Published in final edited form as:

Biomed Phys Eng Express. 2019 July ; 5(4): . doi:10.1088/2057-1976/ab2e4a.

A proton imaging system using a volumetric liquid scintillator: a preliminary study

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Abstract

With the expansion of proton radiotherapy for cancer treatments, it has become important to explore proton-based imaging technologies to increase the accuracy of proton treatment planning, alignment, and verification. The purpose of this study is to demonstrate the feasibility of using a volumetric liquid scintillator to generate proton radiographs at a clinically relevant energy (180 MeV) using an integrating detector approach. The volumetric scintillator detector is capable of capturing a wide distribution of residual proton beam energies from a single beam irradiation. It has the potential to reduce acquisition time and imaging dose compared to other proton radiography methods. The imaging system design is comprised of a volumetric ($20 \times 20 \times 20 \text{ cm}^3$) organic liquid scintillator working as a residual-range detector and a charge-coupled device (CCD) placed along the beams'-eye-view for capturing radiographic projections. The scintillation light produced within the scintillator volume in response to a 3-dimensional distribution of residual proton beam energies is captured by the CCD as a 2-dimensional grayscale image. A light intensity-to-water equivalent thickness (WET) curve provided WET values based on measured light intensities. The imaging properties of the system, including its contrast, signal-to-noise ratio, and spatial resolution (0.19 line-pairs/mm) were determined. WET values for selected Gammex phantom inserts including solid water, acrylic, and cortical bone were calculated from the radiographs with a relative accuracy of -0.82% , 0.91% , and -2.43% , respectively. Image blurring introduced by system optics was accounted for, resulting in sharper image features. Finally, the system's ability to reconstruct proton CT images from radiographic projections was demonstrated

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Conflicts of interest: The authors have no conflicts of interest to disclose.

using a filtered back-projection algorithm. The WET retrieved from the reconstructed CT slice was within 0.3% of the WET obtained from MC. In this work, the viability of a cumulative approach to proton imaging using a volumetric liquid scintillator detector and at a clinically-relevant energy was demonstrated.

Keywords

proton radiography; proton computed tomography; scintillator; CCD camera

1. Introduction

Proton radiation therapy can deliver localized and highly conformal dose distributions to the treatment volume. This is possible because of the nature of the energy deposition from protons, specifically, the Bragg curve characteristic, which allows very high doses to be delivered towards the end of the proton range. The depth of penetration or the range of protons is increased by increasing the energy of the proton beam. Thus, to exploit the full potential of proton therapy, the range of proton beams in patients needs to be calculated as accurately as possible. Treatment planning systems for proton therapy currently use x-ray computed tomography (CT) scans to predict proton ranges in patients. A calibration function relates the x-ray CT-derived Hounsfield units to proton stopping power ratios (SPRs) for the relevant tissues; in turn, the SPRs are used to evaluate the proton range distributions within the patient. However, this indirect approach to determining proton range can be a significant source of uncertainty because x-rays and protons interact with tissues in fundamentally different ways (Yang et al 2012). These uncertainties, along with other sources of errors such as patient positioning, motion, and anatomical changes, are currently accommodated by increasing the range uncertainty margins (typically by 3.5% + 1-3 mm) to generate a robust treatment plan (Paganetti 2012). Consequently, some of the advantage of the sharp distal fall-off of proton beams is lost, and the region of highest biological effectiveness at the end of the beam range can fall in the healthy tissue (Guan et al 2015). Other approaches such as a dual-energy CT technique for generating SPR distributions have been proposed as an alternative to the x-ray CT-based treatment planning methods (Yang et al 2010). Work on dual-energy CT method has been published using both phantoms (van Abbema et al 2018; Bourque et al 2014; Hunemohr et al 2014) as well as through clinical studies (Taasti and Jensen 2018; Wohlfahrt et al 2017). Dual-energy CT is a promising technology with the potential to decrease proton range uncertainties. One limitation in the dual-energy CT approach is the lack of dual-energy CT scanners in most treatment rooms, and in particular the lack of imaging at isocenter. This limits the usefulness of dual-energy CT for image guidance during daily treatment setup as well as for adaptive planning and daily beam range verification.

