deposition. Several experiments with clinical beams have found that the production of SCPs other than protons contribute less than 0.1% of the total dose in the plateau: the higher LET being compensated for with lower production yields and initial kinetic energies [13, 31, 30]. Secondary protons, on the other hand, deposit about 10% of the total dose within the plateau and account for 20% of the equivalent dose deposited in the Bragg peak. This dose tends to be forward focused creating a longitudinal buildup of dose in the beam direction that alters the shape of the flat top of the SOBP if not compensated for [32, 33].

Neutrons are also produced in tissue as a result of proton induced and secondary charged particle nuclear reactions. Neutrons have the capability to deposit dose far from the original treatment site due to their greater penetration depths in tissue. As a result of direct reactions for example, the neutron spectra from proton beams includes neutrons of energies all the way up to the maximum proton energy. For a 250 MeV proton beam, neutrons with energies above 20 MeV account for 35% of the total neutron dose equivalent with higher energy neutrons emitted tighter around the beam axis [34, 35]. Fortunately, the total neutron dose

for typical clinical scenarios is on the order of mSv/Gy but does require that the proton beam not be directed at biological structures that have lifetime limits to radiation damage including the brain and spinal cord. Further, the neutron dose can change by orders of magnitude dependent on the treatment system configuration due to the design of the nozzle, scatter foils, range modulators, compensators, or collimators which has lead to changes in design of newer facilities to replace these optics or move them further upstream of the patient [36].

1.3 Range Uncertainty

Due to the physical dose profile of the protons, it becomes essential to accurately determine the depth of proton penetration in tissue. Non-superficial cancerous lesions of the body typically form at the tissue boundary of organs. Thus, if the Bragg peak position is misaligned, not only might the cancer not be treated but you might even be “treating” the wrong organ entirely. Currently, clinicians are required to modify treatment plans to ensure coverage of the cancer while avoiding nearby sensitive organs. This takes the form of either inscribing buffer regions, safety margins, around the clinically identified tumor volume in patient treatment planning medical scans (Computer Tomography, CT, or Magnetic Resonance Imaging, MRI) or by changing the radiation fields to account for distal beam penetration uncertainty i.e. the beam angle incidence on the patient.

Safety margins are added to clinical treatment volumes to compensate for range uncertainties due to various sources of error. These sources of error include [37, 38]:

1. Patient set-up errors
2. Patient motion, especially in the torso
3. Conversion of Hounsfield values from the planning CT scan to stopping power used for the treatment plan
4. RBE variability of different tissue types, especially at low energy
5. Patient anatomy changes and tissue heterogeneity
6. Beam alignment and variability
7. Proton (longitudinal) range

Of these, the proton range is typically assigned the greatest margin since the Bragg peak itself widens as a function of depth with initial energy while the other sources are independent of treatment depth. For most penetration depths, the 90-10 drop off in dose for the Bragg peak is on the order of several mm [39]. At the aforementioned Loma Linda University Medical Center, for example, the applied margin is 3.5% of the range + 2 mm [37]. But this margin reflects a hedge against additional healthy tissue toxicity at the expense of under

delivering the ideal dose dictated by the physics of the proton beam to the tumor. What this also means is that if there were a way to verify the longitudinal range of the beam to within $\pm 1\text{-}2$ mm, that the error would be on the order of the other sources of error i.e., there would be diminishing returns in further refinement.

It is typically the case that standard prescribed doses in proton therapy are fractionated i.e. split over several treatment days similar to conventional x-ray therapies; a typical example for low grade prostate cancer is about 74 total Gy split across 37 fractions or 2 Gy per fraction. And for proton pencil beams, this dose is "painted" across the total tumor volume in each fraction [40]. Thus, there are also grades to range verification systems based on the required number of protons to make accurate determination of the range within 1-2 mm. Rough order of magnitude estimations for the total number of protons delivered per spot, per fraction, and for the total treatment are 10^8 , $10^9\text{-}10^{10}$ and 10^{11} respectively [41]. Additionally, since most accelerators are AC-coupled the protons are delivered in bunches at regular intervals for which the number of protons can vary in the bunch from 10^4 - 10^5 depending on the accelerators design [42]. Most current methods (see Chapter 2) require at best the entire fraction to be delivered to gather the necessary statistics for their range determination estimates. But if a system were sensitive enough to detect shifts in the proton range using only part of the prescribed dose for each spot that would represent a paradigm shift: from range verification to range finding.

Proton range uncertainty can also change the quantity and angle of the radiation fields used to ensure tumor coverage that can have knock-on health effects such as in prostate cancer. Prostate cancer is the most common new cancer diagnosis of men in the United States and prostate cancer patients make up a majority of the load in PBT centers [20]. The ideal treatment plan, at right in Figure 1.3, would be to direct fields from the anterior across the less sensitive bladder. However, the possibility of overshoot and overdosing of the posterior rectum has instead made the plan at left in Figure 1.3 the standard. Here the beam is oriented orthogonal to the ideal plan to instead tie overshoot to the more well known lateral uncertainty (see previous section). This plan minimizes the maximum possible rectum overdose but at the expense of delivering a larger guaranteed average dose. This dose is likely largely responsible for washing out the theoretical health benefits compared to far less expensive intensity modulated (photon) radiation therapy (IMRT) machines [20, 11].

Lastly, it is also worth noting that any proton range monitoring should ideally be done as close to treatment and, if possible, during treatment itself with the beam on i.e. *in vivo*. Without reliable monitoring systems, the ground truth standard for verifying dose is the use of post-operative high resolution Magnetic Resonance Imaging (MRI) because of its lack of additional dose burden. However, the biological changes from irradiation are not instantaneous and, due to cell bystander effects, inflammation and swelling extend outside the prescribed beam path. As a result, it takes from a week to several months after treatment before an MRI can verify treatment [17, 44, 45]. This is an undesirable outcome for management of more aggressive cancers.

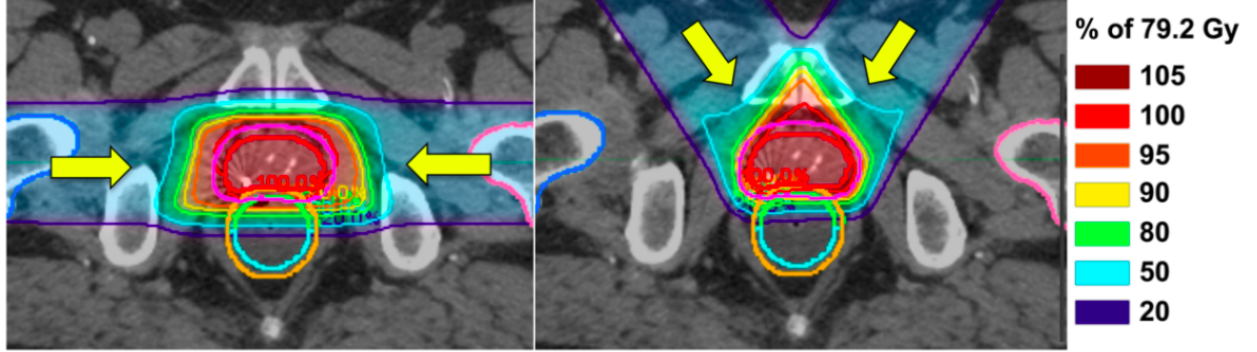


Figure 1.3: At left, typical bilateral radiation field for prostate cancer treatment currently in use. At right, the ideal anterior oblique profile from two beams. The prostate is outlined in red and the organ at risk (rectum) highlighted in orange. Adapted from [43].

1.4 Motivation and Outline of this Work

The issue of range verification is essential to utilizing the full dose kinematic advantages of proton therapy. The dose delivered is dominated by primary and, to a lesser extent, secondary protons along the original direction of the beam. This dose is characterized by a relatively flat entrance channel, a Bragg peak, and a sharp distal falloff. Monitoring should be performed *in vivo* if possible, given the delayed and protracted responses of tissue to radiation. A resolution of 1-2 mm would place the range uncertainty on the same order as other sources of error in treatment planning. This would reduce the required safety margins and need to use suboptimal fields to make the target dose more conformal to the tumor volume while reducing integral dose to other organs in the body. This thesis will hopefully contribute to addressing the outstanding range uncertainty challenges in proton beam therapy in an integrated system for clinical use.

Chapter 2 of this manuscript will describe the current state of the field of proton range verification including current state of the art approaches and outstanding challengers. Chapter 3 will describe the Multi Knife-Edge Slit Prompt Gamma Imager (PGI) system as well as quantify previous limitations of the system. Chapter 4 will walk through the implementation of data processing and image reconstruction software to address those weaknesses. Chapter 5 describes new measurements and postprocessing of the data for real proton beam data. Chapter 6 and 7 focus on the extent to which these new methods and techniques improve the range verification performance of the PGI system. Chapter 8 will summarize the implications of this work and a look forward to future avenues for investigation. The goal of the work is to determine the range of proton beams in tissue to within a few millimeters, which could have a significant impact on the efficacy of treatment and patient prognoses.

Chapter 2

Range Verification Systems

Since protons do not make it outside of the patient, non-invasive *in vivo* monitoring range verification system designs have generally utilized either secondary particle emissions or physiological changes as signals to act as proxies for the delivered proton dose. This chapter will provide a brief overview of this rich field to provide context for the system used in this work. Complete anthologies can be found elsewhere [46, 38].

2.1 Protoacoustics

Protoacoustic, also referred to as ionacoustic, systems use the change in thermoacoustic properties of tissue caused by the deposited dose of the beam that are functions of both space and time. The plateau and Bragg peak regions generate differential pressure waves that can be picked up by the placement of hydrophones placed at the skin. The Bragg peak depth can then be calculated using time of flight if the lateral distance from the beam is known, an example of which is shown in Figure 2.1. Pulsed proton sources ($< \mu\text{s}$) with high current ($\sim \text{pC}$) are required to avoid heat diffusion effects and maximize the acoustic signal strength. By combining this signal with anatomical ultrasound imaging (with a sound property map of the patient using CT) from an array of ultrasound sensors, it can in principle be possible to simultaneously reconstruct the dose profile as well [48, 47]. A recent study using a water phantom achieved a resolution of the Bragg peak of 220 MeV protons of less than a mm [49]. Even given the difficulties from acoustic value errors and heterogeneity, simulation studies have shown it may be possible to achieve < 1.6 mm uncertainty in the range for areas of the body most conducive to protoacoustics given anatomical considerations: liver, breast, and prostate [50].

2.2 Positron Emission Tomography (PET)

Positron emission tomography (PET) imaging has been investigated for proton range verification since the late 1970's [51]. Proton collisions with nuclei form compound nuclei

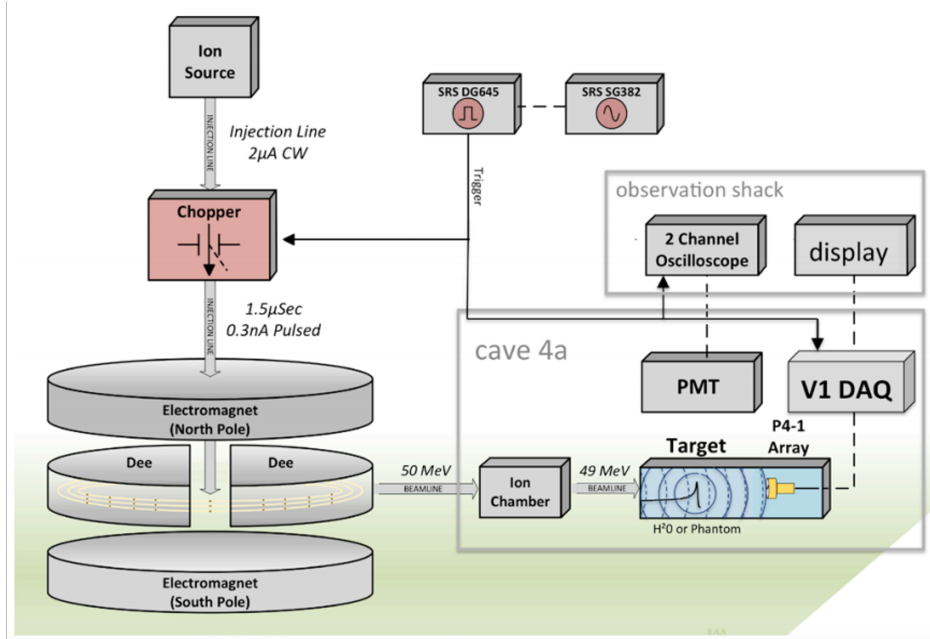


Figure 2.1: Example of protoacoustic method. A trigger pulse is generated that drives a beam chopper and the start of the ultrasound acquisition pulses. A PMT is used to detect the arrival time of the protons into the tissue and detect the offset in the echo signals. Adapted from [47].

that can preferentially and subsequently decay by positron emission. The long half-lives allow for this imaging to take place shortly after irradiation. The coincident 511 keV annihilation photons are then detected by a PET ring for use in image reconstruction by the use of lines of response. The subsequent image is thus only an analog of the dose profile since the beta reaction is largely a result of nuclear interactions instead of the electromagnetic stopping that dominates the energy loss of protons in tissue (see Introduction). The mapping of the dose from the PET image then has to come from comparison to either Monte Carlo [52] or analytical models [53]. An example, Figure 2.2, shows the typical activity profile of a 116 MeV proton beam for a PET system and the underlying ground truth dose depth curve for a tissue equivalent phantom from measured gamma ray yield experimental data and proton transport calculations from the Monte Carlo code TOPAS [54]. The total activity profile is largely flat along the entrance channel with a fall off located several centimeters before the actual Bragg peak. Biological washout as a result of long acquisition times, positron range, and scanner technology limitations broadens the uncertainty frustrating efforts for PET based dose verification [55].

Newer PET system designs have sought to integrate the imaging system into the treatment room [57] or directly into the proton gantry itself [58]. Such approaches seek to reduce the duration and start time of the subsequent PET acquisition to improve signal to noise (SNR) and total treatment times. This typically requires limited angle PET rings that also

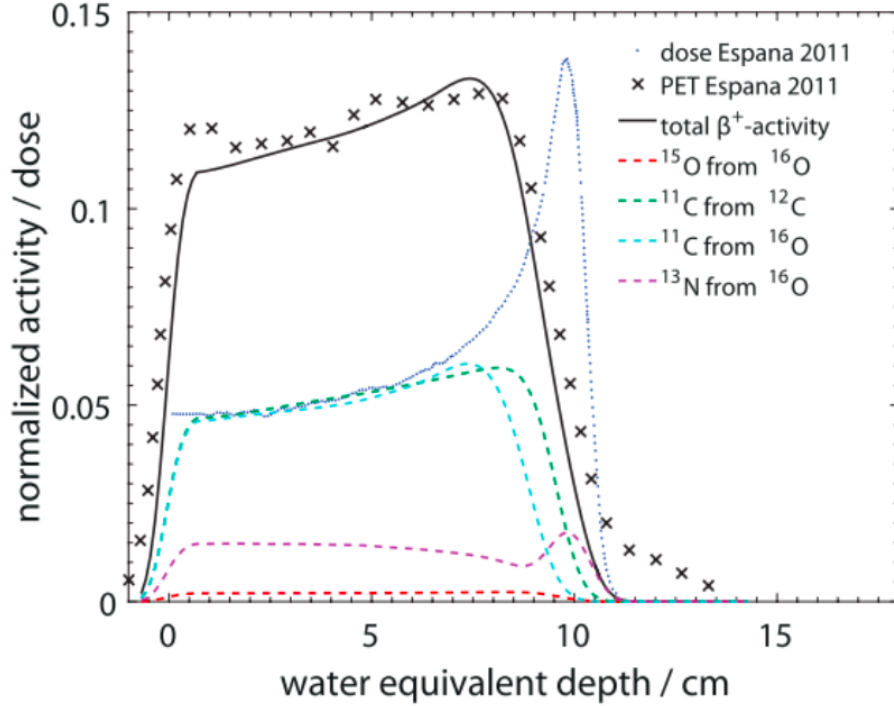


Figure 2.2: Measured depth dose distribution in water and β^+ -activity profiles in a tissue equivalent gel phantom irradiated with a 116 MeV proton beam compared with transport calculations of various β^+ emitters. Acquisition was for 30 minutes after a 15 minute delay. Adapted from [54] (with data from Espana [56]).

must be able to suppress the large prompt gamma ray background (see next section). Efforts to improve the SNR of these systems have focused on pulsed proton beam delivery to preferentially enhance the production of certain high yield, short lived isotopes for use in subsequent imaging such as ^{12}N ($t_{1/2} \approx 12$ ms). Unfortunately, such isotopes also have very high end point energies that translate to large positron ranges (2 cm root mean square for ^{12}N) [59, 60]. Positrons annihilate when thermalized and so the positron range represents a source of blur that serves as a physics based limit to the spatial resolution of the the derived PET image [61]. Thus the spatial resolution of such systems is largely limited to 1-2 cm and poses significant challenges to determining the proton range.

2.3 Prompt Gamma Imaging (PGI)

The physics of prompt gamma (PG) emission offers a number of attractive properties for range verification. When protons pass near nuclei, electromagnetic interactions can cause an excitation of the nucleus (Coulomb excitation). Prompt gamma rays are emitted from the de-excitation of these nuclei within femtoseconds to picoseconds afterward. Thus, prompt

gamma emission does not suffer from the biological washout and secondary (positron) range problems that are physical limits to the resolution in PET [62]. Furthermore, the emission profile is better matched to the underlying Bragg peak as seen in the example of several prompt gamma yields from a proton beam on a water phantom in Figure 5 as compared to Figure 2.2. The yield increases as the proton slows down with a threshold determined by the excited nuclear state and Coulombic excitation. The total production of prompt gammas being an order of magnitude greater than for β^+ emitters. The coulomb threshold is at most several MeV which, for protons, is a residual range of less than a mm [62].

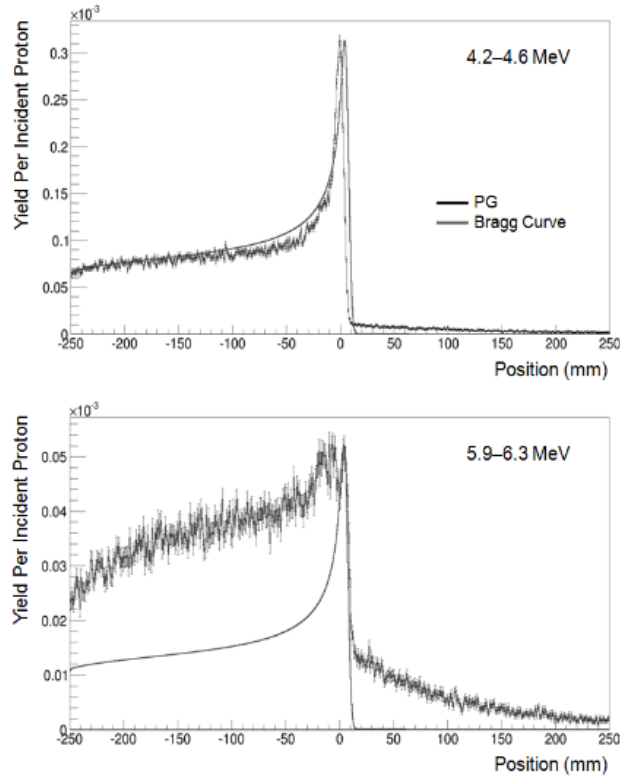


Figure 2.3: Longitudinal PG yield distribution in a digital water phantom with incident 200 MeV proton beam and with energy windows for two lines of interest. The Bragg peak is normalized to the maximum of the gamma yield with arbitrary scale. Adapted from [63].

Prompt gamma rays also present a unique set of challenges requiring specialized detection systems and techniques. PGI systems must acquire their data during proton irradiation of the patient because of the short half-lives of gamma ray signatures of interest. Table 2.1 lists gamma ray signatures of interest for PGI above 2.22 MeV primarily on carbon and oxygen. This includes beta-delayed gamma rays as a result of preceding positron emission (decay scheme given in Figure 2.4) and gamma rays following proton inelastic scattering, (p, p') . Of the various reaction channels that yield the 4.44 MeV gamma ray from ^{12}C , the most significant of these in tissue that are also prompt are $^{12}\text{C}(p, p')^{12}\text{C}$ and $^{16}\text{O}(p, \alpha p')^{12}\text{C}$ with

maximum cross sections of 470 (for 10 MeV protons) and 157 mb (for 23 MeV protons), respectively. The yields of these prompt gamma rays resemble that of the underlying proton Bragg peak such as the simulated yields in solid water targets from Zerafi (Figure 2.3): with a sharp rise near the end of the range and a rapid fall off on the distal side of the Bragg peak with only a slight offset. The $^{16}\text{O}(\text{p}, \alpha\text{p}')^{12}\text{C}$ reaction is also interesting since the maximum cross section is only slightly less than the maximum cross section of $^{16}\text{O}(\text{p}, \text{p}')^{16}\text{O}$, 163 mb for 13 MeV protons [64, 65]. Thus the 4.4 MeV line is significant for both carbon and oxygen environments. These gamma ray lines can be energy gated to filter out the substantial 511 keV and $\text{n}({}^1\text{H}, \text{d})\gamma_{2.2\text{MeV}}$ background. These high energy gamma rays are challenging to attenuate in shielding or stop in radiation detectors. Large neutron backgrounds similarly generate many of the signals of interest and represent a source of background activity. It is possible to suppress much of this neutron background using time of flight (TOF) detection [66, 67] provided that the ToF resolution is less than the proton bunch arrival time (several ns depending on the design of the cyclotron [68]).

2.3.1 Compton Cameras

Compton Cameras (CC) consist of 3D position and energy sensitive detectors. Compton cameras image using gamma rays that interact at multiple locations provided that the first interaction, the second interaction, and the sum total energy of the incident gamma ray can be fully measured. The kinematics of Compton scattering then fix the initial incident angle of the gamma into a cone (because of the angular degeneracy in the physics) that is then backprojected into the imaging space. Such imagers have very high intrinsic efficiencies because they do not rely on physical collimators. First used in medical imaging in 1974 [69], many groups have been working on CCs for use in range verification in clinical settings [70, 71, 72, 73].

To properly reconstruct a Compton cone, all energy of the gamma ray must be deposited within the active volume of the CC. The readout of the induced charge takes place within a finite time window. Thus, CCs are very susceptible to count rate limitations for high energy scatters from partial scatters (incomplete charge collection) and random coincidences (multiple events within the charge collection time window) that must be compensated for in modification of imaging protocols or reconstruction algorithms. A back of the envelope calculation will illustrate why. A typical protocol for a treatment spot in pencil beam scanning is 1 nA for 200 cGy, which translates to $\approx 10^9$ protons in ≈ 250 ms [74]. On average, there is 1 prompt gamma emitted per 10 protons [75] which means, for a CC with 10% solid angle coverage, a required incident event rate of 4 Megacounts/second. Current state of the art double scatter Compton cameras only achieve event rates of about 10 kcps [76], orders of magnitude smaller. And this is a conservative estimate given that nearly all proton accelerators are AC-coupled and so the peak current (and count rate) can be 10x larger due to a 10% duty cycle [77]. The feasibility of such systems is further limited by the cost constraints of the detector volume and readout electronics for CCs.