A proton-based image guidance system is another approach that can reduce or eliminate the reliance on x-ray CT for treatment planning through direct calculation of proton SPRs. Such a system measures the energy loss suffered by protons during their travel through the imaged tissue and can thus determine its water-equivalent thickness (WET). The projected WET distributions obtained from proton radiographs collected at different angles can be used for

constructing a three-dimensional (3D) proton SPR map, also known as proton computed tomography (pCT). Thus, proton imaging systems can provide image guidance, identify day-to-day changes in patient WET, and reduce uncertainties in proton range calculations for treatment planning through direct measurement of SPR distributions.

One widely accepted approach to proton imaging involves proton-tracking systems. These systems measure residual energies of individual proton particles along with determining their location and angular direction using position sensitive detectors placed before and after the patients (Esposito et al 2018; Sipala et al 2011; Pemler et al 1999). This information, when complemented with a suitable path estimation model, can correct for proton scattering, leading to better prediction of proton trajectories within the tissues (Collins-Fekete et al 2015; Williams 2004). These systems are known to provide good quantitative and imaging resolution but can also be expensive because they require high-speed single-event detectors and have complex instrumentation (Johnson et al 2017; Biegun et al 2016; Amaldi et al 2011; Schneider et al 2004). One of the main hurdles for these systems is their limited data acquisition rates, which requires the proton beam to be modified to operate in a special low-fluence mode, and which can lead to long imaging times. Recent proton-tracking system prototypes have successfully managed to achieve operational frequencies on the order of 1 MHz (Johnson et al 2016; Bucciantonio et al 2013). Further improvement with imaging speeds (~ 10 MHz) is desirable for completing a proton CT scan in few seconds. Technological developments enabling faster imaging rates along with a straightforward system setup are needed before the proton-tracking approach can be widely implemented in clinical settings.

Krah et al (2018) recently demonstrated an alternative approach to proton radiography using a commercial range telescope that utilized scanning pencil beam measurements rather than tracking individual proton particles. They used their system in combination with a Bragg curve decomposition method to correctly estimate WETs (Krah et al 2015). A related approach for proton imaging is to determine the proton beam energy loss by measuring the cumulative fluence using a planar detector placed beyond the patient (Zygmanski et al 2000). This beam-integrating approach is compatible with therapeutic accelerator parameters and acquires images more rapidly than is currently possible with the particle-tracking technique (Seco and Depauw 2011; Telsemeyer et al 2012; Poludniowski et al 2014). Compared to proton-tracking, the beam integrating approach captures a mixture of proton paths which cannot be individually tracked and corrected for, leading to poorer image resolution. Proton beam-integrating radiography has been conducted using single planar detectors (Zhang et al 2019; Ryu et al 2008; Testa et al 2013). However, a planar detector requires a time-modulated proton range to capture the Bragg peak (Doolan et al 2015), which increases the imaging dose and acquisition time.

A volumetric scintillator detector (as opposed to planar detector) may also be used to generate proton radiographs. The advantage in choosing a volumetric scintillator detector over a planar detector is its ability to comprehensively capture a wide distribution of residual beam energies produced by a single irradiation within the detector volume. Thus, the need to repeatedly expose the imaged tissue with multiple beam energies, as is the case with planar detectors using time-modulate proton beams, can be avoided. A volumetric detector design

can therefore potentially decrease the total dose and time requirements to generate a proton radiograph.

Tanaka *et al* have demonstrated a beam-integrating proton imaging system using a solid plastic organic scintillator and an inorganic solid scintillator (Tanaka et al 2016, 2018). Their measurements were performed at a facility providing a low-energy proton beam that was spread laterally using magnetic wobbling. The beam energy of 70 MeV, with a maximum range of approximately 4 cm in water, is too low for clinical use in human patients. However, they demonstrated the principle that a beam-integrating detector can successfully produce proton radiographs and proton CT images. They provided a qualitative evaluation of the imaging resolution of their detector by identifying feature sizes of imaged objects that were visible in their radiographs, and they evaluated the accuracy of WET measurements with their detector.

In this study, we present the first proton radiography measurements using a beam-integrating system in a high-energy clinical proton beamline. We use a volumetric liquid scintillator at a clinically useful energy (180 MeV) to produce proton radiographs and measure the WET of calibrated tissue-equivalent phantoms. We also quantitatively measure the imaging performance of the detector and investigate corrections for optical distortions in order to improve image quality.