Table 2.1: List of prominent prompt and beta-plus delayed gamma rays, reactions, and half-lives (granddaughters in parenthesis for positron-delayed gamma rays) above 2.2 MeV. From [64, 65].

E_γ (MeV)	Parent	Reaction	Daughter	$t_{1/2}$
2.31	^{14}N	(p, p')	^{14}N	4.8 fs
		(p, n)	^{15}O	71 s (^{14}N)
4.44	^{12}C	(p, p')	^{12}C	45 fs
		(p, n)	^{12}N	11 ms (^{12}C)
	^{13}C	(p, 2p)	^{12}N	11 ms (^{12}C)
		(p, pn)	^{12}C	45 fs
	^{16}O	(p, α p')	^{12}C	45 fs
		(p, α n)	^{12}N	11 ms (^{12}C)
5.24	^{16}O	(p, d)	^{15}O	122 s (^{15}N)
5.27	^{16}O	(p, 2p)	^{15}N	17 fs
6.13	^{16}O	(p, p')	^{16}O	18 ps

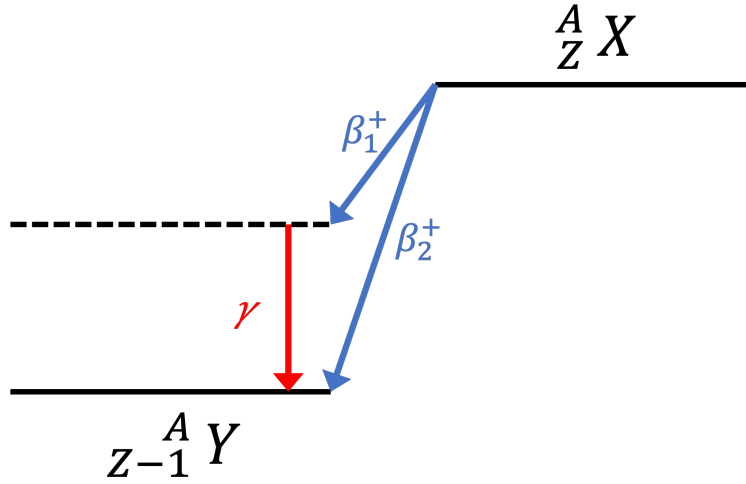


Figure 2.4: Decay scheme for β^+ decay. This decay can either be to the ground state of the daughter, β_2^+ , or to an excited state, β_1^+ , with a subsequent gamma decay to the ground state.

There have been mainly two general approaches to dealing with these limitations for CCs. The first involves drastically reducing the beam current by orders of magnitude in test pulses for initial range verification before administering the full delivered dose. Even with such constraints, it can still take minutes to get the required statistics making such approaches difficult to translate into the clinic [78]. Or the second method which involves complex image reconstruction techniques that factor in additional a priori information and/or the application of many event cuts to the recorded events [79, 70, 80]. The most promising of these approaches, from Draeger using commercial CZT detectors, achieves a resolution of about 3 mm in water phantoms with significant post-processing [74].

2.3.2 Prompt Gamma Timing/Spectroscopy (PGT/PGS)

Due to the short half-lives of prompt gammas, verification systems have been devised to additionally utilize the time structure of prompt gamma emission in accelerators driven with RF fields to determine proton time-of-flight.

In prompt gamma spectroscopy (PGS), a slit collimated fast scintillator (LaBr:Ce) records the time and energy of incident gammas emitted from a fixed location along the treatment path at 90 degrees effectively sampling the beam at one energy. Shifts in the energy/range of the beam are correlated to changes in the prompt gamma emission rates due to a change in the nuclear reaction cross section as a function of energy. The ratios of the 4.4 MeV and 6.1 MeV gamma lines on carbon and oxygen using previous measured yields at 90 degrees for various proton energies, respectively, allow for estimates of the abundances of those elements at the sampled location [81]. Clinical trials are forthcoming but early simulations suggest the ability to resolve range shifts with 4 mm uncertainties in prostate phantoms and 2 mm in water phantoms [82, 83].

Prompt gamma timing (PGT) is a generalization of this technique that eliminates the distal side of the collimator. Similar to PGS, an array of large LaBr:Ce detectors collects the arrival time and energy of incident gammas, using the RF driving pulse of the accelerator as a start time. The resulting two-dimensional spectrum in energy and time can in turn be filtered in either dimension to isolate the neutron induced prompt gamma continuum from the proton induced signal (on the order of the proton bunch length and slowing down time, 1 ns). The emission profile is then deconvolved from the profile using the treatment CT scan and aforementioned gamma ray yield data. A prototype system currently at Massachusetts General Hospital is shortly to be used in clinical trials [84]. Earlier phantom measurements were able to detect a variety of undershoot conditions (for example, beam energy undershoots or air/bone gaps) with sub mm precision by averaging errors across an entire treatment plane. However, the system is bulky due to the onboard electronics and collimation system and fills much of the treatment room [85]. The timing performance of the system is also coupled to the beam RF driving frequency and not to the proton bunch arrival time requiring frequent recalibrations throughout the day [84]. A drift of even 10 ps for the arrival of 200 MeV protons ($\beta = 0.56$) translates into a possible systematic uncertainty of 1.6 mm.

2.3.3 Collimated Systems

Collimated cameras use physical attenuators as masks that cast unique shadowgrams onto the surface of the detector that are mapped to emission points within the field of view (FOV). The first range verification system to reach clinical testing and now under use by IBA is a single knife-edge slit collimator first used for passive scattering beams to achieve 2 mm range uncertainty [86, 87]. This system produces a 1D profile of the beam but requires averaging of nearby beam spots to generate the statistics necessary for 2 mm resolution in brain imaging [88] i.e., the beam requires the entire prescribed dose to generate the diagnostically useful image.

The high gamma energies are significantly higher than those encountered in nuclear medicine, which makes design of multi-slit systems difficult. Here, approaches are limited by the desire for 1D or 2D imaging. 1D imagers use arrays of thin vertical slits with deep septa oriented orthogonally to the beam direction creating 1D count profiles. Such systems are typically limited by the finite size of their detector pixels, finite thickness of septa, and low efficiency: modern systems achieve a resolution of 2-3 mm with 4×10^8 protons or more [89] which is not much better than single slit designs. 2D imagers utilize coded aperture mask designs that increase the detector efficiency versus single slit design by engaging more detector area for any emission point. A later design similar to the system used in this work, using BGO and SiPMs, will be interesting to watch in clinical studies to see if it can match the 1.88-2.73 mm resolution reported in simulation for 150 MeV proton beams [90].

2.4 Summary

Proton beams produce a variety of signals that could potentially be useful for real time dose monitoring and range verification. The radiation field is highly complex both in the energy and time domains. Secondary gamma emissions from proton induced reactions in tissue as well as acoustical signals recorded from radiation induced thermal tissue changes from initial dose deposition could prove invaluable for calculating dose.

For PET, much of the challenge is largely related to physics. The cross section is an order of magnitude smaller than for prompt gamma production with a much higher threshold resulting in a large shift between the beta activity profile to the underlying Bragg peak. The time delay in the subsequent beta decay also presents a challenge from both ends. If longer lived beta emitters are imaged, then biological washout can blur the image. While with shorter lived useful beta emitters, the end point energy of the emitted gamma can create a positron range blur of several centimeters. This in addition to the complexities of integrating PET rings into beam lines without either interfering with one another.

For CCs, much of the challenge lies in count rate limitations related to current detector technology. The enhanced sensitivity through removal of the collimator works against it as it becomes very difficult to resolve individual events from random and scattered coincidences. Much of the effort in turn has pivoted towards increasingly lower beam intensity test pulses

that are impractical for patient settings or complicated image reconstruction algorithms that tend to reduce the CC to a 1D imager that projects back onto a line. The limitations of both approaches are further hampered by their cost and complexity.

Collimated cameras have made the most headway into being realized for broad clinical use. From the simplicity of a single slit camera to the sophisticated PGT system that incorporates cross section data to derive estimates to the range in the energy or time domains. However, in the first case, low efficiency largely requires averaging over dose regions. And in the second, the imager becomes coupled to the performance of the accelerator introducing possible systematic bias in the range calculation.

The system used in this work, and outlined in the next chapter, represents an elaboration on knife-edge slit designs. A 2D coded aperture mask pattern is used to enhance the efficiency of single slit and multi parallel slit designs in imaging of the prompt gamma distribution. It is also much more compact than the PGT system at MGH and uses standard components possibly allowing for direct integration into the gantry. It is important to bear in mind that every mm of spatial resolution counts in the field of range verification.

Chapter 3

Multi Knife-Edge Slit Collimator

The purpose of this chapter will be to both describe the design of the system in this manuscript and review the performance of the system as described in Dr. John Ready's work [91]. Measurements and systematic analysis will be used to attempt to further understand remaining sources of systematic uncertainty in imaging of the proton range.

3.1 Prompt Gamma Imaging (PGI) System

The PGI system is based on a multi-knife edge slit collimator design developed, fabricated, and built at Lawrence Berkeley National Lab [92]. The system consists of a coded aperture mask, detector array, readout electronics, and data acquisition system. The innovation within the design mostly arises from the collimator and detector array, and those will now be briefly described.

3.2 Coded Aperture Mask

The multi-knife edge slit pattern in the collimator (Figure 3.1) serves as a coded aperture mask [93, 94] for prompt gamma imaging in ion therapy. Focusing optics such as lenses do not exist for high energy gamma rays (> 1 MeV) [95] requiring a generalization of the pinhole camera in order to localize gamma emitting sources within an imaging field but at higher efficiency by the use of many pinholes with overlapping projection areas on a position sensitive gamma ray detector. Coded aperture masks are designed such that the shadowgram of the mask onto the detector plane encodes desired possible gamma source locations which can later be "decoded" through use of computational algorithms [96, 97]. A linear discriminant analysis [98] was performed to optimize the location and placement of slits for proton paths to ensure image uniformity, contrast, and minimize sidelobes (cross correlation from nearby points) of the system response: the design here is a 10-fold higher efficiency than single slit designs [92]. Knife-Edge slits were chosen as a tradeoff between the FOV/resolution (from magnification) of pinholes and the efficiency of parallel channels for

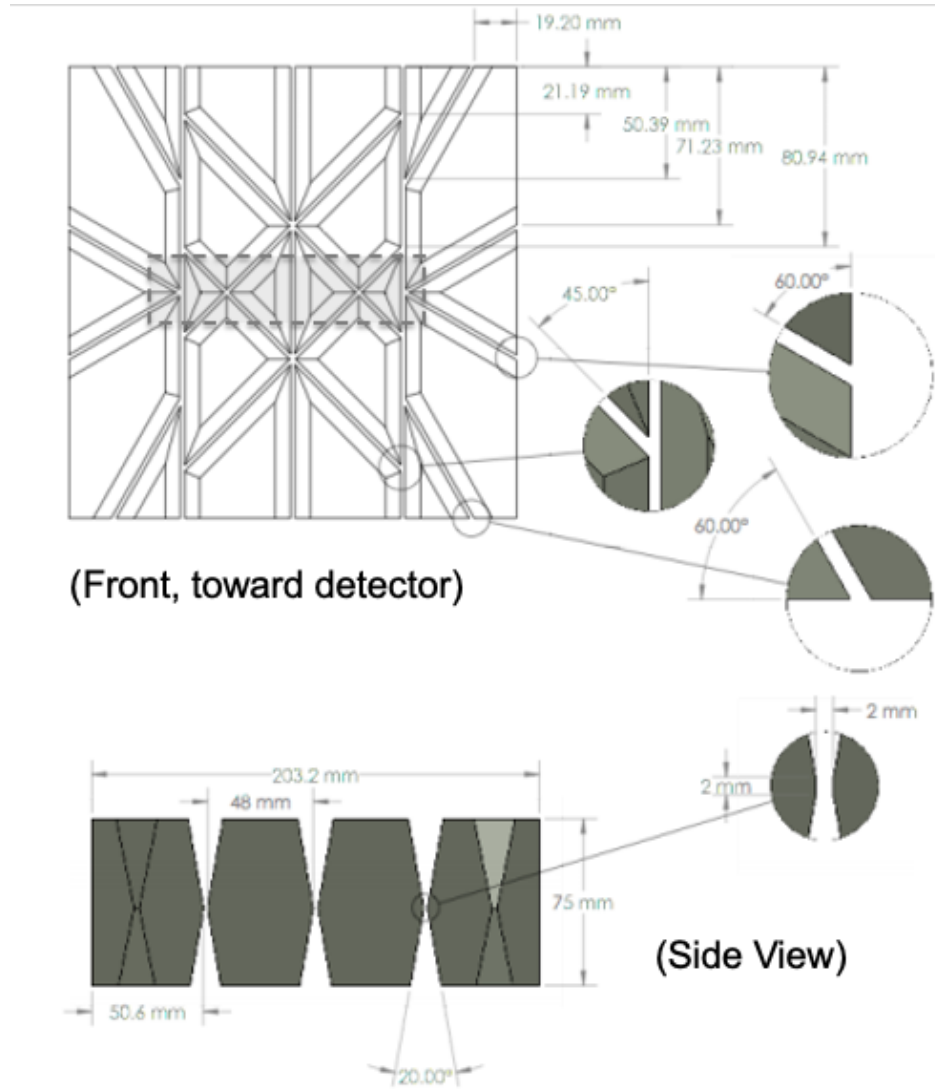


Figure 3.1: Lateral and side views of the mask design as outlined in [92]. A 3D plastic frame holds the Heavimet pieces in place. The lightly shaded grey box was used for the image moment analysis of the system response.

prompt gamma imaging [99]. The mask is 20 x 20 x 7.5 cm and fashioned from 22 pieces of Heavimet (a $\approx 90\%$ W alloy that is still challenging but significantly easier to machine than pure Tungsten) [100] that are held in place by a plastic frame. The lateral dimensions were chosen to cover the FOV for proton therapy and the thickness chosen to attenuate normally incident prompt gammas by 95%. The various angles of the slits allow for full 2D-imaging.

3.3 Detector Array

The detector arrangement consists of a 4x4 planar array of Lutetium Oxyorthosilicate (Lu_2SiO_5 , LSO) detectors. Each LSO detector is a segmented crystal of $4 \times 4 \times 20 \text{ mm}^3$ pixels combined with 4 photomultiplier tubes (PMTs) each with their own gain potentiometer. LSO has been studied as a prime candidate for prompt gamma imaging [101]. A high Z_{eff} (66) and density (7.3 g/cm^3) make it highly effective at stopping high energy gamma rays. The short rise ($\approx 30 \text{ ps}$) and decay (40 ns) time can handle the substantially higher count rates encountered in the radiation fields in ion therapy. A high light yield (30 optical photons/keV [102]) gives an energy resolution of 8% at 662 keV. LSO is not particularly sensitive to neutrons and energy of prompt gamma rays is high enough ($>1 \text{ MeV}$) to avoid the nonlinear light yield regime common to many inorganic scintillators [103]. Energy gates can similarly filter out the intrinsic radiation background (280 Bq/cm^3) of LSO that is the result of a beta delayed gamma ray cascade of 88, 202, and 307 keV photons from ^{176}Lu [104]. The readout electronics and power supplies are set in a single VME crate. The data acquisition system will be briefly discussed in Chapter 5.

3.4 Previous State of Imager Performance in PGI

Much of the work in this manuscript builds on the previous work by Dr. Ready (sections 3.4.1 and 3.4.2) and so a brief review of areas for possible improvement is outlined here and solutions implemented in Chapter 4. Chapters 5-7 reevaluate the performance of the system with those changes implemented.

3.4.1 System Response and Image Reconstruction

A system response was calculated for the imager. System responses map the response of individual detector pixels to point emission locations by either analytical models or MC simulations. The system response previously used a ray tracing algorithm that cast rays from emission points through detector pixels and calculated the total intersection lengths through a 3D polygon mesh model of the collimator and the detector pixels. A $1/r^2$ kernel was applied to account for the falloff in gamma ray flux at larger radial distances from the source. The relative sensitivity map (Figure 3.2) shows the relative probability of various object pixels located in the light shaded grey region in Figure 3.1 to be detected by any detector pixel normalized to the maximum probability pixel. Notice that the overall features in the sensitivity map closely follow the alignment of the slits as one would expect. However, even here, notice the presence of a Moiré pattern [105, 106] that is likely a result of how the rays are sampled. Such a pattern is likely the result of finite sampling resulting in cross talk of the sampling distance with other periodic structures in the collimator (such as the knife slits) or detector (pixel edges). This motivated, in part, a new system response modelling code to be discussed in Chapter 4.

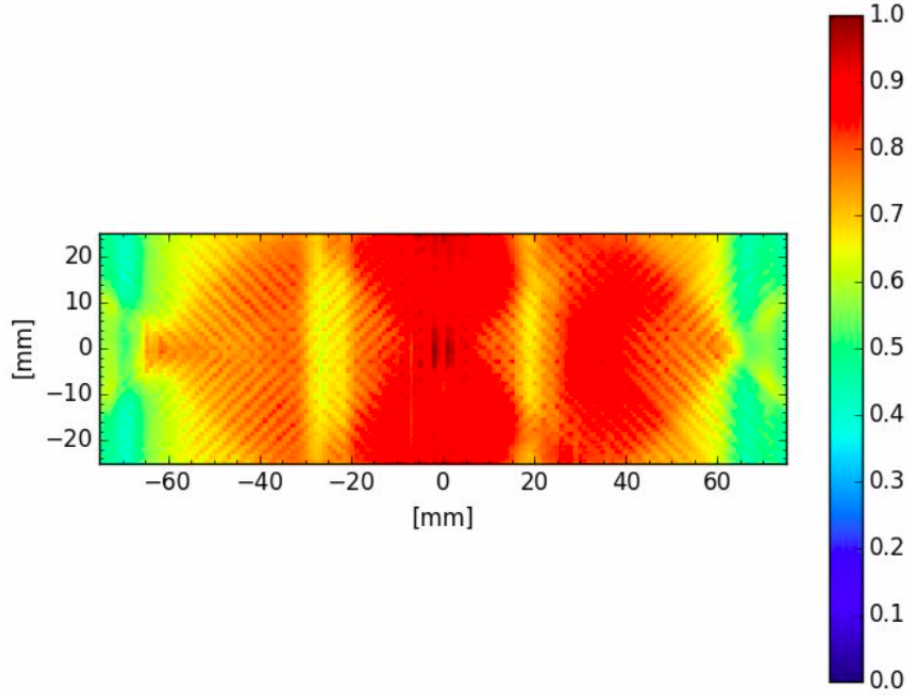


Figure 3.2: Relative sensitivity map generated by the ray tracing algorithm used previously. The FOV is ± 25 mm in the y direction and ± 75 mm in the x direction in 1 mm steps. A Moiré pattern is visible in the map due to sampling. Adapted from [91]

Image reconstruction was performed using the system response, now in the form of a system matrix, as input to the Maximum Likelihood Expectation Maximization (MLEM) algorithm [107]. This standard iterative algorithm for emission tomography attempts to solve the inverse problem of decoding an image projection to the original object emission distribution. This is done by projecting a guess of the object forward onto the detector using the system response, comparing this projection to the known measurements, and then updating the guess for the next iteration. MLEM tends toward maximum probability distributions but is not guaranteed to converge to the global maximum [108] and at high iterations MLEM begins to amplify high frequency noise components in the image [109]. Thus, a stopping criteria was implemented so that the reconstruction stopped when the average change in pixel values dropped below 1% average between iterations. A 4.4 mm full width half maximum (FWHM) Gaussian filter was applied on each update to fold in the FWHM of reconstructed simulated point source measurements using the MC code TOPAS [110].

3.4.2 Range Measurements at 88" Cyclotron

A range verification measurement with the imager was performed at the 88" Cyclotron at LBNL using a 2 cm thick polymethyl methacrylate ($C_5O_2H_8$, PMMA) target: suitable to

fully stopping 50 MeV protons (Figure 3.3, top). A linear stage moved the target in 1 mm increments across the FOV of the detection system at a distance of 13 cm from the face of the collimator. A typical planar image reconstruction is shown (Figure 3.3, middle), for this proton beam incident on the PMMA block. A white line indicates the approximate entry point into the block (from the left) and the red line indicates the 90% depth as calculated using the SRIM ion transport code [111]. The actual locations of the gamma ray interaction in the crystals were determined by the center of mass of the integrated PMT pulse amplitudes, a method developed by Anger [112]:

$$X_{\text{pos}} = \frac{(I_{ur} + I_{lr}) - (I_{ul} + I_{ll})}{I_{ul} + I_{ur} + I_{ll} + I_{lr}} \quad (3.1)$$

$$Y_{\text{pos}} = \frac{(I_{ul} + I_{ur}) - (I_{ll} + I_{lr})}{I_{ul} + I_{ur} + I_{ll} + I_{lr}} \quad (3.2)$$

Where I_{ul} , I_{ur} , I_{ll} , and I_{lr} are the integrated amplitudes in the upper left, upper right, lower left, and lower right PMTs respectively. The resulting histogrammed X-Y gamma ray interaction map is also called the Anger map.

A line profile was generated by averaging the 5 pixels about the row with the maximum intensity profile. The 58% falloff in the intensity was chosen as the reference point for the 90% fall in the proton dose as a surrogate for the proton range [13] as proposed by Polf et al.[41]. This reconstructed reference point of the line profile is plotted (Figure 3.3, bottom) as the target was moved in mm steps with the accompanying residuals. The absolute global position is not known within 2 mm because of the stage but the relative position of each reconstructed falloff should move in mm steps. The total standard deviation of the residual line thus provides a measure of the relative uncertainty in range verification for the system: 0.8 mm at 2σ for the points measured here with 5.6×10^{10} delivered protons. This number of protons is typical of the total number of protons delivered to one spot during a fractionated treatment with pencil beam proton therapy [113].

The results of those measurements were encouraging. A sub millimeter uncertainty in millimeter range shifts of protons on the target with the important caveat that these measurements were done at 0.01 nA, below the 1-2 nA standard for treatment and at a fraction of the 200+ MeV proton energy used to reach deep structures in the body [74]. At higher energies, range straggling becomes wider and the ambient neutron background more intense (see Chapter 1). But those measurements were promising towards realizing prompt gamma imaging for proton range dose verification.