2. Methods and materials

2.1. System design

A $20 \times 20 \times 20 \text{ cm}^3$ acrylic tank was filled with an organic liquid scintillator, OptiPhase HiSafe 3 (PerkinElmer, Waltham, MA), as shown in figure 1. The right tank surface was constructed using transparent acrylic to allow the camera to collect scintillation light generated inside the scintillator volume. Cross-hair markers were imprinted on all the surfaces of the tank to allow calibrations for correcting optical artifacts. The overall imaging resolution of the system (0.4 mm) was also determined through the calibration process. A mirror oriented at a 45° angle to the right tank surface was used to redirect the scintillation light from within the tank towards the camera. Thus, the camera captured a beams'-eye-view projection of the beam without having to directly expose it to harmful ionizing radiation. A base plate was used to mount the scintillator-filled tank and the mirror assembly onto an optical board.

The charge-coupled device (CCD) used in this study was the LucaEM S 658M (Andor Technology, Belfast, UK). The CCD camera had 658×496 pixels with an individual pixel size of $10 \text{ }\mu\text{m}$. The camera was capable of measuring 37 full frames per second and digitized optical signals at 14 bits. Thermal noise resulting from dark current generation within the CCD sensor can elevate the noise floor and impact light intensity measurements under low-light conditions. The dark current was therefore suppressed using an on-board thermoelectric cooler to reduce the operating temperature of the camera to -20°C before proceeding to image. An objective lens (JML Optical Industries, Rochester, NY) with an effective focal length of 25 mm and with the aperture set to f/4 was mounted on the camera. The lens was set to focus at the center of the tank volume, with a focal depth of 11 cm

around the center. The distance between the camera lens and center of the right tank surface was 103.5 cm. In order to reduce light contamination from ambience, treatment room lights were turned off during the measurements.

Several optical artifacts associated with imaging were identified and corrected for (Robertson et al 2014, Darne et al 2017). To ensure that the camera's imaging performance was repeatable, the camera was operated only after it reached a stable operating temperature of -20°C . The background signal image was captured in the absence of any phantom, using an uncovered objective lens, and by setting the camera exposure time to the same duration as the actual beam delivery. The background signal image thus consisted of contributions from ambient light, thermal noise, shot noise, and camera read noise. A 3×3 pixel spatial median filter was applied to eliminate the influence of stray radiation on the sensor. The imaging was conducted using a passive scattering proton beam at the Proton Therapy Center at The University of Texas MD Anderson Cancer Center. The proton imaging system was placed on the patient couch such that the beam isocenter plane was aligned with the left tank surface. The proton images were generated using a 180 MeV energy, having a field size of $10 \times 10 \text{ cm}^2$ (at Bragg peak), and with a 4.72 cGy dose calculated proximal (at a depth of 5 cm) to the Bragg peak. The beam energy selection ensured that the location of the Bragg peak was well outside (behind) the phantom being imaged. The dose was delivered by a single synchrotron spill having a maximum duration of 4.4 s. The gantry angle was set to 270° . All image computations and analyses were performed using MATLAB (version R2016b; MathWorks, Natick, MA).

2.2. Calibration curve

A study quantifying variations in pixel intensities spatially (as a function of pixel locations in an image) and temporally (from one image to the next) was conducted to test the performance of the camera sensor in response to the proton beam delivery. The study was conducted by exposing the scintillator to 10 consecutive proton beam deliveries. Two region of interests (ROIs) at the center of the delivered proton field were chosen for testing pixel variations - $9.8 \times 9.8 \text{ cm}^2$ and a $7.7 \times 7.7 \text{ cm}^2$ ROI corresponding to 50% and 10% change in pixel intensities relative to the maximum pixel intensity. A percentage ratio of the standard deviation in pixel intensities to their mean value ($\frac{\sigma_{pixels}}{\mu_{pixels}_i}$) for a given image i provided the image uniformity. The reported image uniformity or flatness was the mean uniformity calculated over 10 images ($i = 1, \dots, 10$). The pixel intensity variations from one image to the next were quantified by calculating the standard deviation in pixel values over the ROI for 10 consecutive images. A percentage ratio of the mean standard deviation to the mean pixel values ($\frac{\sigma_{pixels}}{\mu_{pixels}_n}$) across all the images ($n = 10$) yielded the pixel variations or sensor noise.