However, the residuals plot in Figure 3.3 (bottom) contain features in the derived range value. The smoothness of the curve and periodicity suggest a systemic bias in the recovered range especially given its dimension. The identification and removal of this systematic bias could potentially reduce the uncertainty even further. This in turn could mean possibly requiring only a fraction of the delivered dose to verify the depth of the beam in tissue. In other words from range verification to range finding.

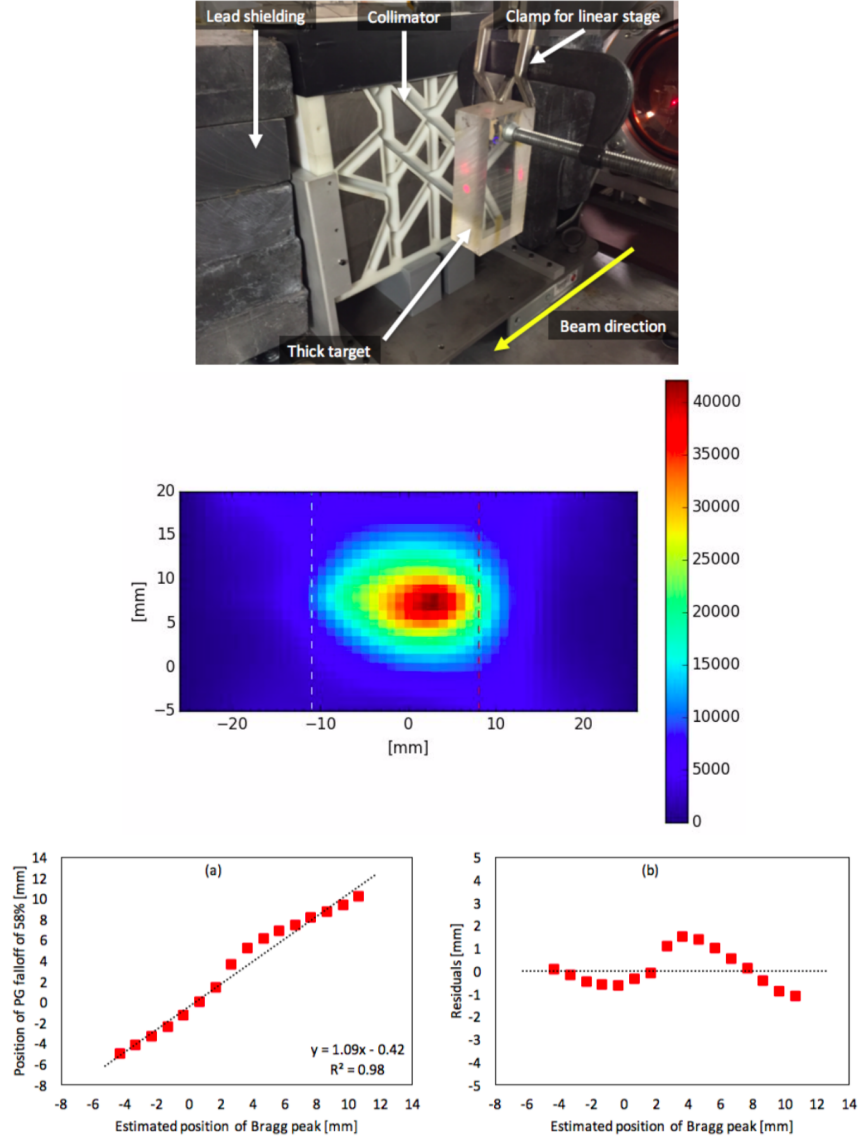


Figure 3.3: Top: Range measurement conducted at the 88" cyclotron at LBNL using a 50 MeV proton beam. Middle: Typical reconstructed image for the beam incident on the thick PMMA block. White line is incident edge of the block and red line the 90% falloff as calculated by SRIM. Bottom: Estimated Bragg (a) peak location and (b) residuals using PG 58% falloff position from averaging the 5 center rows around the maximum intensity pixel. Each point was the result of 5.6×10^{10} incident protons. Adapted from [91].

3.5 Characterizing System Bias

Systematic bias can come from any part of the image reconstruction process. To isolate possible sources of bias, two different studies were performed. The first was a line source measurement to identify possible non-uniformities of extended sources not properly accounted for in the system response. The second was an image moment analysis of the system reconstruction algorithm itself to find any possible periodic shifts in the image space.

3.5.1 Line Source Measurement

A line source was measured using a Th-228 point source with a diameter of 5 mm [114] and a linear stage along the principal x-axis of interest for imaging of proton beams. Th-228 has a complex gamma decay spectrum from its complicated decay chain but emits a 2.6 MeV gamma ray (from Tl-208) which is closest to the energy regime of interest for prompt gammas. The linear stage moved back and forth continuously for 18 hours for ± 5 cm across the center FOV of the collimator, which was the time needed to generate approximately the same number of gamma rays as would be required in a single proton therapy pencil beam spot.

The resulting image is shown in Figure 3.4. There are quite a few features in this line reconstruction. The resulting image is not uniform, with more activity localized in the center than on the sides. There are noticeable drops in the sensitivity near the knife-edge slit locations. The “line” source is also way wider than should be expected. This suggests that the system response fails to capture the complete geometry or physics of the imager that results in distortions in the imaging response. An analysis was next performed to further quantify the local distortions in the image reconstruction.

3.5.2 Image Moment Analysis (of Reconstruction)

Another possible source of bias can come from bias in the system response that introduces periodicity in the sensitivity of the response given the possible spatial frequencies from the detector pixels, sampling areas, and/or knife edge spacing. In an ideal system response, an infinitely small point source either measured or simulated at every point in space should be reconstructed back to a Gaussian centered at the same point: the FWHM of this Gaussian represents the point spread function (PSF) that is central to the approximation of linear shift invariant systems. Non-uniformities in the imaging performance of the system will be reflected in deviations in the PSF from the fixed Gaussian expectation across the object plane [115, 116].

Image moments are weighted averages of pixel intensities for the digital image. The M_{ij} image moment is defined as [117]:

$$M_{ij} = \sum_x \sum_y x^i y^j I(x, y) \quad (3.3)$$

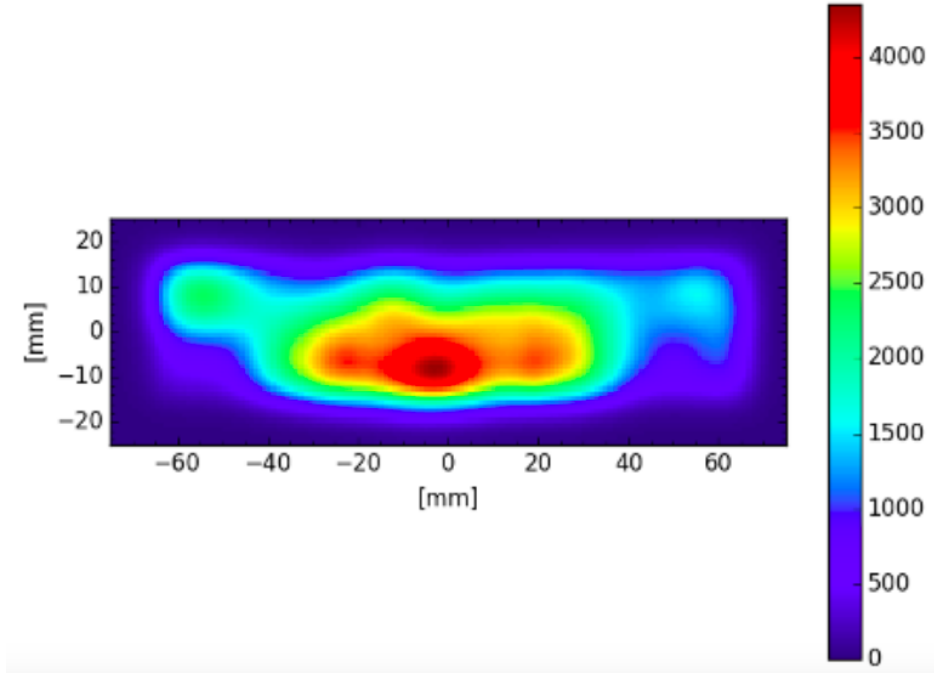


Figure 3.4: Line source reconstruction generated from a Th-228 point moved back and forth from -50 to +50 mm using the same system response as the system response used in Figure 3.3. There are noticeable features in this reconstruction discussed in the text.

where x and y are pixel coordinates and $I(x, y)$ is the image intensity at the (x, y) location. Central moments make these averages invariant with respect to translations:

$$\mu_{pq} = \sum_x \sum_y (x - \bar{x})^p (y - \bar{y})^q I(x, y) \quad (3.4)$$

where:

$$\bar{x} = \frac{M_{10}}{M_{00}} \quad (3.5)$$

$$\bar{y} = \frac{M_{01}}{M_{00}} \quad (3.6)$$

are the weighted mean values in x and y , respectively. The covariance matrix proves to be quite useful for quantifying the distortion of continuous shapes such as the PSF. The covariance of an object is given by:

$$\text{cov}[\text{Obj.}] = \begin{bmatrix} \mu'_{20} & \mu'_{11} \\ \mu'_{11} & \mu'_{02} \end{bmatrix} \quad (3.7)$$

where:

$$\mu'_{20} = \mu_{20}/\mu_{00} = M_{20}/M_{00} - \bar{x}^2 \quad (3.8)$$

$$\mu'_{02} = \mu_{02}/\mu_{00} = M_{02}/M_{00} - \bar{y}^2 \quad (3.9)$$

$$\mu'_{11} = \mu_{11}/\mu_{00} = M_{11}/M_{00} - \bar{x}\bar{y} \quad (3.10)$$

A binding ellipse of the resulting image can be subsequently be generated from the covariance matrix. The angle of the major axis with respect to the horizontal axis and eccentricity of the ellipse are given by, respectively [117]:

$$\Theta = \frac{1}{2} \arctan \left(\frac{2\mu'_{11}}{\mu'_{20} - \mu'_{02}} \right) \quad (3.11)$$

$$e = \sqrt{1 - \frac{\lambda_2}{\lambda_1}} \quad (3.12)$$

where:

$$\lambda_i = \text{eigen}_i(\text{cov}[\text{Obj.}]) \quad (3.13)$$

Image analysis using image moments can help to quantify nonlinearities in imaging systems since imaging systems act as low pass filters requiring only a small number of moments to approximate the underlying image/object distribution [118, 119].

This analysis was performed with the system response used for the LBNL measurement and for the sensitivity map of Figure 3.2. The procedure is outlined in Figure 3.5. At every point calculated in the system response, a point (delta function) source is simulated at that location and then projected forward after the addition of Poisson noise (scatter is not simulated). Then the resulting image is reconstructed. The resulting shape is then analyzed by calculating the root mean square of the standard deviation of the second order moments to give the FWHM, the angle (in degrees) calculated from Equation 3.11, the eccentricity from Equation 3.12, and the displacement based on the total shift of the mean value of the distribution given in Equation 3.5 and Equation 3.6.

The results are presented in Figure 3.6. In general, the same pattern seen in the sensitivity map is also seen in the various image moment metrics of the reconstructed point sources. The various metrics are best near the center of the collimator and get worse as one moves outward to the less sensitive edges. By far the dominant spatial frequency in the images comes from the spacing of the knife edge slits. The long vertical lines in all 4 maps indicate there is a cross talk between the edges of the slits and the vertical lines in the grid of the detector crystals. Rays being drawn along these directions are near the boundary between pixels and can cause even entire shifts (displacements) in the resulting reconstructed point source of one mm. Such artifacts are likely caused by the same interactions between spatial frequencies as the Moiré-like pattern in the sensitivity map. These non linearities and variations are most pronounced along the direction ideal for imaging of proton beams.

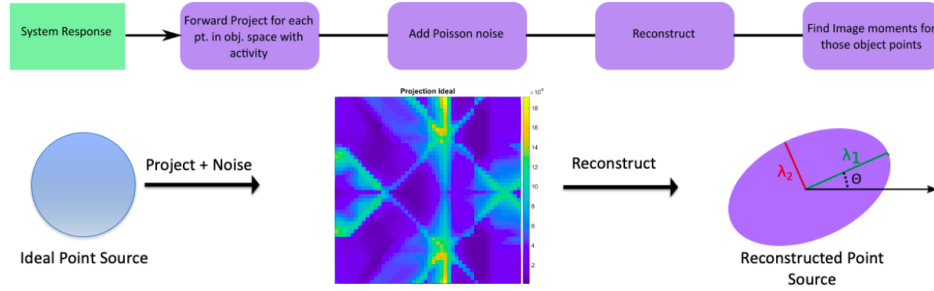


Figure 3.5: Procedure used in the image moment analysis of the system response used at LBNL. Point sources are projected onto the detector and then reconstructed after the addition of Poisson noise. Distortions in the reconstructed point source will be reflected in higher order moments.

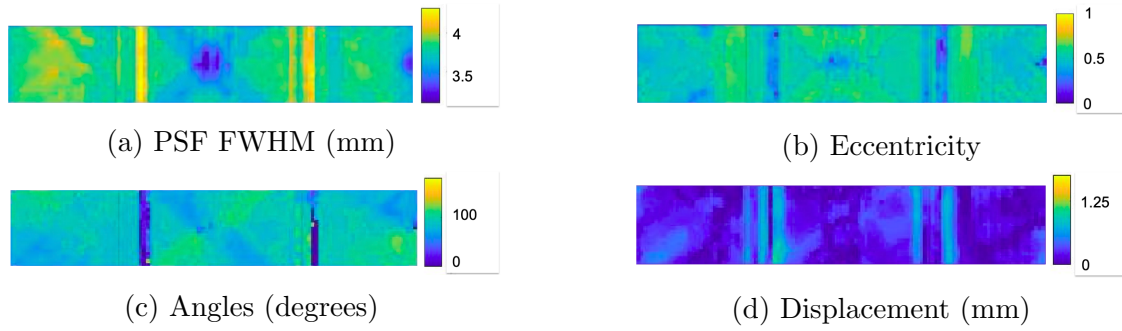


Figure 3.6: Image moment analysis of the system response as used in the LBNL measurements. a) FWHM, b) Eccentricity, c) Angle, and d) Displacement of resulting reconstruction at each point in the object plane.

3.6 Remarks

This chapter described the PGI system under investigation here as well as summarized previous work in imaging of proton range in a PMMA target using a 50 MeV proton beam. The resulting range measurements as the target was shifted showed periodic variation that suggests systematic bias in the calculated system response and image reconstruction. Each of these was separately studied through a line source measurement and image moment analysis, respectively. The overall conclusion to be drawn is that the features seem to be consistent in both and represent spatial interference between the periodicity of the sampling (definitely seen in the sensitivity map), the periodicity of the detector pixel spacing, and the spacing of the vertical knife edge slits.

Chapter 5 will look at how these issues were addressed while subsequent chapters will apply this new system response and image reconstruction to another similar proton beam measurement. Reduction in the systemic bias should further reduce the uncertainty in the range from the imaging of prompt gammas. This could permit range verification with only

a fraction of the beam and thus, range finding.

Chapter 4

PGI System Improvements

This chapter covers the new architecture for the system response generating software and data acquisition (DAQ) software used with the imaging system. The first is motivated by trying to address possible sources of systematic bias that may be degrading the performance of the imager as outlined in the previous chapter. The new response function will be described and then tested by re-analyzing the line source measurement. The second was undertaken to fully enable relevant functions of the digitizers used with the system and allow for on-the-fly parsing, a necessary step in data processing for real time display necessary for pre-clinical use and beyond.

4.1 New System Response

In an attempt to identify possible sources of systematic bias in the system response for the PGI system, the following issues were identified and corrected for in the system response rewrite:

1. Flat detector plane assumption
2. Centered detector plane (relative to collimator) assumption
3. Irregular sampling in polar space without normalization
4. Discretization of collimator with polygon map
5. Only partial FOV coverage
6. Slow calculation speed. 30 minutes for 1 source point using a CPU

The first two of these were simplifications for simpler code that were removed. The actual LSO array is actually a fan beam with a focal length of 42 cm and the center of the array is offset by 2.5 cm in the horizontal direction so that sources in front of the center knife edge vertical slit do not project onto a gap between adjacent center LSO modules. This

also means that the system is slightly more sensitive on the “right side” (when facing the front of the collimator) than the left. The third issue is related to sampling. Rays in both system response codes are chosen by choosing points in the object plane and then casting rays through the center of every detector pixel to ensure uniform sampling through the sensitive volume of the system. However, care must be taken to account for the relative solid angle of each adjacent detector pixel relative to the source point to prevent overestimating the interaction probability in oblique angle detector pixels: this is crudely analogous to projecting the detector pixel area onto the celestial sphere of the source point location. The last two issues, 4 and 5, required a fundamental change in how ray intersections were calculated with the detector and collimator.

The solution chosen to address all of these issues was to vectorize the ray calculations and discretize the ray path instead of the various system volumes (Figure 4.1). Closed vector forms of the slit apertures were created and stored when calculating the system response. The casted rays are discretized in 0.1 mm steps (which is less than the machine precision of the collimator edges) and a check is performed simultaneously for all steps if they intersect in the opening of any slit using vector calculations. The total number of steps inside the collimator is then used to calculate an attenuation probability for the ray. For detector volume intersections, a check is first performed of which detectors are crossed by the ray and in what order. Afterwards, each ray point’s relative position to the center axis of the detector is histogrammed in units of the detector pixel size. The total number of points inside each detector is used to calculate the probability that the ray makes it to the next crossed detector. Each detector interaction probability histogram is updated as more rays from the source point are drawn. Once finished, these are saved to disk and then cleared for the next source point calculation. By discretizing the ray instead of the volumes it is hoped that they can remove the spatial frequency harmonics from the periodicity of the various volumes of interest: mm spacing in the point source locations, 48 mm in the spacing of the vertical slits (Figure 3.1), 48 mm width of the individual detector modules, and 2 mm width of the knife-edge slits.

An additional benefit to this method was a large speedup in system response calculation times after the addition of further optimizations related to only allocating memory for ray points that crossed the detector and collimator planes. Previously, the response for a single source point could take upwards of 30 minutes on a CPU mostly as a result of long for loops that had to project and then interpolate the polygon mesh for intersection points. The new system response code performs that same calculation in 4 seconds, a speed up of about 450x, with the ability to subsample detector pixels at arbitrary fineness for higher sampling but corresponding increase in computation time.

An example of such point source calculations can be seen in Figure 4.2 for point sources at different object to collimator distances but normal to the center of the collimator. In the near field in a), only part of the pattern (Figure 3.2, Chapter 3) is visible while in b) the far field the entire pattern is visible including the edge of the collimator because of the relative shift in the centers of the collimator and detector array.

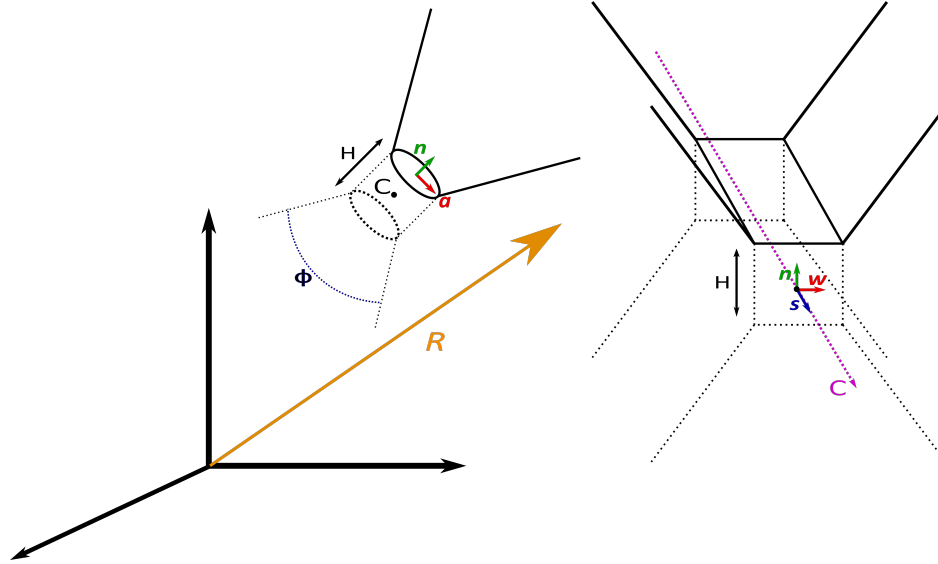
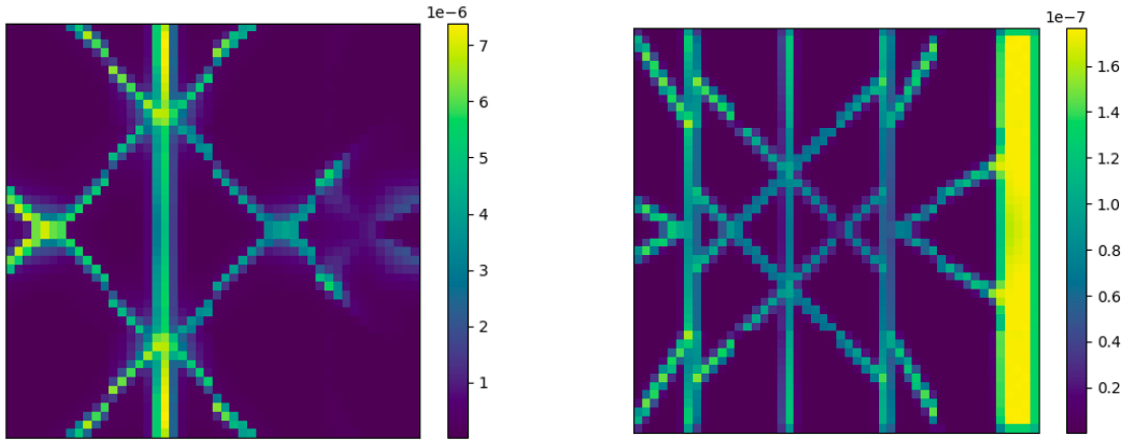


Figure 4.1: Sample aperture parameters utilized in the new system response code for pinholes and knife edge slits. C is the center point or center line of the aperture for pinholes or knife edge slits, respectively. H is the height of the channel (can be zero) and n is the (n)ormal of the aperture with a being the radius of the aperture for pinholes. Once the (s)lit axis is set, the (w) axis is automatically calculated as the cross product of the n and s vectors. Rays being traced through the collimator are discretely vectorized as R .



(a) Projection from Point Source at 11 cm

(b) Projection from Point Source at 150 cm

Figure 4.2: Centered point sources at a) 11 cm from the collimator and b) 150 cm from the collimator i.e. far field. Due to the shift of the center of the detector array relative to the collimator, it is possible to get a direct line of sight to the detectors of the right most edge.

4.1.1 New Sensitivity Map

A new sensitivity map was generated but for the entire FOV (20 x 20 cm) because of the substantially reduced computational time. The accompanying sensitivity map in Figure 4.3 clearly reflects both the overall shape of the collimator mask but also the asymmetry of the left and right halves of the FOV. The patterning artifacts are largely gone except for vertical line ghost artifacts. These are largely the result of the finer sampling of the horizontal versus vertical dimensions since the interest is in proton beams directed along the x-axis. The artifacts are real reflections of the dominance of the vertical knife-edge slits in horizontal variations in the sensitivity. The system response (201 x 201 x 48 x 48) takes about 186 mb of system memory.

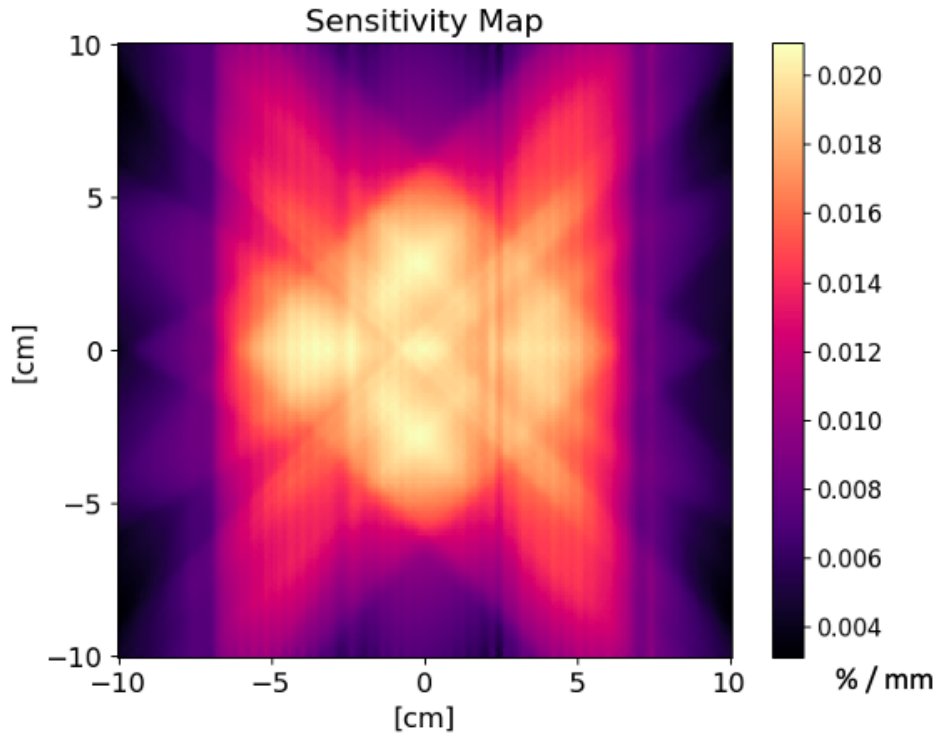


Figure 4.3: Sensitivity map of the entire FOV using the new system response code. Maximum is 0.021 % / mm and the average is 0.0116 % / mm.

4.1.2 Line Source Measurement Revisited

The line source measurement (Figure 3.4, Chapter 3) was repeated using the new system response. The result can be seen in Figure 4.4a. The line source now appears much more uniform and is centered at the y midplane of the FOV as expected. Folding in the dimensions of the button disk source (the active volume a cylinder of 5 mm diameter and height of 3.18 mm) into the response gives the image reconstruction of 4.4b which now includes the entire

FOV. The FWHM of the line source, 4.4c, was found to be 100.14 mm, which is close to the original extent of 10 mm. Lateral slices, 4.4d, give a FWHM in the lateral dimension of 2.5-2.7 mm at different x locations with the point source extension deconvolved. This gives confidence that the system response better encapsulates the geometry and physics of the system.

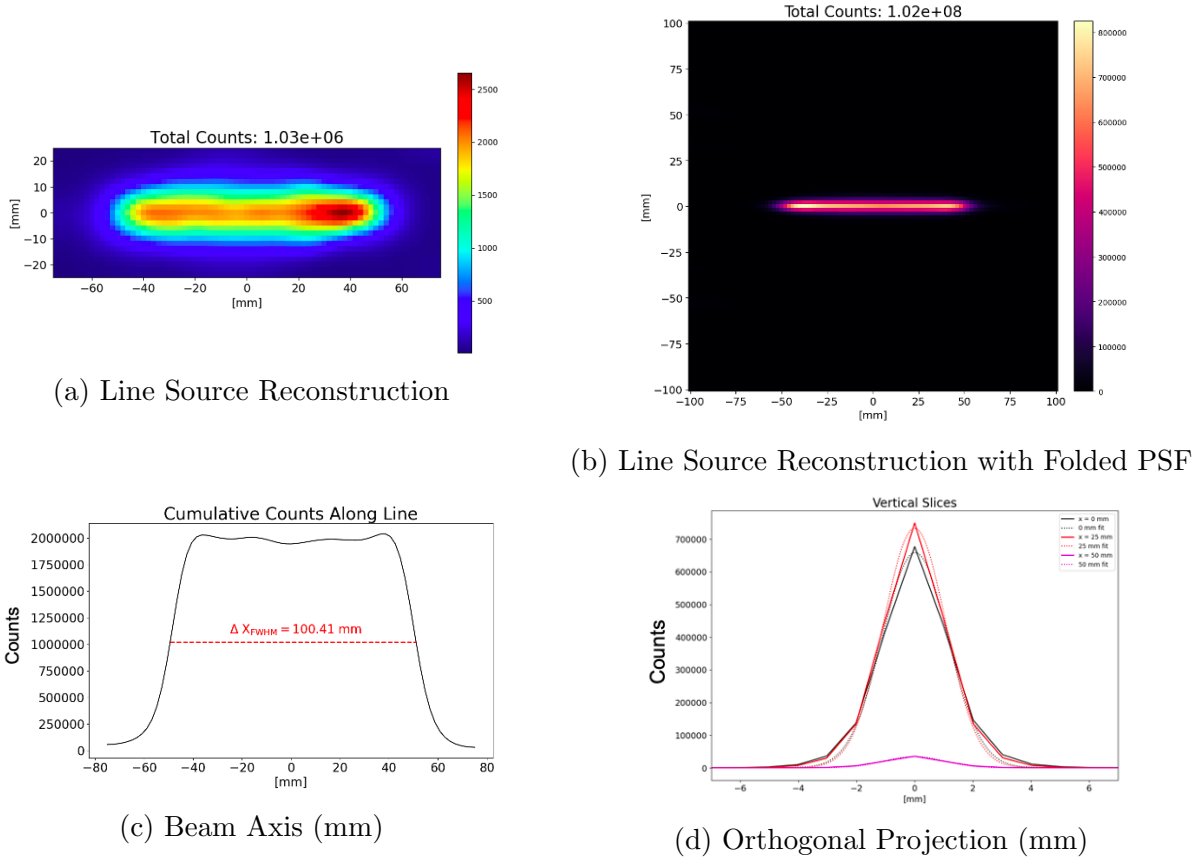


Figure 4.4: Repeat of line source measurement and reconstruction from Chapter 3 using the new system response. a) Line source reconstruction appears more uniform and closer to the dimensions of the “line source” than Figure 3.4 and along the $y = 0$ axis. b) Same line source but with the finite dimensions of the source folded into the response. c) Projection along the horizontal (x) axis of b). The FWHM of the distribution is 100.41 mm. (original line source is 100 mm wide). d) Orthogonal (y -axis) line slices of b). FWHM fits of 2.7, 2.5, and 2.5 mm at $x = 0, 25$, and 50 respectively.

4.2 Data Acquisition Rewrite

In a general clinical environment, the processing, image reconstruction, and calculation of the range should ideally occur coincident with the treatment spot such that dose corrections

could be made with subsequent spots (range verification regime) or subsequent bunches could be tuned for the same spot (range finding regime). To that end, the data acquisition code was rewritten to make it more compatible with this goal. It also had the additional benefit of making it more modular and compatible with other internally developed software or future applications.

The digitizers used in the system are Struck SIS3316 16-channel 250 MHz, 14 bit analog-to-digital converters [120]. Each board comes equipped with 4 Field Programmable Gate Array (FPGAs) and 8 dual-readout DDR3 [121] chips split evenly among the 16 channels. The boards are capable of a wide array of features related to timing, clock timing, NIM I/O, energy spectroscopy, triggering, pulse shaping, and digital pulse processing that can be read out and configured through VME or VXS using further vendor software or through ethernet using a small form-factor pluggable (SFP) cage connector at the front of each board [122]. Four boards are required to read the 64 total PMT channels of the PGI system in this work. They are synchronized using 1 clock as a master that drives the others using a front panel LVDS (Low-Voltage Differential Signalling) ribbon connector on the front panel of the board.

The code package is written entirely in the Python programming language [123] and requires only a few additional packages: NumPy [124] and PyTables [125]. The choice of Python was to make the data acquisition software agnostic to the data acquisition computer's operating system and remove potential software library compatibility issues. NumPy provides a library of python wrappers for C++ matrix and array manipulation subroutines for speed and automatic garbage collection. PyTables was chosen to provide access to Hierarchical Data Format 5 (hdf5) [126] file management subroutines. The PyTables hdf5 functionality gives access to fast subroutines to read, write, and append to paged files for larger than RAM data sets. The emphasis of the code is on speed and scalability for simultaneous parsing and saving (or eventually, displaying) of digitizer events in real time.

The important features of the new overall object-oriented code framework are summarized in Figure 4.5. Different parts of the DAQ system are represented in the abstract by objects on the local machine at run time. Python class variables and functions are mapped to specific memory addresses and flags in the boards bidirectionally for reading and writing. Backend routines parse and distribute UDP packets [127] through gigabit ethernet connections between the local machine and the boards while handling network congestion, lost data packets, polling of onboard memory flags, and beginning data reads. In 4.5a, the module manager class sets the parameters of individual boards further delegated to FPGA level (group), channel level, and board level (temperature monitoring or sampling frequency) functions including configuring of trigger logic. A higher level class, daq manager in 4.5b, further abstracts to the entire data acquisition system as a whole across multiple boards. Communication for a multi-board system is handled through network interfacing via an ethernet switch. The front end of daq manager, 4.5c, allows for the entire configuration of the system to be set from a human readable text file with open ended functions to allow this to be handled by a graphical user interface (GUI). The front-end also automatically opens and begins saving to extendable hdf5 files or raw binary (useful for speed) after parsing incoming data words on-the-fly. A structured python data dictionary is also temporarily stored

virtually that can be transmitted to further user provided sub routines.

This code package streamlined the entire data acquisition process for the PGI system in this work and allowed for far more reliable data readouts and debugging of network failures. This was true even in high count rate applications such as measurements involving prompt gamma imaging from proton beams (see Chapter 5). This codebase will likely serve as the backend for a real time display of the current range of the proton range in a future fully realized clinical implementation of the imager.

4.3 Remarks

The system response was rewritten to remove possible sources of bias within the imaging response of the system as a means to further improve the resolution of the end of range of proton beams. The new system response achieved this by changing the ray tracing paradigm to emphasize speed and remove possible geometric and sampling errors. A marked improvement was found in the imaging of a distributed line source and in the resulting sensitivity map.

The DAQ system was also rewritten with an eye towards speed and reliability for measurements involving beams. Eventually, the system will need to be integrated into the clinical workflow and be able to both process and display the current range estimation in real time for diagnostic usefulness for clinicians as they adapt treatment.

These improvements then encouraged performing another measurement at a real proton beam line which is the subject of Chapter 5.

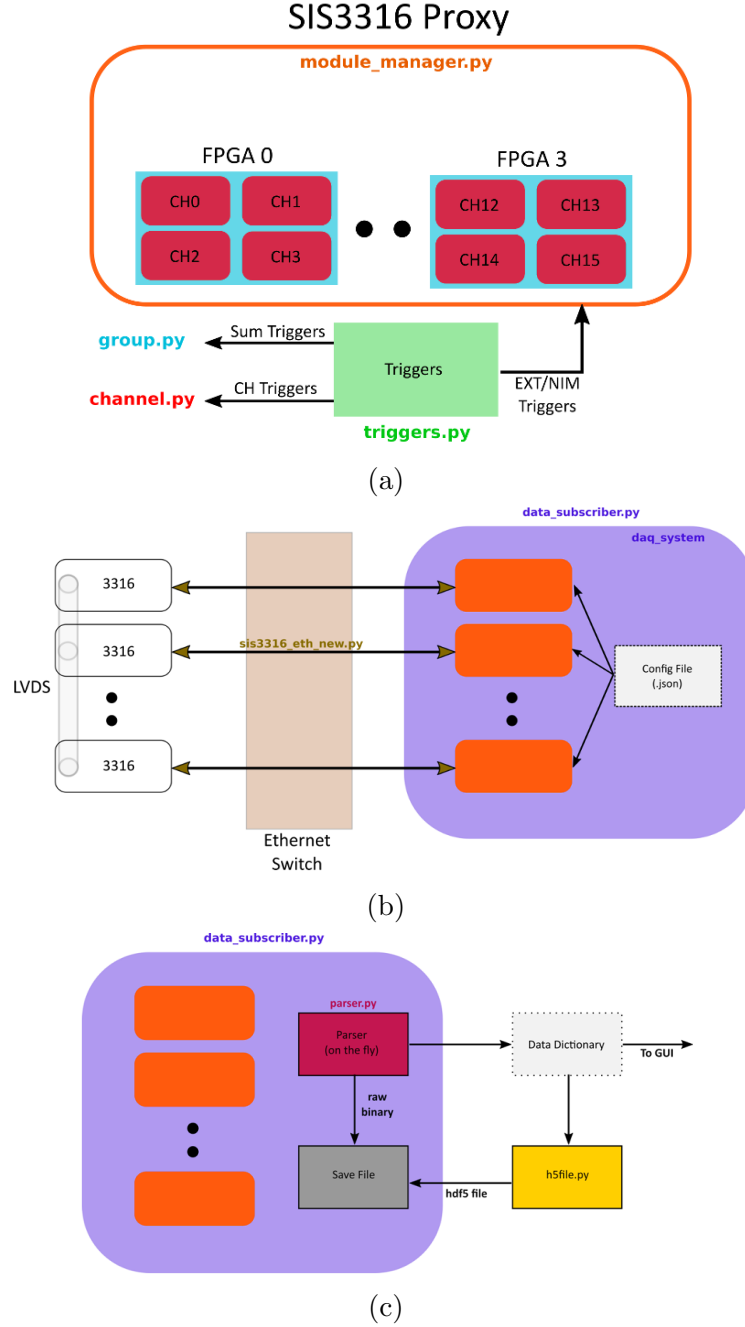


Figure 4.5: Organization of the new DAQ system code for PGI for the a) board level and b-c) system level. The b) back end handles communication of the local machine and the boards through UDP while the c) front end handles the saving and transmitting of the incoming data packets in the local machine. A full description of the code is provided in the text.

Chapter 5

Measurements and Postprocessing

To test the improvements made to the signal and data processing chains of the system, a series of measurements were conducted using a real proton beam. This chapter will outline the setup and methods as well as the additional post-processing steps that had to be undertaken to correct beam-line induced errors in signal processing that are likely the result of high intensity background radiation. The rest of this thesis, Chapter 6 and 7, analyzes the data from these measurements and its implications for proton range verification.

5.1 Materials and methods

Measurements were performed with the radiation effects beamline at the 76-inch cyclotron at the UC Davis Crocker Nuclear Laboratory [128]. The setup can be seen in Figure 5.1. The camera sits on an adjustable optical table and is adjusted perpendicular to the beam. A 2 inch cube pure polymethyl methacrylate (PMMA, acrylic) block sits on a remotely controlled linear stage that gives two additional degrees of freedom for the block. Tungsten and paraffin shielding was located proximal to the beam port to shield undesirable background radiation from the window; in particular, carbon prompt gammas from the Kapton window and neutrons.

Prompt gamma rays from oxygen and carbon (see Chapter 2) were produced from irradiating the acrylic block with a 0.1 nA proton beam at 100 target positions spaced 1 mm apart using the linear stage across the central 10 cm of the imager's FOV: the linear stage was found to have a precision of less than 0.1 mm. The current used represents about 1/10 of the typical proton beam current used for treatment [74]. The spacing of the points represents the desired sensitivity ($\sim$ mm) to range shifts in the beam. The beam energy was set to the maximum beam energy of the cyclotron for protons of 67.5 MeV: this energy corresponds to a range of approximately 3.3 cm in acrylic or 3.8 cm in water [129].

A hardware sum trigger of the 4 PMT channels above 2 MeV was set for each of the 16 LSO modules to remove gamma ray background from the recorded data, especially the annihilation photons. This background was primarily from the abundant annihilation photon

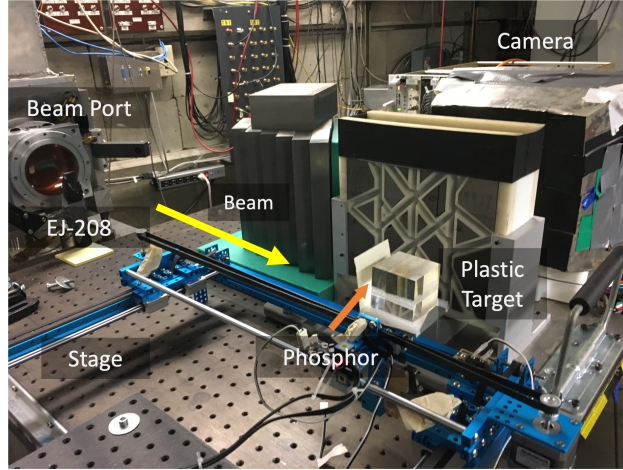


Figure 5.1: Photo of the system in place for measurements at 76-inch cyclotron at Crocker Nuclear Laboratory. The beam enters from the left hand side of the image to strike the thick 2" plastic cube. A linear stage allows the block to be moved in mm increments in front of the camera. 10 inches of Heavimet is used at left to shield flux from the Kapton window (which itself contains Carbon). A 1 mm thick plastic scintillator, EJ208, was placed near the beamport to measure the arrival time of the proton beam. The indicated phosphor was used for beam alignment.

background from long lived beta-plus decay and the deuteron gamma ray line. This filter is well below the lowest prompt gamma ray of interest: the 4.4 MeV carbon line.

Finally, a thin plastic scintillator was placed in the beam path near the beam port (Figure 5.1) and before the target as a preliminary investigation into synchronizing the produced gamma ray interactions in the LSO array with the arrival of the proton bunch similar to the Prompt Gamma Timing (PGT) and Prompt Gamma Spectroscopy (PGS) systems outlined in Chapter 2 to possibly remove neutron-induced gamma ray events or constrain the image reconstruction space and improve image contrast/quality. LSO has a timing resolution of about 300 ps [101, 16] which, for a 250 MeV proton, translates to a spatial distance of 5.5 cm in the FOV: this is a nearly 2 factor reduction in the FOV of the slits which would improve contrast in the image reconstruction. This resolution is also sufficient to observe the arrival of a 2 ns proton bunch in a 44.4 ns period possibly removing up to 96% of the continuous neutron induced and (long-lived) positron-delayed background also significantly improving image contrast. The protons delivered from a cyclotron are not delivered continuously (Figure 5.2, Top), but instead in bunches with an arrival time spread τ that occur with the cyclotron RF period T ; for the UC Davis radiation effects beamline, τ is estimated to be about 2 ns with a cyclotron period of 44.4 ns (22.5 MHz RF period). Given the short lived states of the proton induced gamma ray signatures of interest (see Chapter 2, table 2.1), it is similarly expected that the desired gamma ray signatures for prompt gamma imaging would likewise follow a similar time profile provided that the arrival

time of the protons is known. This can be done using the RF signal from the cyclotron itself, but the drift of protons relative to the RF can induce systematic drift over time. A thin detector placed in the beam path itself could directly measure the arrival time based on the rising edge of the light signal from the incident proton beams provided the decay time is much smaller than the cyclotron period. EJ208, from Eljen Technologies (Sweetwater, TX), was chosen for the direct detection of the proton beam for its fast rise/decay time (1 and 3.3 ns, respectively), machinability, light yield (10 optical photons/keV) and radiation hardness (less than 50% fluorescence loss at 0.8 MGy exposure)[130]. A 1cm x 2cm x 1mm piece of EJ208 was seated with optical grease into a 2 mm groove in a fishtail waveguide coupled to a 1 inch diameter fast Hamamatsu PMT (model: H10580) [131] and then wrapped with optical tape to make it light tight (Figure 5.2, Bottom). The 1 mm thickness was chosen as a compromise between structural integrity and energy loss of the beam (less than 1 MeV for a 67.5 MeV proton beam from SRIM). The dose rate to the plastic at 0.1 nA and $\approx$ cm spot was approximately 5 Gy/s.

The plastic scintillator signals were digitized and readout independently of the LSO array signals using its own Struct 3316 board but with a synchronized clock. This was done to allow for possible discrimination and investigation of both proton induced and neutron induced signals for the imager. A hardware dead time of 1000 samples (4 microseconds) was set for each triggered event to not overwhelm the bandwidth of the ethernet readout to the acquisition computer.

5.2 Post Processing of Projections

A number of post-processing steps were necessary to correct for aberrations in the recorded counts of the LSO modules and thus caused distortions in the recorded projections. The major effect was a noticeable drift in the gain of the PMTs during beam irradiation. The likely cause of these artifacts is related to temperature dependent (but wavelength and voltage independent) gain coefficients of the dynodes, secondary emitters, and photocathodes since the PMTs were not temperature regulated during beam on acquisition [132, 133, 134]. The resulting gain shifts meant a shift in both the spectra of the PMTs relative to beam off conditions and shifts in the weighted sums of the PMT signals in each module causing errors in the resulting Anger map. These distortions required additional calibration beyond standard benchtop calibrations. The next subsections will go over the procedures by which these corrections were performed directly.

5.2.1 Beam Induced Gain Shift Correction

Shifts in both the relative gains of the PMTs within each module and between modules themselves was seen in the resulting spectra. Correcting for these two gain shifts was done using two different data sets.