An energy-specific calibration curve was constructed for the imaging system to calculate the WET of any phantom being imaged. The calibration curve was plotted by stacking 8 plastic water slabs of known physical thicknesses (5, 10, 20, 40, 60, 80, 100, and 110 mm) in front of the scintillator volume. The slabs were positioned in the x-y plane (see figure 1) such that their thicknesses were along the z-axis. Measurements were performed by sequentially

stacking slabs on and pressing them tightly against one another (to avoid air gaps) while maintaining contact with the left surface of the tank.

A passive scattering proton beam with a 180 MeV (unmodulated) energy was delivered for each phantom thickness, and the resulting change in the integrated scintillation light signal, represented by the measured pixel intensity, was captured by the camera. A baseline image without any phantom (thickness 0 mm) was used as a reference data point. The WETs for the plastic water phantoms were plotted as a function of the mean camera intensities. The calibration plot was normalized to the reference data point. This normalization ensured that image ROIs experiencing unattenuated proton beams, for example, regions outside the imaging phantom but within the proton field ($10 \times 10 \text{ cm}^2$), yield 0 mm WET while the phantom itself provides a map of positive WET values. A fit for the calibration curve was generated through these measurement points, and utilized for calculating the WETs of subsequently imaged phantoms. The measurements were repeated 3 times to determine the noise in the calibration process.

The system signal-to-noise ratio (SNR) was calculated by exposing the scintillator volume to doses ranging from 0.008 cGy to 15.73 cGy calculated proximally (at a depth of 5 cm) to the Bragg peak. For each dose, the SNR (dB) was calculated using the equation,

$$20 \log_{10} \frac{I_{ROI}}{\sigma_{ROI}}, \quad (1)$$

where I_{ROI} is the mean pixel intensity over the chosen ROI ($10 \times 10 \text{ cm}^2$) and σ_{ROI} is the mean standard deviation in the pixel intensities for the ROI. The image contrast metric was included in this study to determine the density resolution for the system which allows it to accurately distinguish between image ROIs belonging to different tissues with different WETs. The image contrast was calculated by sequentially imaging stacks of plastic water with increasing thicknesses. Nine different plastic water thicknesses (no phantom, 5, 10, 20, 40, 60, 80, 100, and 110 mm) were used and stacked in front of the scintillator volume. A constant dose of 4.72 cGy was delivered for each thickness. The mean pixel intensity (I_i) was evaluated for each phantom thickness over a $10 \times 10 \text{ cm}^2$ imaging area and the contrast was calculated using the following equation,

$$1 - \frac{I_i}{I_{ref}}, \quad (2)$$

where, I_{ref} is the mean pixel intensity calculated for the unattenuated beam (i.e. no plastic water slab). Both SNR and CNR values were determined by repeating the measurements 3 times.

The ability of the calibration curve to accurately convert the recorded pixel intensities into corresponding integrated WET for phantoms was tested using 3 cylindrical Gammex inserts (Sun Nuclear Corporation, Melbourne, FL) - solid water (1.02 g/cm^3), acrylic (1.17 g/cm^3), and cortical bone (1.82 g/cm^3), each with the same physical dimensions (diameter 2.8 cm, height 7 cm). The 3 phantoms were placed together with their cylindrical axes parallel to the

beam direction (see figure 4a in Results section). The theoretical WETs for the phantoms was calculated using the equation,

$$WET = (t_m) \left(\frac{\rho_m}{\rho_w} \right) \left(\frac{\bar{S}_m}{\bar{S}_w} \right), \quad (3)$$

where t_m is the physical thickness of the imaging phantom, ρ_m and ρ_w are the mass densities of the phantom and water, respectively, and $\bar{S}_m$ and $\bar{S}_w$ are the mean values of mass stopping powers for the phantom and water, respectively. The mass stopping powers were calculated at 180 MeV energy using the PSTAR program (<https://physics.nist.gov/PhysRefData/Star/Text/PSTAR.html>).

The image resolution was determined from a graph of modulation transfer function (MTF) evaluated for the imaging system. The MTF graph provides a relationship between the available imaging contrast for given image features and the corresponding spatial resolution. Hander et al (1997) developed a method for quick assessment of intrinsic image resolution for gamma cameras by calculating an estimate of their MTFs. The method was based on determining the first and second order statistical moments, mean (μ) and variance (σ^2), of selected ROIs from bar phantom images. The moments' were calculated based on the assumption that the imaged bar patterns were sinusoidal in nature. They compared their approach to available methods for evaluating MTF, such as manufacturer-supplied full-width at half maximum and peak-valley method, and found the moments' method to be robust yet consistent with these existing methods. Based on their findings, an estimate of MTF was obtained using the equation,

$$MTF = \sqrt{2(\sigma^2 - \mu)/\mu}, \quad (4)$$

where σ and μ represent the standard deviation and the mean for the chosen ROI in the image, respectively. A megavoltage image quality phantom used for quality assurance studies (MV-QA phantom, dimensions 12.7 (L) $\times$ 10.2 (W) $\times$ 2.5 (D) cm, SUN Nuclear Corporation, Melbourne, FL) was included in this study. The MV-QA phantom consists of ROIs having sinusoidal line-pair patterns that could hence be used for estimating MTF of the imaging system based on the moments' method. As shown later in figure 5a (Results section), the phantom has 4 regions containing line-pair (lp) patterns with increasing spatial frequencies - area A with 0.09 lp/mm, area B with 0.19 lp/mm, area C with 0.49 lp/mm, and area D with 0.98 lp/mm. The MTF graph was plotted based on analysis of these 4 ROIs.

2.3. Monte Carlo simulations

Monte Carlo (MC) simulations of the proton imaging system served as a reference for the experimental results. The passive scattering proton beam delivery system at MD Anderson was modeled using the TOPAS MC system (Perl et al 2012). The double scattering system, the beam collimation system, and other components of the treatment nozzle were fully modeled. A 180 MeV unmodulated proton beam was defined, and a 10 $\times$ 10 cm² uniform proton field was formed on the isocenter plane (x-y plane located on the left tank surface, see figure 1). The standard electromagnetic physics package (option 4) and the hadronic physics package QGSP_BIC_HP were selected to provide the physical interaction cross-

sections and models. A total of 1×10^{10} proton histories were simulated. Multiple built-in physical quantity scorers available in the TOPAS system were used. The water phantom ($20 \times 20 \times 20 \text{ cm}^3$) was defined as the sensitive volume to score dose, linear energy transfer, and proton fluence. The volume of each scoring voxel was $1 \times 1 \times 1 \text{ mm}^3$ in the water phantom. 2D dose projection was generated from the 3D simulated dose distributions by integrating the dose along the beam direction (z-axis). Noise analysis on the dose projection was performed using data analysis software, ROOT (Brun and Rademakers 1997). The dose in each scoring bin of the 2D map (called histogram in ROOT) was found to meet the statistical uncertainty requirement (the relative error of the dose in each bin $< 1\%$) when the dose was larger than 5% of the peak dose. MC simulations of 3D dose distributions were carried out separately for 2 cases - with and without (baseline) the simulated Gammex solid water insert. The difference in the dose projections obtained from these 2 cases provided the net dose projection. The net dose projection was converted into corresponding WET map using a calibration curve. The calibration curve was formed by using the simulated baseline 3D dose distribution. The following equation describes generation of dose projections (I) with various WETs (i) along the z-axis,

$$I_i(x, y) = \int_{z=i}^{200} D(x, y, z) dz, \quad (5)$$

where D is the baseline 3D simulated dose delivered to the water volume and $i = 1, 2, \dots, 200$ represents WETs (mm) over the total thickness of the water volume (20 cm). The calibration curve was constructed by plotting the mean dose value obtained from the simulated projection (I) against the corresponding WET (i). A polynomial fit to the calibration curve was used for calculating WETs.

2.4. Determination of the point spread function (PSF) for the system

An optical imaging system like the one presented in this work is inherently susceptible to image blurring. A combination of effects, such as proton scattering within the phantom being imaged, photon scattering inside the liquid scintillator, light refraction at the air-scintillator interface, and imperfections associated with practical camera lenses, are responsible for this blurring. It was previously shown that photon scattering is minimal for a system similar to the one presented in this work and that its simple system geometry allows for refraction correction (Robertson et al 2014). Therefore, in the present work, the focus was on accounting for the image blurring contributed by the optical lens, by evaluating the PSF for the lens.