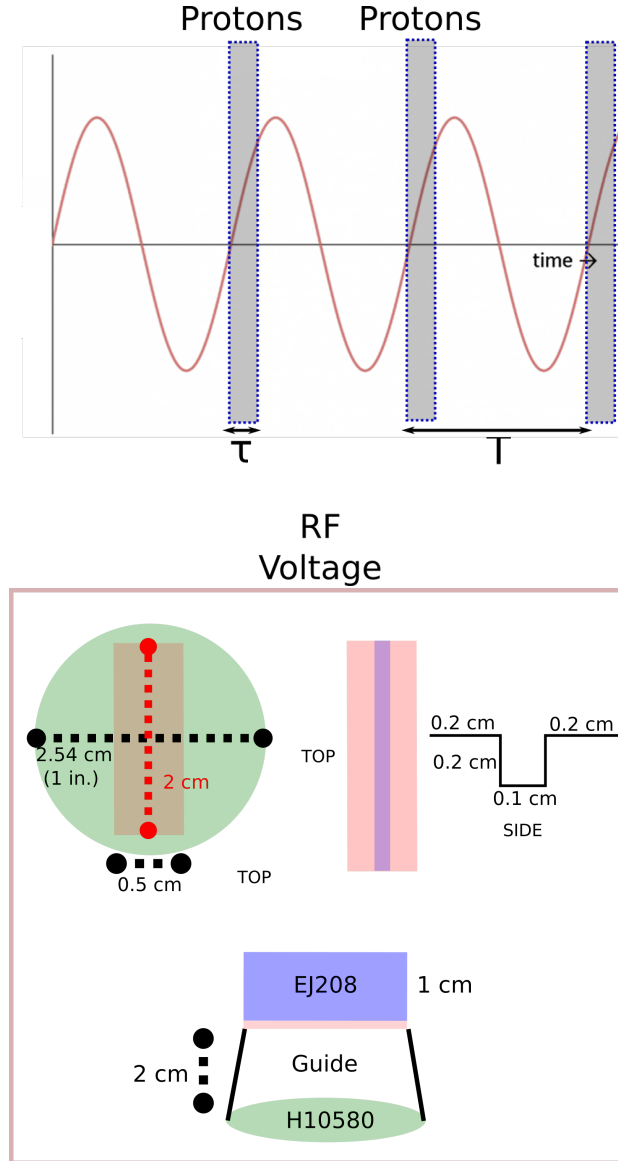


Figure 5.2: Top: Schematic of time structure of a cyclotron proton beam. Proton bunches are delivered with variable bunch times τ (in gray) synchronized with the RF driving period T . These parameters are design dependent. Bottom: Schematic of plastic scintillator placed in front of the beam. A EJ208 fast, radiation hard plastic scintillator is coupled to a Hamamatsu 10580 fast PMT using a fishtail waveguide. The signal was digitized independently of the LSO signals but with a synchronized clock

For the PMT gain shift, an overnight measurement done on site and the data were used to correct for the PMT shift. The measurement was taken using a Th-228 check source (because of its simple gamma ray signature) located at the block's position at the center of the imager FOV with the beam off. Because light is shared among the four PMTs for all

interaction positions within the segmented LSO crystal, it is impossible to completely isolate the spectrum of one PMT independent of the others. However, events localized near the corners of the Anger map (see section 3.4.2) are more heavily weighted to the corresponding nearby PMT. Thus, the resulting spectra of the PMTs from masking all but the “corner” events give approximately the energy spectrum of just that PMT itself. Gain corrections can then be applied based on the features in these spectra by normalizing to overall intensity (ideally, a flood measurement would be performed without the collimator).

An example of the calibration procedure is given for one of the modules in Figure 5.3. Part a) shows the original ADC histograms of events from the overnight measurement for all four PMTs and b) is after the segmentation algorithm is applied. The segmentation algorithm uses the spectrum, c), generated only from those events that lie near the four corners, d), of the Anger map (the segmentation map is covered in the next section). The four spectra look very similar with some scaling factor differences between them. A reference point was chosen to scale each of the gains of the PMT to the same ADC value. This reference point was the ADC bin corresponding to the fifty percent falloff from the max intensity bin. The corrective scaling factors are applied to generate new ADC histograms of all events in the module. This software gain correction results in better matched PMT spectra even without the use of a flood source.

Gain shifts between modules were handled in a similar way but using actual beam data once the PMT corrections were applied. Due to the hardware trigger threshold of 2 MeV, the 511 keV line from annihilation could not be used. So instead, the 4.4 MeV photopeak, single escape, and double escape peaks were used to apply gain shifts for the entire module. To increase the SNR, only events within the center of the Anger map were used instead. This can be seen in the spectrum for one of the modules, 5.4, at one target position with the reference peaks for carbon in the zoomed in image at right. This region of the module has the highest probability of stopping incident high energy gamma rays and shares the light between four separate PMTs.

5.2.2 Direct Crystal Segmentation

In addition to gain shifts as a result of the radiation fluence from the beam, changes in the Anger map were also observed. Instead of manual segmentation, an automatic segmentation algorithm was developed and deployed to correct the crystal map directly for each of the projections. This algorithm was based on projecting the total Anger map onto the x and y directions and then choosing the crystal edges by finding the minimum of these profiles. In general, the distortion of the Anger map was reflected in a linear scaling of the range of the center of mass values and not distortion effects seen in pixelated optical cameras as a result of changing light sharing of sensors such as pincushion, barrel, or mustache distortion [135]. It was further found that these distortions for each module did not vary by target position but only by the presence of the beam. However, the segmentation algorithm was applied for each module at each position.

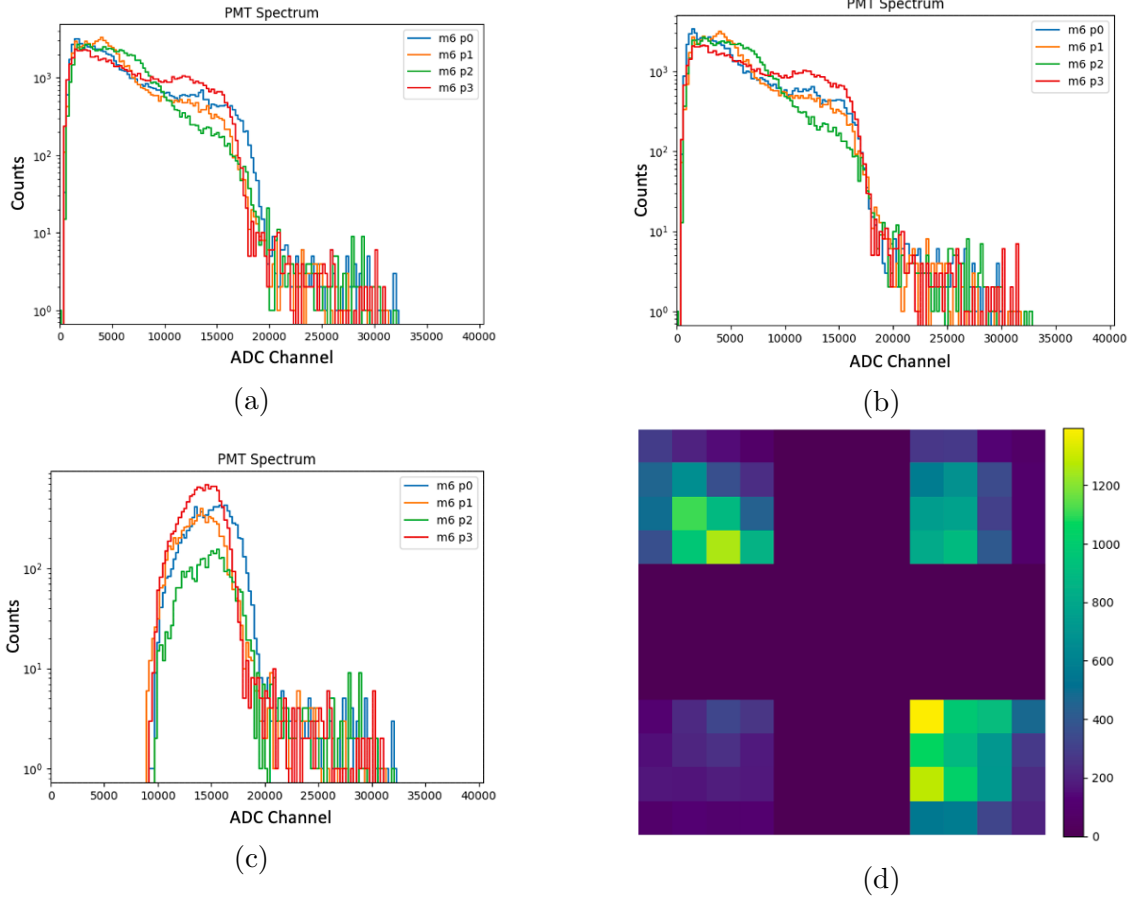


Figure 5.3: Example of PMT calibration using overnight on-site Th-228 data for one of the modules. a) Original PMT spectrum for all events for (m)odule 6 and its 4 (P)MT channels. b) Same as a) but with the software gain corrections. For the correction a c) PMT spectrum was generated using only those events located near the d) corners of the flood map. The 50% falloff was used as a reference point to scale the gains of the individual PMTs in each module. Resolution is limited due to energy loss for corner pixels.

The workflow is represented in Figure 5.5 to correct the crystal map for one module at one target position. In a) and b), are shown the spectra the Anger map with delineated crystal boundaries and the resulting pixelated count histograms (projections) for the detector. However, a) uses the crystal map as a result of benchtop measurements using check sources. The new map results from the automatic segmentation algorithm, c), that finds the minimum of the projection of the Anger map onto the two cardinal directions. These new boundaries become the crystal map for b). In general, since the distortion mostly resulted in a scaling of the radial components of the center of masses this distortion was most pronounced near edge pixels.

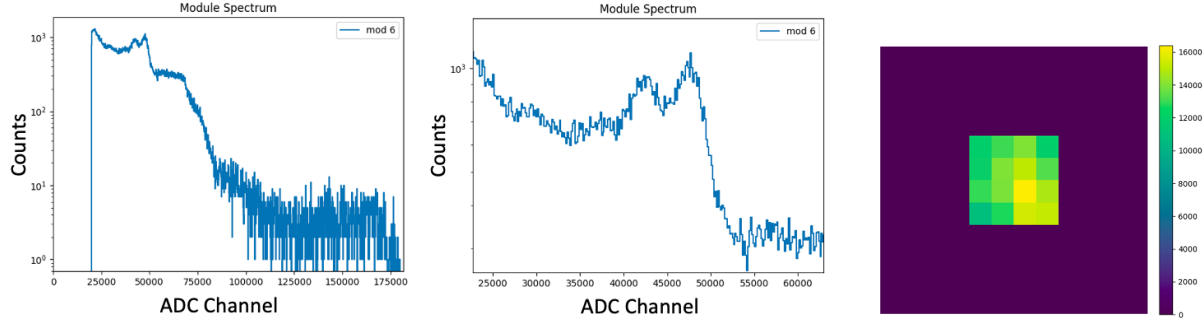


Figure 5.4: Left) Example module spectrum using beam data for gain calibration. Middle) Zoom in of the carbon photopeak, single escape, and double escape prompt gamma peak. Right) Region of Anger flood map used to generate the spectrum.

5.3 Corrected Projections

The result of PMT gain correction, module gain correction, and crystal resegmentation gives the spectrum and projection seen in Figure 5.6. The pattern of the mask can clearly be seen in the projection and the energy calibration allows for filtering the counts for further image reconstruction. For the purposes of subsequent analysis, several regions are outlined on the spectrum as well. The counts in these regions will be referred to as carbon escape (CE, 3-4 MeV), carbon photopeak (CP, 4-4.8 MeV), oxygen escape (OE, 4.8-5.8 MeV) and oxygen photopeak (OP, 5.8-6.4 MeV). The energy resolution is worse than expected as a result of per pixel gain variations. There was insufficient time to gather necessary statistics with the beam to perform this calibration as has been done by Hueso-Gonzalez [101].

5.4 Remarks

This chapter outlined the measurement performed at the radiation effects beamline at Crocker Nuclear laboratory at UC Davis. Before further analysis, distortions were found that were a result of the beam irradiation. These effects were corrected for in post processing by direct use of the data itself. As these effects were tied to the presence of the beam, this suggests that the automatic software correction methods proposed here will likely be needed for the system in the future for higher energy and more intense beams.

The remainder of this manuscript focuses on the resulting images from the PGI. In particular, the extent to which differing images result from filtering based on different gamma lines. And the insights that can be inferred from such differentiation of the image into energy bins.

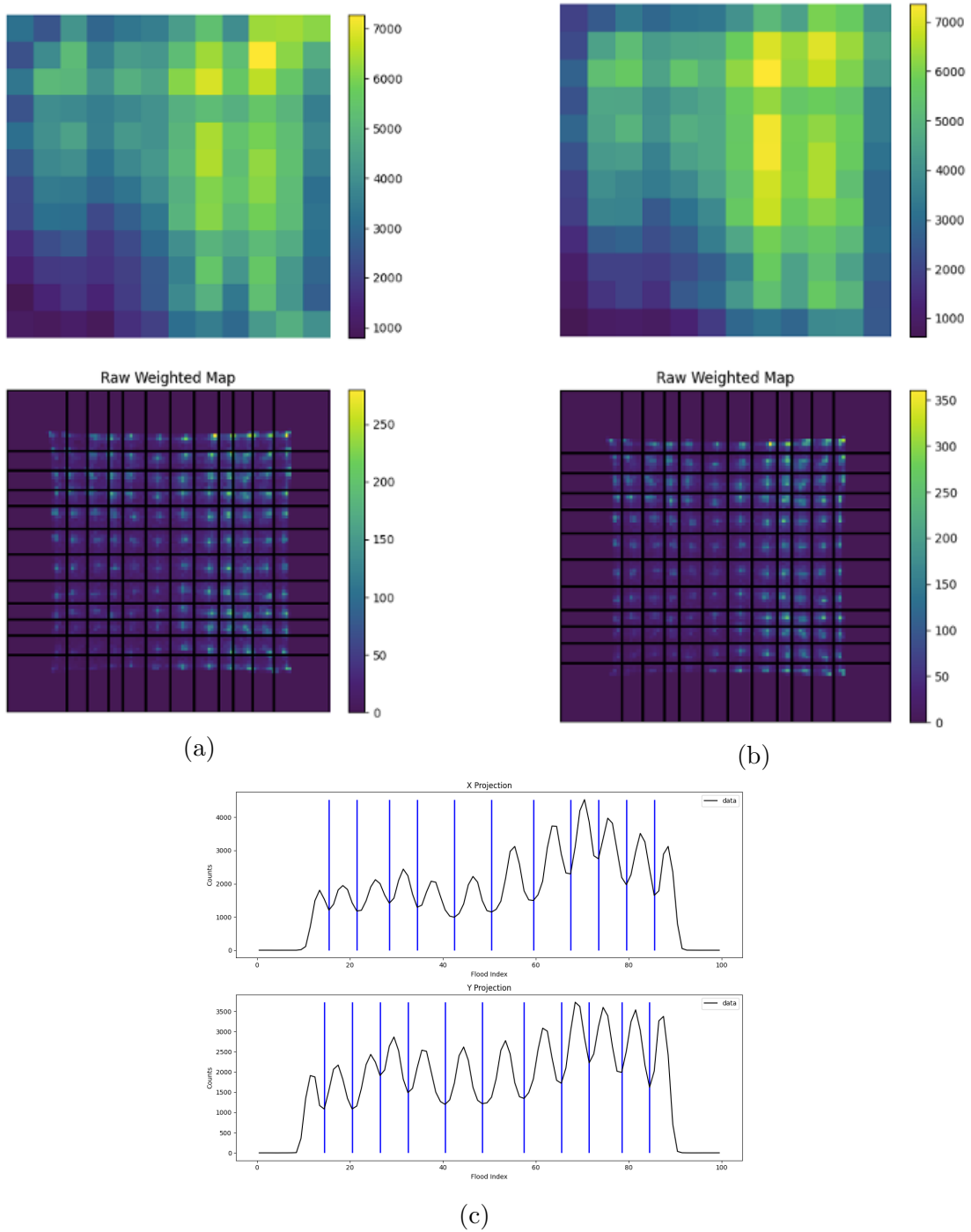


Figure 5.5: a) Example of an uncorrected crystal map for a module during beam irradiation with target including Anger map and resulting projection. b) Same as a) but with the edges determined from c) a crystal edge finding algorithm that projects the counts onto x and y then finds the minima of the resulting curves

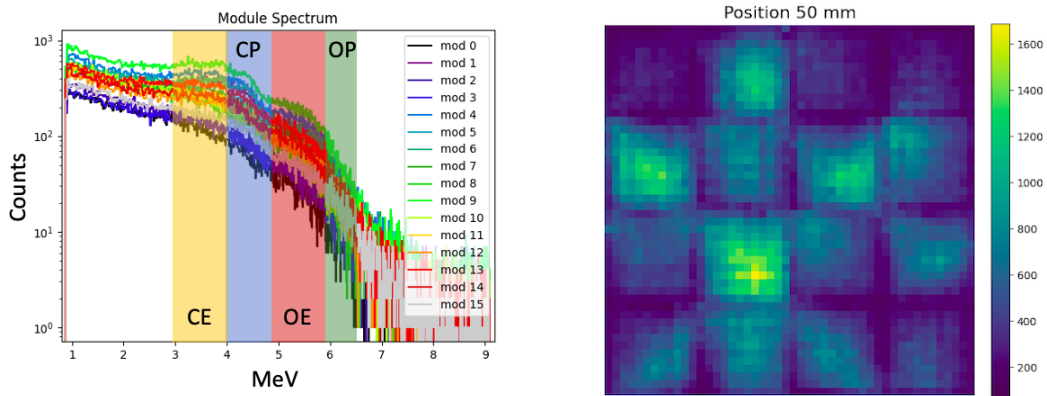


Figure 5.6: Left) Example energy spectrum from all detectors at one target position after gain corrections. Various regions of interest for analysis indicated in transparent boxes. (C)arbon (E)scape: 3-4 MeV. (C)arbon (P)hotopeak: 4-4.8 MeV. (O)xygen (E)scape: 4.8-5.8 MeV. (O)xygen (P)hotopeak: 5.8-6.4 MeV. Right) Projection after applying the automatic segmentation algorithm.

Chapter 6

Range Uncertainty Reassessment

This chapter focuses on an initial range reassessment and uncertainty analysis using data collected at UC Davis (see Chapter 5) and with new data processing and system matrix methods (Chapter 4). These data are at a higher current than that collected at LBNL previously (0.1 nA vs. 0.01 nA) and at a greater penetration due to higher energy (~ 3.4 cm in PMMA at 67.5 MeV versus ~ 1.9 cm in PMMA at 50 MeV). These conditions are closer to a more realistic clinical scenario wherein range verification would be of utility. This analysis is done using different energy windows to investigate the impact of gamma ray energy on the statistics necessary for range determination. Chapter 7 will then add a new kernel-based method to improve the image quality of the resulting image reconstruction based on the physics of prompt gamma emission. Much of this part of the chapter is based on earlier published work which can be consulted for further details [136].

Unfortunately, the EJ208 plastic scintillator was unable to provide the necessary timing information to separate out proton beam induced signals from the gamma ray LSO detectors. Possible reasons why will be explained in this section. These weaknesses can be iterated upon in future work to avoid the possible sources of timing error. One such solution will be presented in the last chapter.

6.1 Initial Range Uncertainty Results

6.1.1 Image Reconstruction and Range Determination

Figure 6.1 shows an example of an image reconstruction and resulting range determination measurement. MLEM is performed using the corrected projections until the updates (iterations) in the source distribution are less than 1% of the total projected counts. The resulting image shown in Figure 6.1 is the result of a 60 second irradiation with a 0.1 nA, 67.5 MeV proton beam or approximately 3.7×10^{10} total protons. The image pixel intensities are normalized to the total incident protons during the irradiation. The shape of this distribution appears as only a slightly asymmetric Gaussian but with the expected width

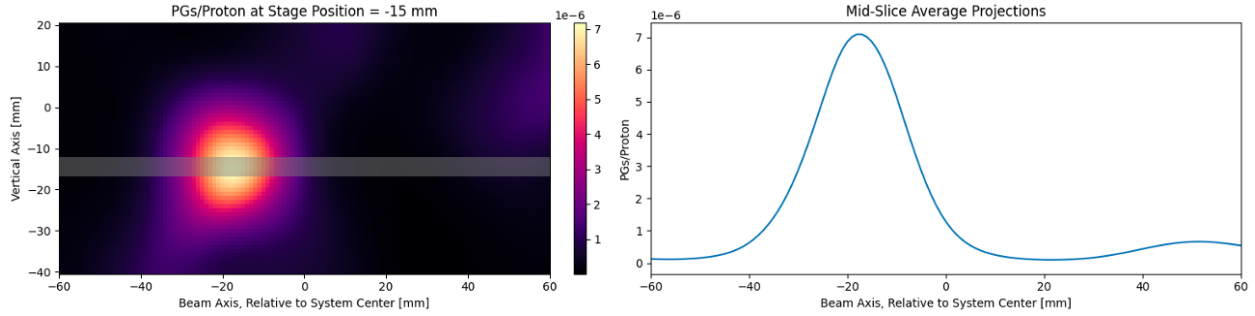


Figure 6.1: Left) Example image reconstruction using 3.7×10^{10} protons. Right) 5-Slice Average line profile from the reconstructed image represented as a faded white box in the image.

for protons at this range in PMMA. The falloff in the the prompt gamma distribution is not the sharp edge as is expected from the physics (see, for example, Figure 2.3). However, at these low proton energies (≈ 3 cm depth) and large proton spot widths (≈ 1 cm) it is difficult to tell how much of this is due to the beam, the generated system response, or the image reconstruction (suggested by the faint image artifact at about 50 mm). Imaging using protons of higher energies in a pencil beam at larger depths would ideally generate relatively flat entrance channels and serve as a check on the extent to which this broadening is tied to the specifics of the beam.

A 5-Pixel (5 mm wide) slice is taken through the image centered along the maximum intensity pixel represented by the faded white band in the image. The average of these 5 1 mm slices is used to generate the line profile at the right hand side. The stage center was aligned to approximately the depth of protons in the PMMA block. The penetration of the protons within the PMMA block causes an offset in the resulting range determinations in the stage and system coordinate systems. The 58% falloff from the maximum value on the distal side of the line profile is taken as the reference point for the 90% fall off in the proton dose as determined previously [136], and by others [41]. Shifts in the position of the target then correspond to shifts in this fall off position and the use of this fall off was found to provide consistent results.

6.1.2 Systematic Range Uncertainty Analysis

A systematic analysis of the performance of the PGI was performed by imaging, reconstructing, and then determining the 58% falloff in the averaged line profile of the block as it was moved in mm steps across the front of the collimator. This analysis was performed using different energy filters to generate the projection histograms and with different numbers of total incident protons. The energy regimes are the same as those used in the previous chapter: carbon (3-4.8 MeV), oxygen (4.8-6.4 MeV), and the “full” energy range (3-6.4 MeV).