The PSF for the objective lens was determined using a method described in ISO standard 12233 (ISO 2000). This method involved capturing a photograph of a slanted edge within a flat phantom. The phantom was constructed by machining and gluing together a flat strip of black plastic to a white plastic. An image of this edge submerged within the scintillator was used to calculate the edge-spread function (ESF). The derivative of the ESF provided the line-spread function, which is the 1-dimensional (1D) equivalent of the PSF. Such edge detection method for determining optical PSF with a similar scintillator-based setup has previously been published by the authors' group (Robertson et al 2014). A 2-dimensional

(2D) PSF was formed by rotating the measured 1D PSF and then deconvolved from the system-acquired images to minimize blurring introduced by the objective lens. A built-in MATLAB deconvolution algorithm using a Wiener filter (Gonzalez and Woods 2002) and an estimate of the noise-to-signal ratio calculated from the image SNR were used for the deconvolution operation. The features of the PSF were evaluated by fitting it to the following equation,

$$\text{PSF} = A \cdot \exp\left(-\left(i - K/2\right)^2/\sigma^2 + 1/(1 + \left(i - K/2\right)^2/\gamma)\right), \quad (6)$$

where A is the weighting factor, i is the pixel index, and K (128) is the array size of the measured light distribution (Ponisch et al 2009). The above equation is a combination of two terms with parameter σ for the Gaussian function (first term on the right) describing the spread around the peak of the PSF while γ for the Lorentzian function (second term on the right) parametrizes a fit for the low-intensity tail of the PSF.

2.5. Proton CT

The primary purpose of this work was to demonstrate the feasibility of a volumetric liquid scintillator-based imaging system to generate proton radiographs and to improve their resolution by eliminating blur induced by associated imaging optics. The impact of the proton radiograph spatial resolution on the reconstructed proton CT image was also evaluated.

For this study, a single and homogeneous solid water Gammex insert was chosen (refer section 2.2) in order to demonstrate the feasibility in reconstructing a proton CT scan from the measured proton radiographs. The phantom insert was oriented such that its cylindrical axis was perpendicular to the beam direction, as schematically shown in figure 1 (also shown in figure 6a). Since the current system prototype lacked a rotation stage, this orientation of the insert presented an opportunity to exploit its radial symmetry. The radial symmetry made it possible to assume that a given system-generated radiograph will be identical (except for the effects of noise) to any other radiograph acquired by the system at a different angular rotation around the phantom.

The limited synchrotron beam time availability for system testing allowed acquisition of only a few proton radiographs of the phantom. Hence, the CT imaging dataset was composed of only 10 measured radiographic images of the solid water insert. These 10 projections were captured to take into account the influence of stochastic noise of the camera sensor on the reconstructed images. The proton CT dataset comprised of 10 system acquired radiographs in addition to 170 statistically generated radiographs. The 170 images were calculated in MATLAB software based on the measured imaging dataset (of 10 frames) by randomly selecting a subset of 5 images from these 10 frames. Each new frame was formed such that a pixel in the new frame had an intensity that was a median of the corresponding pixel intensities from the 5 images. This procedure was repeated to generate the remaining 170 images. Thus, a proton CT dataset consisting of 180 projections that simulated a 1° rotational step around the phantom were obtained.

A filtered backprojection (FBP) algorithm was chosen in this study for proton CT reconstruction. FBP algorithm has been used extensively with photon-based tomography systems as well as with proton-based tomography systems (Vanzi et al 2013; Cirrone et al 2011; Collins-Fekete et al 2016). The FBP algorithm presents advantages such as short computational time, modeling simplicity, and computational efficiency. They can therefore either be used independently for proton CT reconstruction or can be used as an initializing guess for relatively complex iterative reconstruction techniques (Scaringella et al 2014; Penfold et al 2010). For this study, we used FBP algorithm along with a Hamming filter. A MC-simulated proton CT for the solid water insert was also included for comparison.

3. Results

Figure 2a shows an image of a proton radiograph captured by the CCD in absence of any intervening phantom. It was generated by integrating the scintillation light intensity produced within the volumetric scintillator along the z-axis. The mean relative pixel uniformities evaluated across such a radiograph for 2 different ROI sizes - $9.8 \times 9.8 \text{ cm}^2$ and $7.7 \times 7.7 \text{ cm}^2$ were found to be 16.8% and 3.4% over 10 beam deliveries, respectively. The uniformity for the $9.8 \times 9.8 \text{ cm}^2$ ROI was affected by low intensity pixels located around the edges of the delivered field ($10 \times 10 \text{ cm}^2$). The mean relative standard deviation in pixel intensities or noise for the 10 consecutive beam deliveries for the same ROIs were 0.46% and 0.54%, respectively, suggesting that inter-frame pixel noise was low.