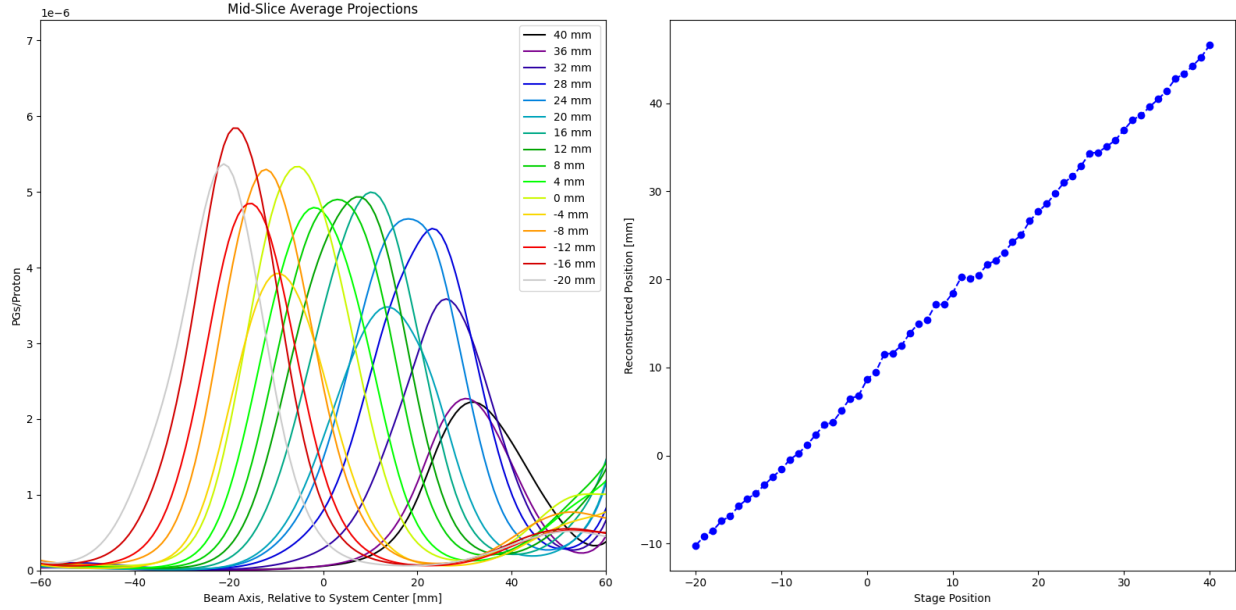
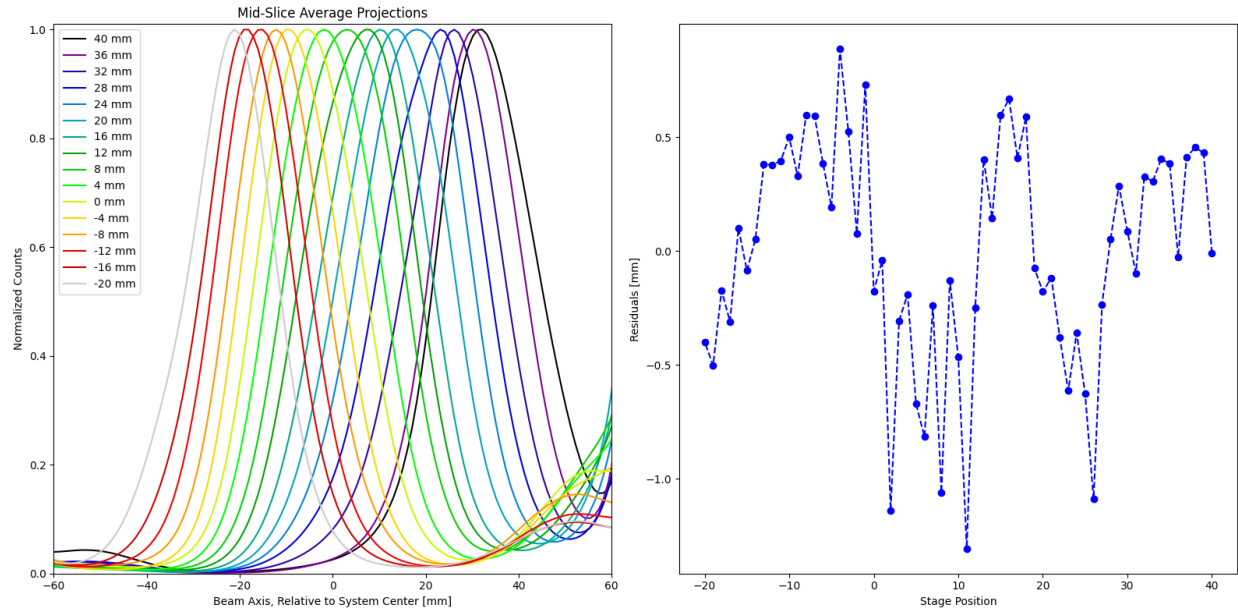


Figure 6.2: Left) Line profiles at each of 15 positions spanning 60 mm in total for ease of viewing. Right) Reconstructed position vs. stage position. An offset exists between both as a result of penetration into the block.

Figure 6.2 shows the line profiles for 15 different target positions spanning 60 mm of the field of view and the resulting reconstructed ranges versus target positions. The energy filter was set to include the carbon and oxygen peaks, including first and second escape peaks. The maximum intensity of the line profiles begins to drop as the target is moved away from the center of the system, reflecting the loss in sensitivity of the imager near the edges of the collimator. The resulting plot of stage position versus reconstructed proton range shows a linear relationship as is to be expected. The offset between the origin of both coordinate systems can be taken care of by using a single water tank measurement, a standard device at proton treatment facilities used for quality assurance [137]. What is the focus of this analysis is the relative shifts in reconstructed profile as compared to the known mm shifts in the target using the motorized stage.

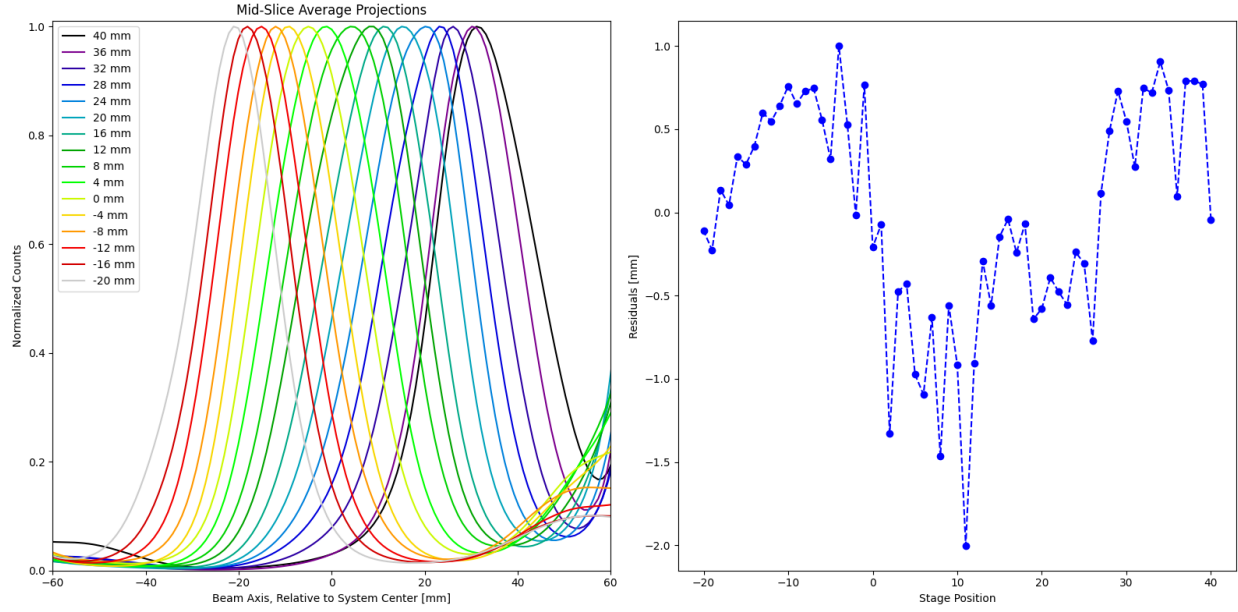
Figure 6.3 shows normalized line profiles for different energy regimes and residuals of the resulting linear regression fits of the reconstructed ranges. Figure 6.3a shows the line profiles of Figure 6.2 but where each line profile is normalized to its maximum intensity pixel. The residuals of the resulting linear regression fit are also provided. Slight artifacts can be seen in the image at 50 mm, which is approximately also the location of a slit suggesting a degeneracy in the response given that the target was placed 11 cm from the collimator (instead of the 13 cm as per the design). Figure 6.3b and Figure 6.3c, show the line profiles and residuals but only for the carbon and oxygen energy range. The standard deviations of the residuals for the total images, carbon images, and oxygen images were found to be

0.49, 0.66, and 1.4 mm, respectively. In general, the more counts in the projection, the greater the reduction in this uncertainty in the range. The sharp rise in the range error for oxygen near 18 mm for the stage also corresponds to points where the line of sight lies along the gap between adjacent detectors. This regime dominates the uncertainty for oxygen but contributes little to the overall prompt gamma profile because of the far fewer counts (by a factor of 100) at these higher energies further worsened by the drop in efficiency of pixels at the edges of the modules. With current detector dimensions and the low efficiency of the system to 6.1 MeV gamma rays, an energy gate above 4 MeV seems sufficient for determining the proton range.

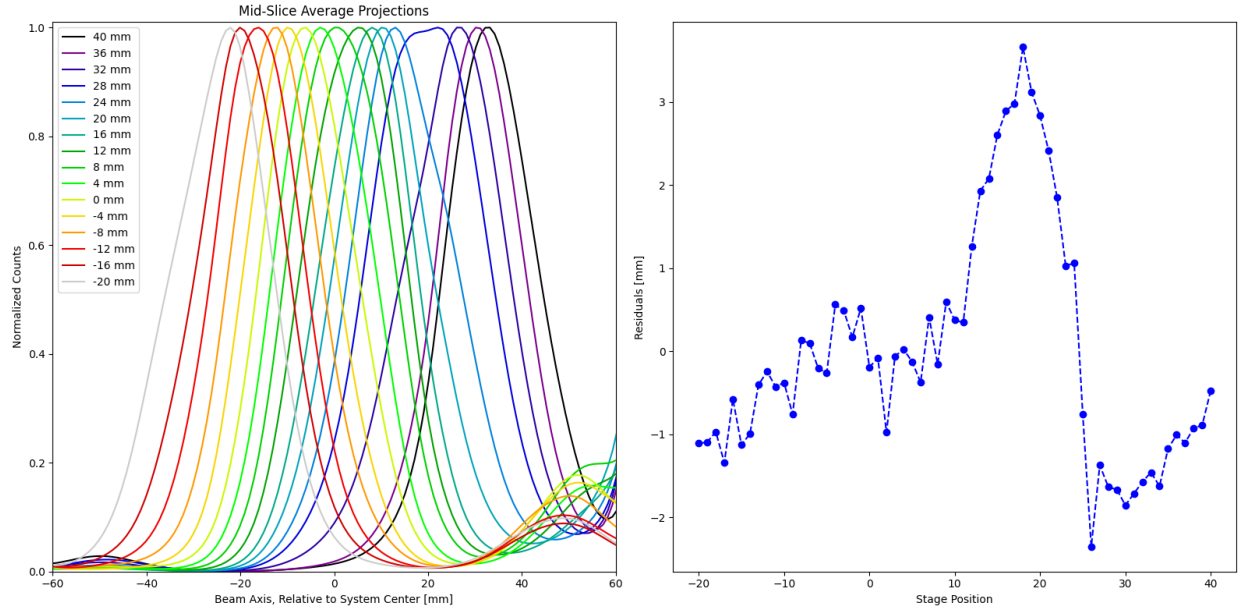


(a) Full Energy (CE + CP + OE + OP)

Figure 6.4 shows the 2σ -range uncertainty of the reconstructed range using different numbers of total protons. These projections were simulated in several steps by use of a uniform random number generator for values from 0 to 1 for each count in each bin of measured projection. Counts were included in the new simulated projection if this value was below the ratio of the new and original number of protons. This kept the independence of each measured event across the desired time interval. Recovery of the range at each decade means fewer protons are required which, as noted in Chapter 1, are important milestones in the regime by which the system could operate (range verification to range finding): 10^9 - 10^{10} is generally the number of protons delivered in one fraction. The lower limit of about 5×10^7 protons is about the number of protons delivered in one spot in dose painting for pencil proton beam scanning [41].



(b) Carbon (CE + CP)



(c) Oxygen (OE + OP)

Figure 6.3: Line profiles and residual plots from a linear regression plot of the reconstructed range for a) Full (3-6.4 MeV), b) Carbon (3-4.8 MeV), c) Oxygen (4.8-6.4 MeV) projections for 3.7×10^{10} total incident protons on a PMMA target. Standard deviations of each residual plots are 0.49, 0.66, and 1.4 mm, respectively. 60 points were measured but only 15 are plotted to aid in visual clarity. These lines are labeled by the stage position.

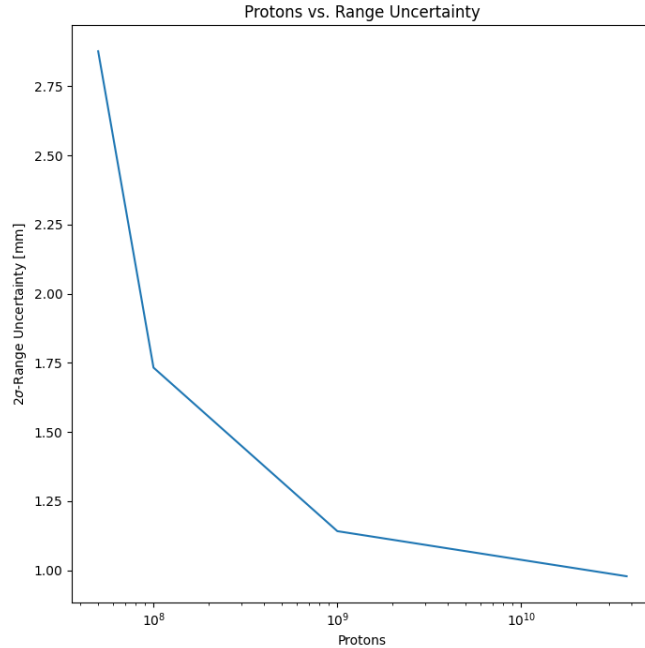


Figure 6.4: 2σ -uncertainty vs. number of delivered protons. These uncertainties correspond to standard deviations of the residual fits of 1.48, 0.87, 0.57, and 0.49 mm for 5×10^7 , 10^8 , 10^9 , and 3.7×10^{10} protons.

6.2 Timing Information

6.2.1 Traces

The oscilloscope and digitized traces from the EJ208 plastic scintillator (see Chapter 5) as a result of the passing proton beam can be seen in Figure 6.5. The long oscilloscope trace in Figure 6.5a shows the periodic wave structure of the passing proton beam, in this case a period of 44.4 ns. The number of saved samples from the digitizers was set to twice this to see both the preceeding and following proton induced light signals in the plastic (Figure 6.5b). However, there is a great deal of variability in the peak amplitude of each of these pulses from both the oscilloscope and the SIS3316. Likewise, the range of peak amplitudes was found to be much lower than expected given the expected energy deposition of about 1 MeV from each of the protons in the proton bunches. Further, this range of peak amplitudes was found to *decrease* at higher proton beam currents and *increase* with lower applied voltage to the PMT suggesting a power limit of the associated PMT (the stated maximum current for the H10580 is 0.1 mA [131]). Such a limitation required setting the trigger threshold to only about 30 mV, much closer to the noise floor than anticipated.

The individual waveforms themselves had one of two typical shapes, a wider “long” light

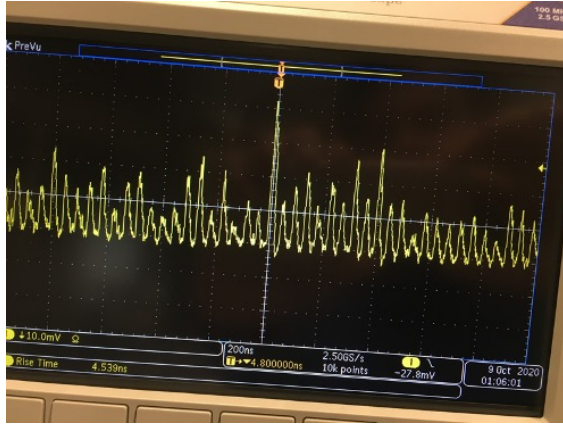
signal with a brief plateau region followed by a gradual decay (Figure 6.5c) and a “short” pulse with a decay time more typical of the EJ208 plastic scintillator (Figure 6.5d). In both cases (4 ns/div), the amplitudes and rise times are similar only differing in the subsequent decay shape (and thus, total light yield). The periodicity of the waveforms suggest that both are a result of protons from the proton beam and that the difference between them has to do with power fluctuations of the PMT at these high event rates. The “long” waveform with a linear decay suggests saturation effects of the PMT while the “short” waveform is more suggestive of the expected light pulse for a several ns width proton bunch and a 3.3 ns decay time of the plastic. Such variability in pulse shapes and amplitudes presents challenges to reliable timing for the digitizer given the 4 ns sampling rate.

6.2.2 Time Correlation

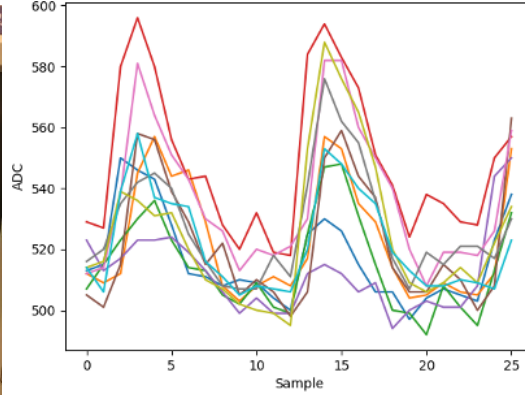
Two different methods of creating time correlated spectra (and thus, time correlated images) were attempted and can be seen in Figure 6.6. The first of these two methods shown with one of the target positions, Figure 6.6a, involved filtering events if they occurred within the time window of a saved proton induced waveform in the EJ208 plastic scintillator (Figure 5.2) to create a time and energy 2D plot. Here the x-axis, time, is defined as the time stamp of the LSO gamma ray events relative to the nearest saved proton event (± 44.4 ns for $\pm$ one cyclotron RF period). Because of the long dead time introduced into the digitizer for the plastic scintillator pulses due to bandwidth constraints, the 2D plot contains a small fraction of the total gamma events. This translates to a largely featureless 2D spectrum even with very coarse binning. The standard deviation of the number of counts across the relative time bins is only about 8.3%. In an attempt to boost the counting statistics, a second method was used that instead binned all gamma ray events in the LSO array by taking the timestamp modulo the cyclotron RF period. As an example, events from the most illuminated module at one of the target positions, highlighted in red in Figure 6.6b, was used to generate the spectra of Figure 6.6c. The various spectra are events from this detector in 10 evenly spaced time bins modulo the RF cyclotron period. And again, it appears that the time correlation has been lost given that there is little variation between spectra in this plot. This is especially prevalent given the 4.4 MeV carbon line (and escape peaks) which should have a higher yield during the passage of protons at only a fraction of the RF period. The standard deviation in the total counts here is less than 1%, suggesting that the timing information has been lost. Thus, the projections (and thus images) are identical when filtered in both the energy and time domains.

The limitations of these approaches in correctly time correlating gamma ray signatures in the LSO array with the proton induced signatures in the plastic scintillator could be attributed to the following:

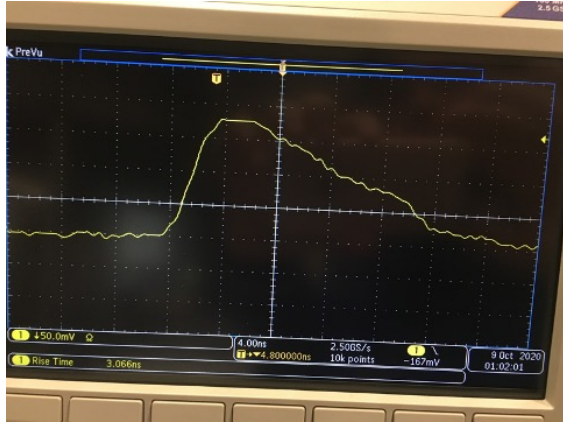
1. Cyclotron RF frequency drift or deviations from 22.5 Mhz assumption
2. Time jitter of proton signals in the plastic as a result of the digitizer sampling frequency and variable height waveforms



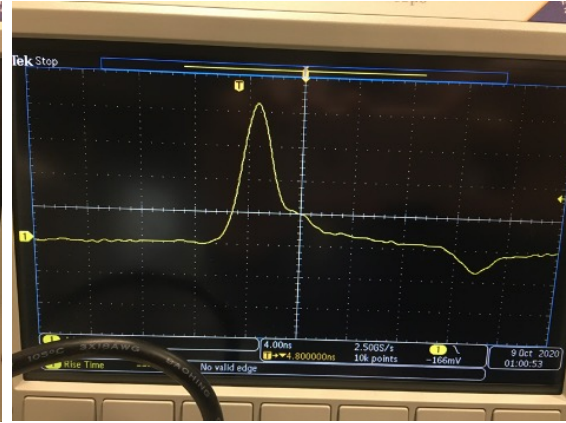
(a) Long inverted trace of EJ208 waveforms on oscilloscope. 200 ns/div and trigger at 27.8 mV with 10 mV/div. Offset to see baseline of the signal.



(b) Ten example raw traces saved using the 250 MHz (4 ns/sample) SIS3316 digitizers. The trace length was set at twice the period of the RF from the cyclotron, 44.4 nanoseconds, centered about the trigger sample.



(c) The first of two typical waveforms from the plastic scintillator, the “long” waveform. See text for details.



(d) The second of two typical waveforms from the plastic scintillator, the “short” waveform. See text for details.

Figure 6.5: Oscilloscope and digitized traces from direct measurement of the proton beam passing through the plastic scintillator (see Figures 5.1 and 5.2).

3. Efficiency losses from the introduced hardware dead time for the plastic scintillator pulses to meet bandwidth constraints

The first of these issues introduces aliasing artifacts for the modulo binning of the second method. Removal of this issue would likely entail measuring the RF pulse with a synchronized digitizer with sufficiently high sampling rate to correct for RF drift in real time. This is effectively what is done in the Prompt Gamma Timing technique (see Chapter 2).