The calibration curve used for converting the recorded pixel intensities into corresponding integrated WET is shown in figure 2b. The camera records 2D light projection image by integrating 3D light distribution within the scintillator volume along the beam direction. Thus, the projection image includes contributions from non-linear dose deposition by the proton beam, especially around the Bragg peak, which introduces non-linearity in the plot. The measured calibration curve was fitted using both a linear fit as well as a 2nd order polynomial fit. The R-squared values for both these fits were 0.991 and 0.999, respectively, demonstrating that the measured plot can be fitted more accurately using the polynomial fit. The polynomial fit used for calculating WET from the measured pixel intensity is described by the equation,

$$(3.60 \times 10^{-6})x^2 + (0.02)x + (0.47), \quad (7)$$

where x represents the mean value of the measured pixel intensities (arbitrary units, a.u.). The standard deviation in camera pixel intensities for each of the 9 plastic water slab thicknesses was also determined. The mean variance over the 9 measured data points was 16.88 a.u. which upon converting into WET by using equation 7 gave 0.81 mm. This value indicated the mean error in converting camera measured intensities into WET values.

Figures 3(a) and 3(b) show the SNR and contrast for the imaging system shown in figure 1. The SNR graph was plotted using equation 1 for dose ranging from 0.008 cGy to 15.73 cGy and is seen to increase with higher dose deposition. An image contrast graph was generated by plotting contrast (using equation 2) for plastic water slabs with increasing WETs. The image contrast changes because of progressive loss in the cumulative scintillation light

intensity measured by the CCD with increasing WETs. Each data point on the contrast plot was calculated by taking ratio of the mean pixel intensity for a given plastic water slab thickness to the mean pixel intensity for the unattenuated beam energy (i.e. with no phantom). The plot therefore shows zero contrast for the first point (0 mm). The low contrasts for thinner phantoms was due to lower loss in signal intensities relative to the unattenuated proton beam energy (or in other words smaller shifts in the proton beam ranges relative to the unattenuated beam). For thicker phantoms this relative signal loss was greater resulting in better imaging contrast.

Figure 4a shows orientation of the 3 stacked Gammex inserts with respect to the beam direction and their placement with respect to the left tank surface. The theoretical WET values for the 3 cylindrical Gammex inserts (solid water, acrylic, and cortical bone) were calculated using equation 3. The stopping powers for the phantoms were calculated from the PSTAR program at 180 MeV beam energy. The theoretically measured WET values for solid water, acrylic, and cortical bone were determined to be 7 cm, 7.97 cm, and 10.64 cm, respectively. Figure 4b shows the system acquired WET image of the stacked phantoms. The WETs measured from the proton images were 7.06 cm, 7.89 cm, and 10.90 cm for solid water, acrylic, and cortical bone, respectively. Thus, the percentage accuracy in experimentally determining WETs relative to the theoretically calculated values was found to be -0.82% , 0.91% , and -2.43% , respectively. The maximum standard deviation for the measured WET values was determined to be ± 0.90 mm which was consistent with the noise in the calibration curve. Figure 4c shows a plot of WET line profiles across the inserts. The line profile across the acrylic phantom provided the full-width at half maximum (2.78 cm) value that is close to the physical diameter (2.8 cm) of the acrylic insert. The smooth edges of the line profiles were likely due to cone beam projection of the inserts resulting from a combination of proton beam divergence (2.12° , for a 10 cm^2 field area formed by beam source placed 270 cm away from the isocenter plane), as suggested by Tanaka et al (2016), and from camera system divergence (Hui et al 2015).

Figure 5a is an image of the radiograph for the MV-QA phantom (the inset shows a picture of the MV-QA phantom) that was included in this study to determine the spatial resolution of the system. The image contains 4 highlighted ROIs (A to D) containing line-pair patterns of varying spatial densities. Equation 4 was used to plot a graph of the estimated MTF for the imaging system at 180 MeV beam energy using these 4 ROIs, as shown in figure 5b. The MTF graph displays the imaging contrast (y-axis) for these line patterns as a function of their spatial densities (x-axis). Thus, ROI A with relatively less dense line-pair patterns has higher imaging contrast compared to the other densely situated line-pair patterns (ROIs B to D). This can also be qualitatively observed from figure 5a, where the finely spaced line-pair patterns in ROIs C and D cannot be visually distinguished. In figure 5b, corresponding to these two ROIs the estimated contrast is zero.