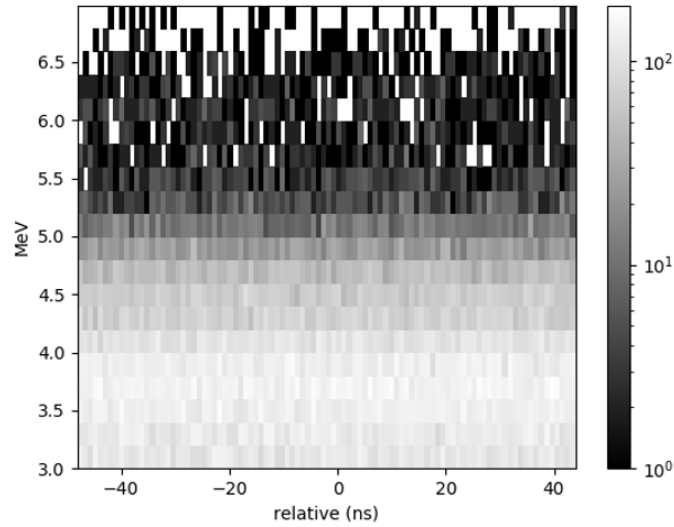
The second and third point present the likely complications of recovering timing for the first method. The rise and decay time of these signals (Figures 6.5c and 6.5d) is of the

order of 4 ns which is the same as the digitizer sampling frequency. The variability in these amplitudes (Figure 6.5a) additionally adds time jitter when using a threshold trigger scheme to generate time stamps. Addressing of this issue will likely entail a combination of using a higher sampling frequency digitizer and redesigning of the plastic detector assembly. In particular given that much of the distortion is likely due to saturation effects of the PMT from the light signal, further iterations of the design could focus on making the PMT coupling less efficient to help discriminate noise and avoid saturating the PMT. Possible changes include roughing the EJ208 crystal edges, painting the sides of the light guide black, or even indirect coupling of the signal using photodiodes instead of a PMT to avoid saturation issues entirely. The last point remains a limitation only so far as it is desired for the plastic waveforms to be saved. Once the timing between LSO and plastic scintillator is reliable, the correlation can instead be done in hardware to optimize the signal by filtering on only proton induced events. One such proposed system is left in discussing future work in Chapter 8.

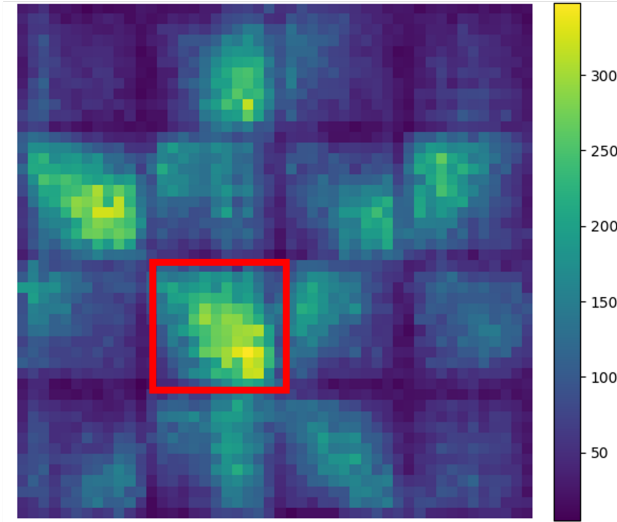
6.3 Remarks

This chapter outlined the range uncertainty using the new post processing and system matrix calculations for measurements at UC Davis. These measurements were done at an order of magnitude higher delivered beam current (0.1 nA vs. 0.01 nA) than done previously and at a higher energy (67.5 vs 50 MeV). The analysis was also performed across 4x the total field of view (6 cm vs. 1.5 cm). Higher energies and beam currents represent more challenging environments given the induced background field, especially of neutrons. However, even still, the range uncertainty was determined to within 1 mm with the delivery of 10^{10} protons.

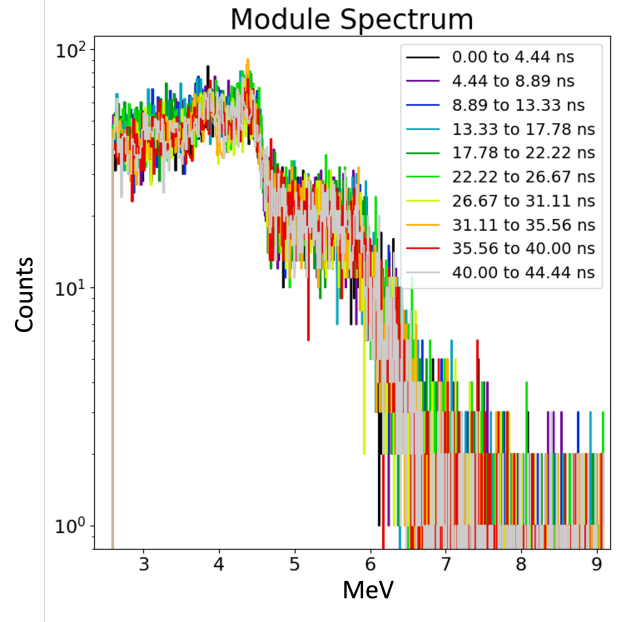
Efforts were undertaken to correlate gamma ray events with proton events using either the relative time stamps of the events or by binning the events relative to the RF period. Although unsuccessful in this first iteration, the incorporation of such information into image reconstruction should prove valuable in further reducing the proton range uncertainty. Solutions have been proposed to address the source of the likely limitations of these approaches.



(a) Example of 2D time-energy histogram from all LSO modules at one of the time positions. Only those gamma ray events that fell within the time window of a proton event are taken. The time is defined as the gamma ray timestamp relative to the saved proton event timestamp.



(b) Example projection.



(c) Gamma ray spectrum using events from module highlighted in red in (b). Each spectra results from binning the timestamp modulo the RF period (44.4 ns).

Figure 6.6: Schemes to correlate gamma ray events with the arrival of the proton beam using (a) the relative timestamps of gamma ray events relative to proton induced events in the plastic scintillator and (b-c) using the RF period of the cyclotron.

Chapter 7

Physics Kernel

This chapter investigates incorporating additional information related to prompt gamma emission. The previous chapter dealt with range retrieval using new experimental data from the Crocker Nuclear Laboratory at UC Davis across a larger field of view, at significantly higher current, and slightly higher energy. But that approach largely performs the task using the collimator as an imager without regard to the underlying imaging task i.e., imaging of prompt gammas. The production yield of prompt gamma rays can be measured experimentally and folded into a new kernel that accounts for the energy loss of protons in the material from physics models or measurement: in this case PMMA. First, the theoretical background of the new kernel is introduced and derived. This is then folded into the system response and its effect on the range retrieval problem investigated quantitatively.

7.1 Physics Based Kernel

7.1.1 Derivation

Prompt gamma emission is generally anisotropic given the directionality of the beam and the short half-life of the excited nuclei [138]. The prompt gamma rays of interest are primarily the result of Coulomb excitations reactions on nuclei located in tissue. Due to the axial symmetry of the inelastic collision, the angular distribution of gamma rays is a function only of the incident proton energy E_p and angle θ made with the beam axis. Provided these proton induced prompt gamma ray yields $W_{\gamma I}(\theta, E_p)$ are measured for various target species I, these cross sections are expanded in Legendre polynomials $P_l(x)$ over the angular momentum number l with weighting coefficients $a_{l\gamma I}$ as:

$$W_{\gamma I}(\theta, E_p) = \sum_{\substack{l=0 \\ l \text{ even}}}^{\min(2J, 2l_\gamma)} a_{l\gamma I}(E_p) P_l(\cos \theta) \quad (7.1)$$

where $l_{\max}$ is the minimum of twice the multipolarity of the gamma ray or twice the spin of

the decaying state [139]. The ground spin and parity of ^{12}C and ^{16}O is 0^+ . The 4.4 MeV gamma ray from carbon is the result of an E2 transition from a 2^+ excited state while the 6.1 MeV line from oxygen is a result of a E3 transition from a 3^- state [140]. This means there are 2 terms for carbon and 4 for oxygen.

To generate the kernel, it is necessary to integrate this function for incident protons of fixed known energies down to the end of the range as they slow down in a target material. The emission intensity from a segment of the line profile at a position $\vec{R}$ relative to the end of range of the proton beam is:

$$Y_{\gamma I}(\vec{R}, u_i, u_f, \Delta x, \Delta y) = \int_{-\frac{\Delta x}{2}}^{\frac{\Delta x}{2}} \int_{-\frac{\Delta y}{2}}^{\frac{\Delta y}{2}} \int_{u_i}^{u_f} N_p(x', y', z') N_I(x', y', z') \left(\frac{d\sigma_{\gamma I}(\vec{R})}{dx' dy' dz'} \right) dx' dy' dz' \quad (7.2)$$

where:

$Y_{\gamma I}(\vec{R}, u_i, u_f, \Delta x, \Delta y)$ = Yield at detector position $\vec{R}$ from proton beam line segment

u_i, u_f = Points along proton beam path defined relative to end of range

$N_p(x', y', z')$ = number of protons at (x', y', z')

$N_I(x', y', z')$ = number of particles of species I at (x', y', z')

$\sigma_{\gamma I}(\vec{R})$ = γ -emission probability detected at $\vec{R}$ from species I

$\Delta x, \Delta y$ = kernel widths lateral to beam

z' = distance from end of range

Some simplifications and approximations are now used. The coordinate system can be chosen such that the origin is at the end of the range with the z' direction taken as the beam direction. The mean number of protons can be approximated as a step-wise constant function that reaches zero at the end of the range:

$$N_p(x', y', z') = \begin{cases} N_p & z' \leq 0 \\ 0 & \text{otherwise} \end{cases}$$

This approximation is taken since the lateral spread of the beam is much smaller than the longitudinal range of the beam and because nuclear losses are less than 1% per centimeter in water (see Chapter 1). Averaging $N_I(x', y', z')$ across the lateral dimensions, $n_I(z')$, gives the following proportional relationship:

$$Y_{\gamma I}(\vec{R}, u_i, u_f, \Delta x, \Delta y) \propto \int_{u_i}^{u_f} n_I(z') \frac{d}{dz'} \sigma_{\gamma I}(\vec{R}) dz' \equiv P_{\gamma I}(\vec{R}, u_i, u_f) \quad (7.3)$$

where $P_{\gamma I}(\vec{R}, u_i, u_f)$ is the probability of gamma emission from species I to a position $\vec{R}$ from the proton line profile segment u_i to u_f . Further:

$$\begin{aligned} P_{\gamma I}(\vec{R}, u_i, u_f) &= \int_{u_i}^{u_f} n_I(z') \frac{d\sigma_{\gamma I}(\vec{R})}{dE_p(z')} \frac{dE_p(z')}{dz'} dz' \\ &= \int_{u_i}^{u_f} n_I(z') \frac{d}{dE_p(z')} W_{\gamma I}(\theta, E_p(z')) \rho_t(z') S(E_p) dz' \end{aligned} \quad (7.4)$$

where:

$\rho_t(z')$ = target column density at z'

E_p = proton energy

$S(E_p)$ = stopping power (Equation 1.2)

θ = angle of $\vec{R}$ relative to beam axis

$W_{\gamma I}(\theta, E_p(z'))$ = angular emission probability

θ , as defined in Figure 7.1, can be found using the following:

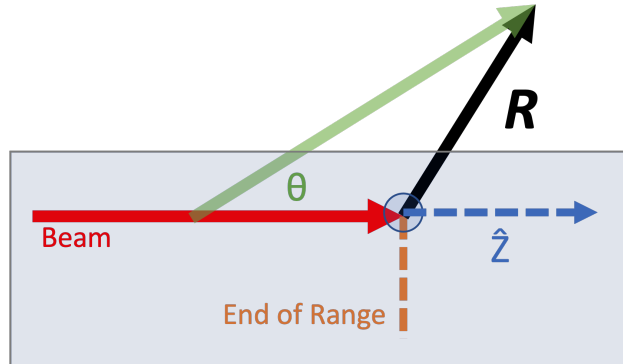


Figure 7.1: Illustration of new physics line basis. $\hat{Z}$ is taken along the beam axis. $\mathbf{R}$ is an arbitrary vector to a point in space. θ is the angle between $\mathbf{R}$ and an infinitesimal section of the proton beam path. The end of the range is chosen as the local coordinate system origin.

$$\cos \theta = \frac{(\vec{R} - z\hat{z}') \cdot \hat{z}'}{\|\vec{R} - z\hat{z}'\|}$$

Lastly, the total probability, L_{γ} , that an emission from a line profile that ends at (x', y', z') = (0, 0, 0) is:

$$L_{\gamma}(E_o, \Delta z, \vec{R}) = \sum_I \sum_{n=0}^{\frac{R(E_o)}{\Delta z}} P_{\gamma I}(\vec{R}, -n\Delta z, -(n+1)\Delta z) G_{\gamma}(\vec{R} - n\Delta z \hat{z}) \quad (7.5)$$

where:

Δz = step length in z

$R(E_o)$ = mean max range for protons of initial energy E_o

G_{γ} = geometric efficiency from source location to detector pixel as calculated in Chapter 5

Equation 7.5 requires the known angular cross sections for the reactions of interest and the stopping power inside the material. The more complete the data on either, the more this approximation better matches the physics of emission and detection.

7.1.2 The Kernel

Complete proton induced prompt gamma excitation functions (in angle and energy) on oxygen and carbon are known only up to about 20 MeV from Kiener [141], with sporadic measured data points from various sources that are often not in agreement above that energy range [142]. This energy range represents only the last approximately 4 mm of the proton range in PMMA but this range is also where much of the Coulomb excitation occurs. Figure 7.2 shows the physics kernel used in the rest of this work using the available data from Kiener. The kernel was generated by averaging the cross section over the average remaining proton energy across each pixel as determined by SRIM calculation. The 4 pixel long kernel is oriented along the beam's axis which is along the horizontal axis of the collimator. The normalized cross section for each step (PO, P1, P2) is shown for both isotopes. In both cases, there is no emission in the last pixel because the proton energy is below the threshold for prompt gamma emission. It is interesting to note that for oxygen, emission at 90 degrees relative to the beam axis (i.e. towards the collimator) is a local maximum while that is a local minimum for prompt gamma emission from carbon. The angular span of the detector array is approximately 40 degrees for the center point meaning a variation of about 30% in intensity relative to the isotropic emission assumed in the previous chapter. Along the centerline of the beam the angular deflection of protons is at a minimum which minimizes the effect of proton momentum spread about the beam axis. It should also be noted that this method ignores the 4.4 MeV gamma emission from oxygen via the $^{16}\text{O}(\text{p}, \alpha\text{p}')^{12}\text{C}$ reaction which is more of relevance to the entrance channel and serves as noise in the filtered images.

7.2 Results

Figure 7.3a and 7.3b again show the reconstructed line profiles from 60 different target positions for carbon and oxygen but this time with the use of the physics kernel. For

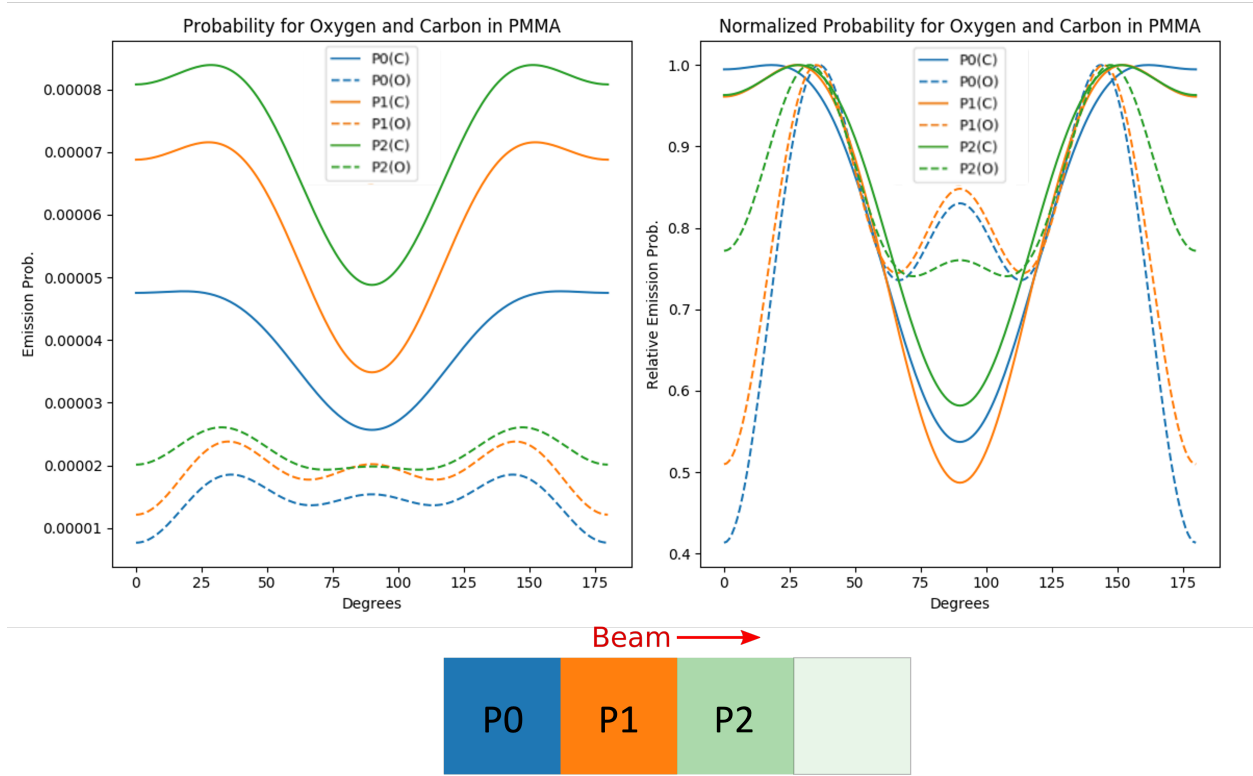
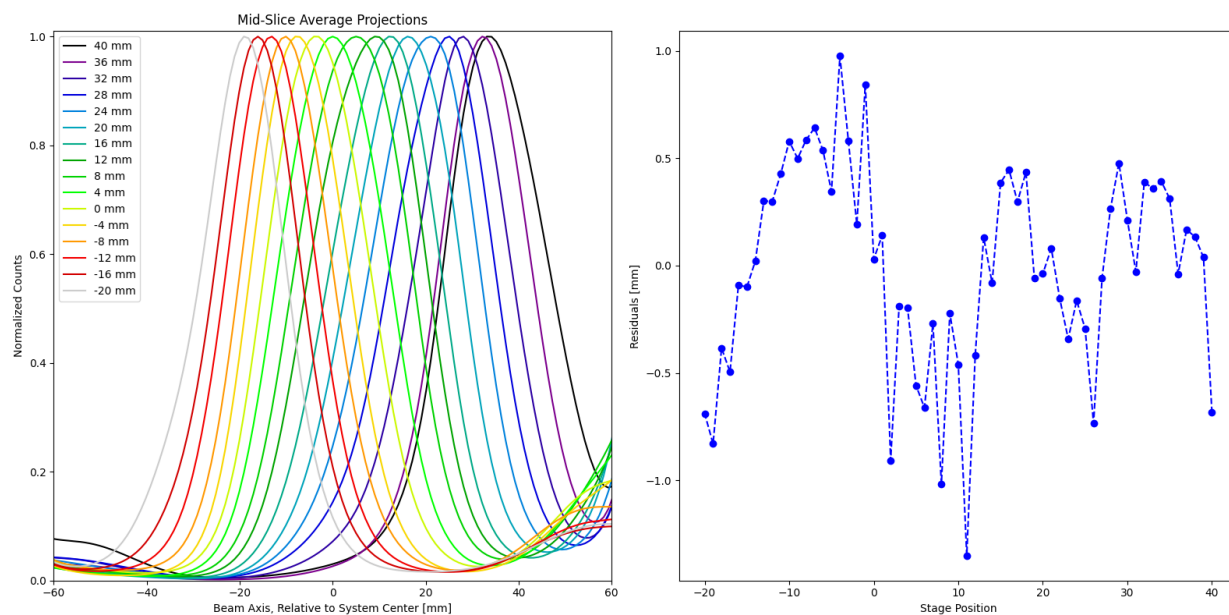


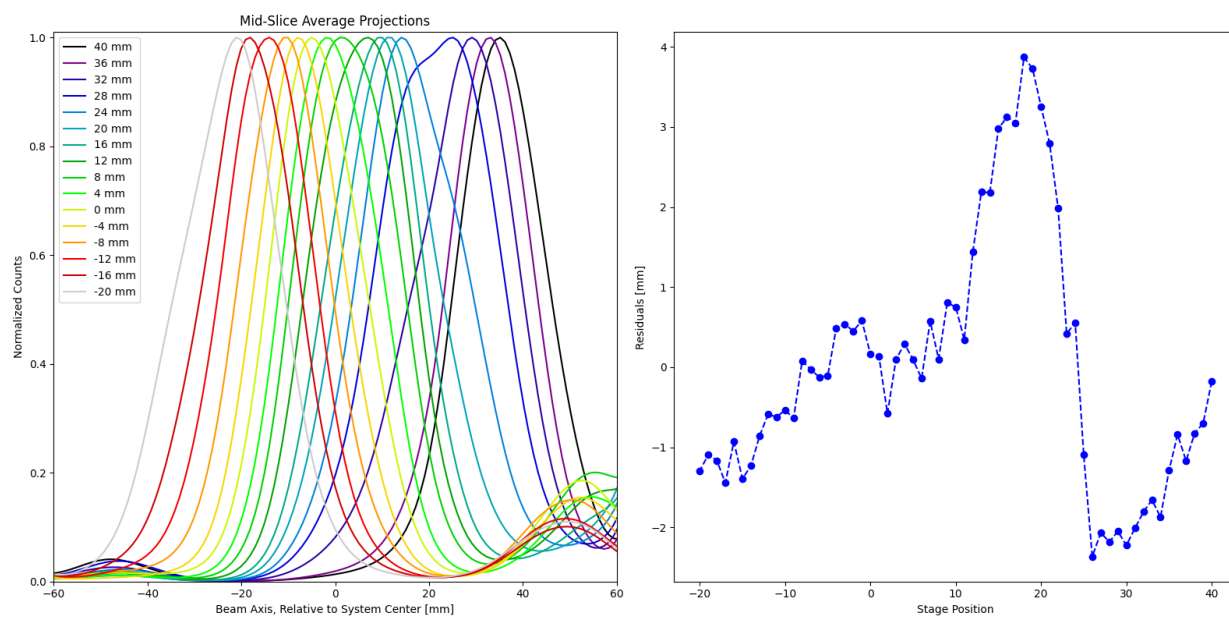
Figure 7.2: Physics basis generated from available measured cross section data for the 4.4 MeV and 6.1 MeV gamma lines from proton induced reactions on carbon and oxygen respectively. Shown is the absolute emission probability, at left, and the emission probability normalized to its max value, at right. Available data only goes up to 20 MeV which is about 4 mm in PMMA. Defined along the beam axis, the first pixel is P0, followed by P1, and P2. The last pixel has no activity because the proton energy is below the threshold for prompt gamma emission in this last pixel for both gamma lines.

the carbon image, the residual plot looks even more evenly spread about 0 while oxygen has likewise improved except for a large deviation at the 20 mm position mark similar to previous observations in Chapter 6. This region has a line of sight to a detector gap, that reduces the sensitivity of the imager to these gamma rays which are tightly focused at this roughly 90 degree angle to the beam. Figure 7.3c shows the range uncertainty plot as a function of protons. The carbon image improves for greater numbers of protons similar to the original system response but the oxygen images appear to suffer from large systematic bias which limits its performance at higher energies.

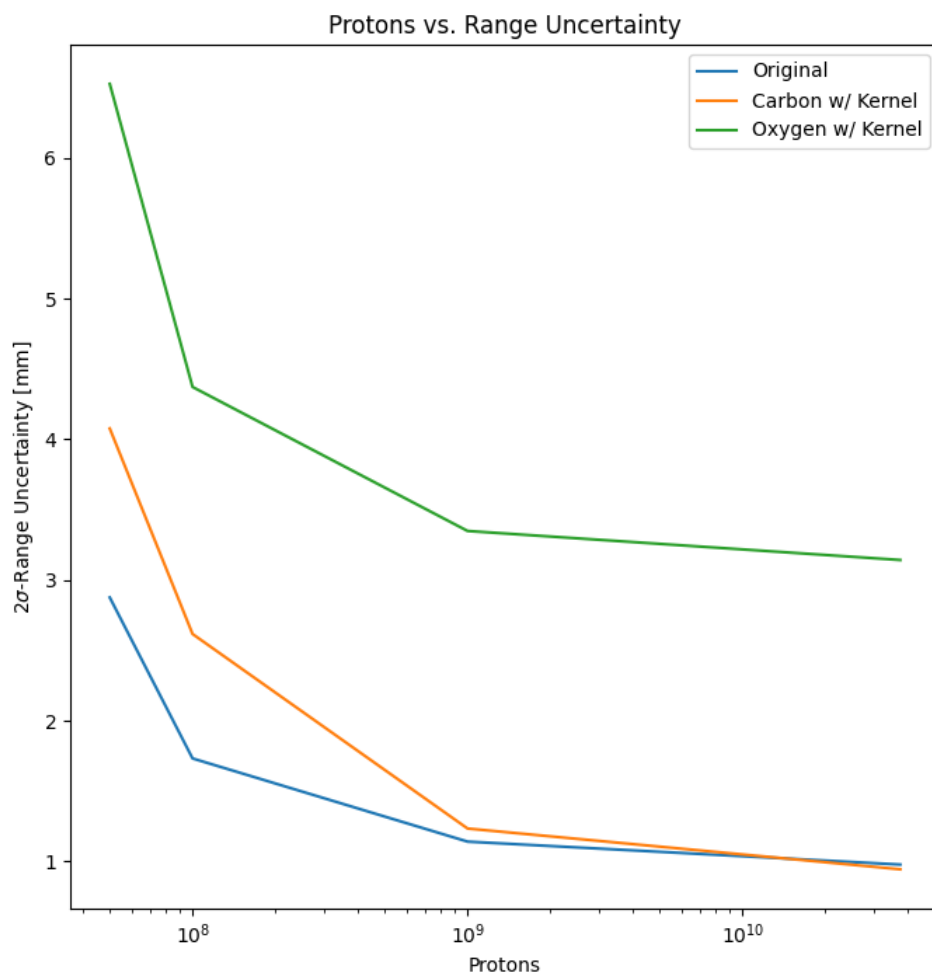
Lastly, as a point of interest, the difference in the reconstructed ranges between the carbon and oxygen images was taken as well as the ratio of the maximum intensity of the line profile between both sets of images at every location. Since the target is uniform, both the difference in the reconstructed ranges and the ratio of the maximum intensities should be uniform across the field of view. Figure 7.4 shows deviations for both of these metrics. The



(a)



(b)



(c)

Figure 7.3: Normalized 5-Slice Line profiles for a) Carbon and b) Oxygen using the new physics kernel for image reconstruction and 3.7×10^{10} protons. It is interesting to note that the large error at 20 mm position seen in Oxygen (4.8-6.4 MeV) is absent in the Carbon (3-4.8 MeV) images. c) Range uncertainty vs. delivered protons for both those regions as well as from the previous chapter (“original”). At high enough proton number, the carbon image with the physics kernel begins to perform as well as the entire full spectrum image, likely due to the effects of oxygen.

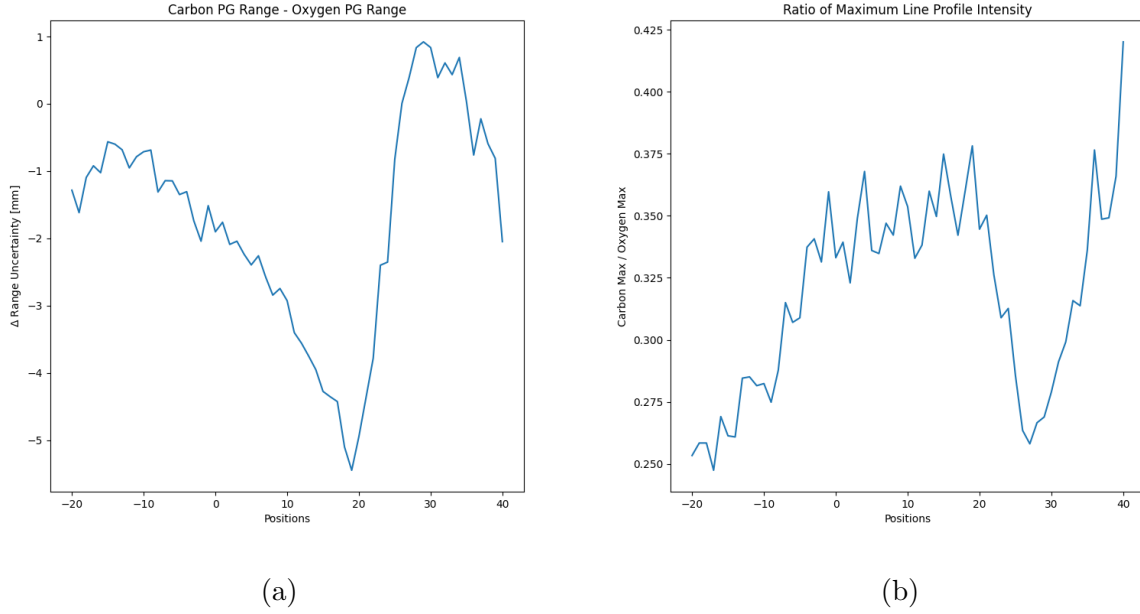


Figure 7.4: a) Difference in the reconstructed ranges between carbon and oxygen as a function of stage position. b) Ratio of the maximum intensity pixels between carbon and oxygen in the line profiles as a function of stage position.

dominance of the shift in oxygen at 20 mm is clearly visible but the difference grows even earlier than the shifts seen in the oxygen images. This might be a result of the asymmetry of the detector's center as well as the greater penetration of these higher energy gamma rays that may more easily penetrate the sides of the knife edge slits. This conclusion seems born out by the ratio of the maximum intensities. Overall this ratio increases as the beam is adjusted further to the "right" of the collimator field of view. This would broaden the mask pattern. Given the poor statistics at these higher energies, these results could support ignoring these higher energy gamma rays. At least for this particular detector and collimator configuration.

7.3 Remarks

This chapter introduced the theory and described the generation of a physics kernel for use in proton range verification. Cross sectional data is limited, but improvements are still seen in the imaging task. Oxygen largely does not appear to benefit much from this treatment, in addition to much lower counting statistics as a result of lower overall cross section and crystal interaction probability for such higher energy gammas. However, with carbon an improvement was found even given the limited data used in generating the kernel. More data, especially at higher energies, would likely be of great benefit to more

accurately modelling the emission profile about the beam's central axis and further reducing the uncertainty in the range estimation of the beam.

Chapter 8

Conclusions and Future Work

8.1 Summary of Work

Proton therapy offers a number of therapeutic benefits over conventional radiation modalities in the treatment of cancer. The proton trajectory is better defined than for photons or electrons, and deposits much of its energy within a few millimeters near the end of the range. The RBE is further enhanced by the higher density of ionizations for protons that contribute to better cell killing per unit dose delivered to tissue. However, the lack of an exit dose is both a positive and negative for protons. The lack of a distal dose allows for more flexibility in the fields used while also sparing more sensitive tissue from unnecessary radiation. But that also means that protons stop within the patient which eliminates the possibility of verifying that the dose is delivered to the tumor volume directly with external sensors.

Interest has thus been focused on secondary particle emissions of interest including acoustic emanations, annihilation photons from proton induced positron emission, and proton induced prompt gamma ray emission. Of these, the furthest along in clinical development are prompt gamma ray imaging systems which leverage the enhanced yield near the end of the range to act as a close surrogate to the dose distribution. A collimated multi knife edge slit collimator system was used as a compromise between sensitivity and count rate limitations. The mask pattern allows for greater sensitivity compared to single slit designs while also allowing for simple energy gates that dramatically reduce the significant background count rate that overwhelms Compton cameras. Unlike the PGS/PGT systems, timing information is additive to the coded aperture mode of the imager and the measure of the range is not sensitive to the stability of the proton accelerator. It is also more compact and could possibly be integrated into the gantry to colocate the center of the imager with the center of the patient bed. The work of this thesis was to iterate on previous studies involving the collimator to further push the sensitivity of the imager by incorporating the physics of prompt gamma ray emission and to implement features that will make it more amenable to use in clinical treatment environments.

The results of this thesis are encouraging as a further elaboration of previous work. But use of more realistic beams will certainly be a key next step for the imaging system mostly in regards to performance loss as a byproduct of more sophisticated background radiation fields. However, at 1/10 of a typical proton current and 1/5 the maximum proton energy used clinically, the total pile-up of the system was less than 0.1% suggesting that the hardware will likely not be a limitation in more realistic scenarios. Integration into the gantry of an actual clinical proton beam could also provide additional contextual information for use in the image reconstruction such as from computer tomography (CT). More work is necessary, but the imaging of higher energy beams seems possible.

8.2 Future Avenues for Investigation

8.2.1 System Hardware

The system as originally designed uses LSO detectors that were originally intended for use in PET imaging. Future iterations of the design could use different crystal configurations to improve the efficiency of the detector array to fully stopping gamma rays in the detector as well as reduce or eliminate the need in gaps between detector modules which serve as sources of sensitivity loss. The mean free path of prompt gamma rays in tissue (4.4 MeV - 6.1 MeV) is 3.7 cm with a 1% variability across the energy range: nearly twice the 2 cm thickness of the current crystals. The mean range of 4 MeV electrons in LSO is about 4 mm [101] which places a lower bound on detector pixel size. Thus, the aspect ratio (crystal length/width) would decrease and subsequently the timing resolution and performance of the detectors [143]. Higher density materials such as Bismuth Germanate (BGO) and LaBr:Ce could be investigated as possible alternative detector materials with simulation studies to account for tradeoffs in energy resolution, timing, efficiency, and sensitivity [101, 144]. Because these detectors are difficult to machine in large monolithic blocks, the periodic drop in spatial sensitivity could be compensated by offsetting the rows of the detectors so that no source location would place the large vertical slits of the mask onto vertical gaps in the detectors (See 8.1a). This would also eliminate the need to offset the entire center of the detector array. Silicon photomultipliers (SiPMs) could further reduce the footprint and total weight of the imager [145], practical concerns for integration of the system into treatment gantries.

Investigations based on lessons learned could inform future iterations of the mask design. The addition of pinholes near the periphery of the mask could compensate for the loss of sensitivity near the edges of the FOV (See Figure 8.1b). Newer mask designs might attempt to increase the required source to collimator distance beyond 13 cm for general application in imaging of the body. The addition of timing to constrain the image reconstruction (and required field of view) could allow for the use of converging adaptive collimators for greater patient to collimator distances and improved resolution from magnification [92].

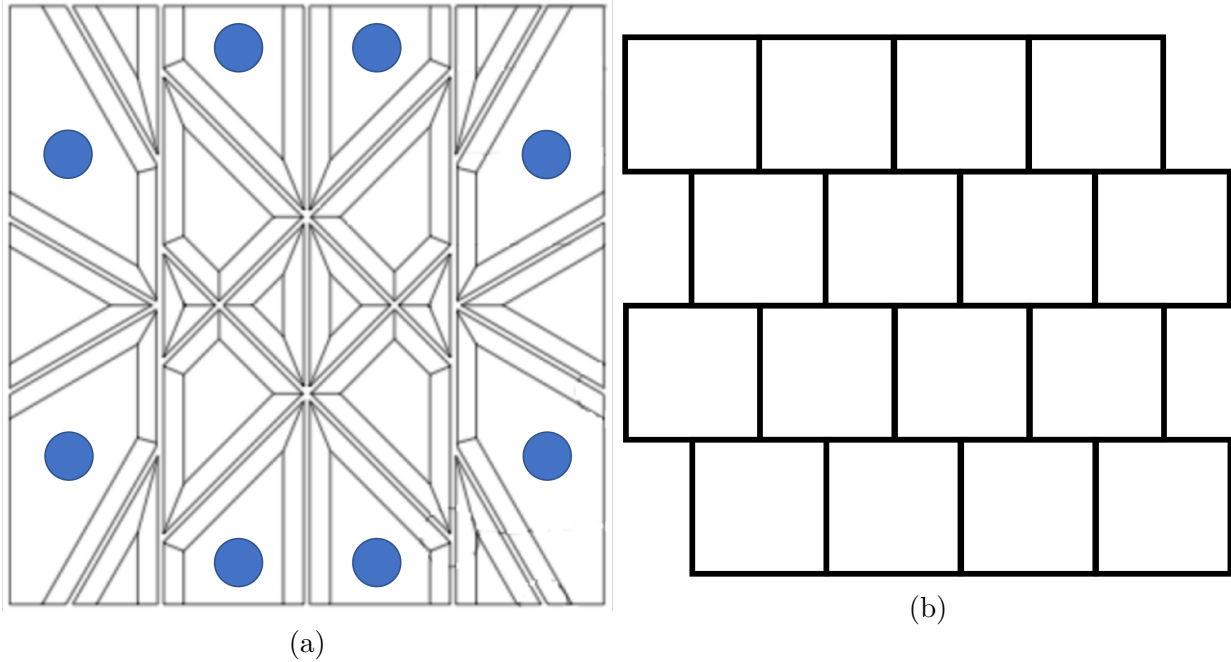


Figure 8.1: a) Proposed modification to existing collimator design 3.1 with the addition of pinholes to enhance the sensitivity of the imager to regions near the edge of the FOV (see 4.3) b) Possible new detector layout so that no vertical slit can fall entirely on the gap between 4 rows of detectors.

8.2.2 Timing Hardware

As discussed in Chapter 6, the detector configuration for waveforms generated from the passage of the proton beam through the plastic scintillator has a number of limitations which confound the ability to correlate gamma ray signatures with the arrival of the proton beam. But issues that were only apparent once measured. Some of the major challenges being tied to the bandwidth of the saved waveforms and the time jitter introduced from the digitizer sampling frequency. A proposed solution to these issues can be seen in Figure 8.2. Hardware triggering using either the rising edge of the (1) RF or (2) the rise time from the proton waveforms in a new plastic scintillator setup would be fed into the gamma ray digitizers as a gate signal. This would remove the need to save these waveforms and thus any need to save the waveforms themselves, bypassing current bandwidth constraints and improving counting statistics. Both methods would ideally use a fast analog constant fraction discriminator to generate a global gate signal for the LSO gamma ray signatures to avoid time the jitter from signal digitization. This would optimize the signal collection time (and SNR) to only during the window when proton-induced (as opposed to neutron induced) gamma rays are expected in tissue. Use of the first method would be a generalization of methods currently being used by single slit designs [84]. The second method represents a novel method of timing that bypasses the drift of proton bunches relative to the driving cyclotron RF. Furthermore, the

neutron induced continuum could be investigated by turning the global gate generated from the CFDs into a global veto for the LSO array. And it may be necessary to investigate both methods to characterize the relative times of the RF, proton bunch, and gamma ray signals to each other. Such investigations would very likely be of great interest to the field.

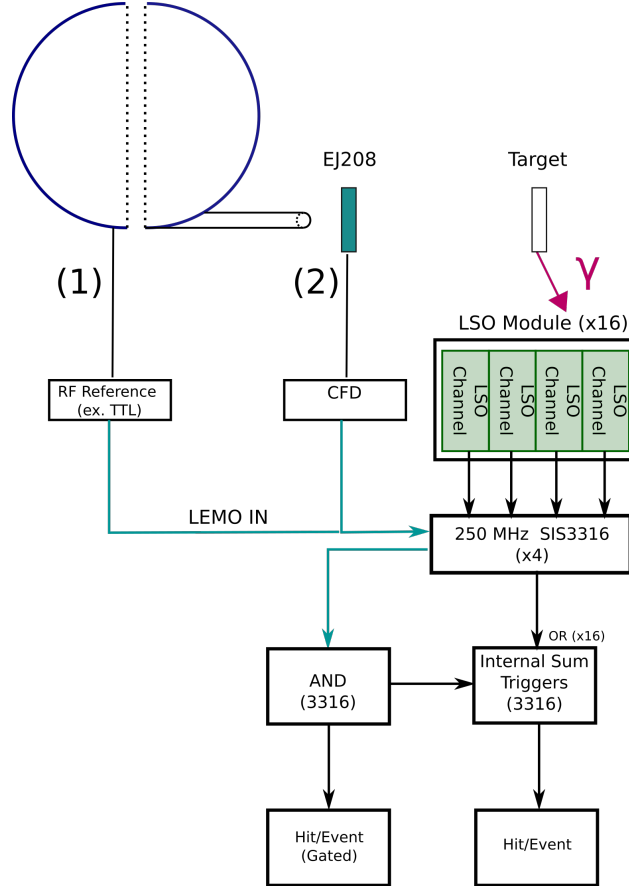


Figure 8.2: Proposed new hardware timing schemes for correlating gamma ray signatures with proton bunch arrival. A constant fraction discriminator (CFD) generates a gate signal either from the (1) cyclotron RF or (2) rising edge of the waveform generated by the passage of protons in the plastic scintillator EJ208. This gate signal is used as a global AND for the internal triggers of each of the LSO modules. The gate can also be turned into a veto to emphasize neutron induced events.

8.2.3 Monte Carlo

Monte Carlo codes as currently implemented do not correctly simulate the prompt gamma ray reaction cross sections, angular distributions (including erroneous isotropic emission profiles [34]), yields, and shapes for proton induced reactions on tissue [91] as compared to experiment [146] or to other Monte Carlo codes [34]. This is likely due to the complexity

and interconnectedness of the underlying physical processes (direct, pre-equilibrium, and compound reactions) that confound simple analytical treatments [138] and, in lieu of this, a sparsity of complete experimental data at energies relevant to radiation therapy [147]. Such limitations continue to confound benchmarking and design studies for prompt gamma ray imaging systems [148, 149]. Fortunately, Kiener has made recent progress in this regard for ^{12}C with protons up to 100 MeV using new and older experimental data to calculate predicted line shapes for 4.4 MeV that match well with experiment: a forthcoming publication will do a similar treatment for ^{16}O [142]. Further work and data will be needed to extend this treatment to the entire clinical energy range and for all the lines of interest.

The lack of reliable modelling also poses significant challenges to translating the prompt gamma ray distribution into a dose map for the proton beam. The dose from protons is a consequence of inelastic scattering of atomic electrons while prompt gammas are a result of nuclear reactions with atomic nuclei. Modelling of the former is reliable and well documented to match with experiment [32]. Further work will be necessary to describe this relationship, although some work has already been attempted using deep learning approaches that are limited to high fidelity PG images in the brain [150].

8.2.4 Image Reconstruction

The image reconstruction algorithm and system response used in this thesis were for measurements of 67.5 MeV proton beams in 4 cm depth of tissue equivalent plastic and could be elaborated upon. Further work will be needed to adapt the image reconstruction workflow to be integrable into clinical workflows. In realistic treatment scenarios, the reconstruction and range determination would be performed synchronously with the delivery of a proton beam to allow for adjustments during treatment. The image reconstruction will need to be fast and incorporate pre-treatment plan MRI or CT scans to account for patient specific tissue inhomogeneity. The system response code as described in Chapter 4 (already parallelized) could be adapted for GPU clusters to accelerate calculations involving 3D patient anatomical data [151]. Pixel-based order subset maximization (POSEM) could likewise be investigated as a possible means to reduce the number of iterations required to produce useful PG images with less memory overhead [152].

8.2.5 Clinical Implementation

The last step will be to perform clinically relevant measurements with the system. Higher energy, higher intensity beams would also help to better completely characterize the performance of the system for more intense and complicated radiation backgrounds. And to also incorporate different imaging scenarios where range verification would be most useful such as undershoots (from high density materials such as bone), overshoots (from air gaps), and global shifts as a result of gantry/beam misalignments [88]. Such measurements would be invaluable in dictating areas for future investigation and refinement with the imager.

8.3 Final Thoughts

The issue of range verification has long been an outstanding challenge for proton therapy. As proton therapy centers continue to proliferate and expand worldwide, growing questions have been building about if the health benefits of such systems are worth the costs of such facilities given the reliability of IMRT [153]. Despite being criticized as the “Death Star” of the healthcare industry specifically in regard to prostate cancer [154], the health benefits of protons for pediatric, breast, non-small lung, liver, kidney, head and neck cancers are well documented [11]. Prompt gamma imaging represents the most clinically advanced method to eliminate uncertainty in the beam range and improve patient health outcomes.

This will likely be even more important in the future given the trajectory of newer proton therapy beamline designs to account for new treatment paradigms. Traditionally as in photon or electron therapies, the dose is fractionated to allow for healthy tissues to repair radiation induced sublethal DNA damage. However, with ions including protons nearly all of the damage is lethal [155, 156] which has pushed newer designs to deliver the entire prescribed dose -2 Gy per fraction over weeks, 70 Gy total for protons in the prostate - into as few fractions as possible. The FLASH therapy system from Varian, will deliver 10 nA - 1 mA to the patient at a dose rate of 40 Gy/s with the express goal of delivering the entire prescribed dose in a single fraction [157]. It will be even more imperative that a real time, fast monitoring system exists to act as a vital diagnostic tool for proton therapy. PGI systems, such as the one proposed here, offer a promising solution to this challenging problem and a real opportunity to help the lives of patients of all ages across the world.

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