In order to reduce the influence of image blurring caused by the objective lens, the lens PSF was measured. A fit to the measured optical PSF was obtained using equation 6 and provided values of A, sigma, and gamma to be 0.018, 2.577, and 1.587, respectively. A Wiener filter was used for deconvolving the optics-induced blurring from the measured images. Figure 5b shows MTF graph with greater imaging contrast for the same ROIs after

carrying out the deconvolution operation. It can be observed from this MTF plot that the system is able to resolve line-patterns of at least 0.19 lp/mm without correcting for blur caused by proton induced scattering.

Figure 6a shows orientation of the solid water insert with respect to the beam direction for proton CT imaging. Proton radiographs (figures 6b and 6c) and proton CT slices (figures 6d and 6e) obtained from measurements (left column) and MC simulations (right column) are also shown. An FBP algorithm was applied to these datasets to reconstruct the proton CT slices. The MC simulations were conducted with 10^{10} particles over a $10 \times 10 \text{ cm}^2$ field, and the resulting images contained substantial statistical noise. One approach to reducing the statistical noise is by simulating scintillation photon generation for every proton particle incident within the scintillator volume. MC simulations to determine the photon yield in the liquid scintillator upon proton particle interaction are currently under investigation and will be reported in future studies. Image artifacts observed in the proton CT slices were attributed to amplification of image noise during the reconstruction process and from undersampling of the sinogram constructed using limited measurement dataset.

Figure 7 is plotted by integrating the SPR distributions shown in the reconstructed slices (figures 6d and 6d) along the vertical direction to obtain WET profiles for the solid water insert. As seen in the figure, after deconvolution the reconstructed WET value for the insert matches well (with a relative accuracy of 0.3%) with that obtained from MC reconstructed slice along the largest cross-section of the insert (or in other words at the center of the profile). While the MC-simulated and experimentally measured profiles are similar, the experimental profile has a wider distribution around the tail region. This is due to the image blurring from the lens which was corrected using a Wiener deconvolution algorithm resulting in profile sharpening especially around the tail regions. It can also be noted that the tails of the deconvolved profile rise towards the edges which does not match the simulated profile. This could be attributed to the imperfections in the measured PSF. In the future, better measurements will be conducted to improve the PSF determination. The figure, however, shows that a modest improvement in image resolution can be achieved by eliminating the optical blur contributed by the objective lens.

4. Discussion

4.1. Clinical applicability

In this study, we report the first measurements of a beam-integrating proton imaging system at a clinically-relevant proton energy. The organic liquid scintillator volume is capable of imaging objects with a WET of up to 20 cm, and the maximum object thickness can easily be increased to 30 cm by constructing a larger container for the liquid scintillator and utilizing a 220 MeV beam, which is available at most clinical proton therapy facilities.

While our proton facility includes a spot scanning gantry, for this work we used a passively scattered beam because of its easy availability. However, our technique could be easily implemented using a scanned or wobbed proton beam or any method of producing a uniform distribution of quasi mono-energetic protons. Furthermore, we acquired this data

using clinical dose rates and beam delivery parameters. This illustrates the ease of using this type of proton imaging detector at any type of clinical proton center.

4.2. Image quality

Spatial resolution—The physical dimension of an individual CCD pixel used in this study was 10 μm which was more than sufficient for proton imaging application. The image resolution was limited by the choice of the objective lens used for imaging which resulted in an effective pixel size of 0.4 mm. However, the primary reason for proton image resolution degradation is multiple Coulomb scattering of protons. It can be observed from the MTF plot (figure 5b) that there is no available image contrast for spatial frequency patterns of 0.49 lp/mm and higher. Thus, for the developed imaging system, without accounting for proton scatter corrections within the imaging phantom and possibly within the scintillator volume, the image resolution was between 0.19 lp/mm to 0.49 lp/mm. A lack of additional line-pair patterns between 0.19 lp/mm and 0.49 lp/mm also prevented us from precisely determining the system resolution. For this study, we therefore report the imaging resolution of the system to be 0.19 lp/mm.

Tanaka *et al* reported that features of approximately 1 mm were visible with their beam-integrating proton CT system. However, their use of a low-energy (70 MeV) proton beam resulted in less multiple Coulomb scattering than that occurring in higher-energy clinical proton beams, such as the one used in this study. Beam-integrating proton radiography systems operating at energies high enough for patient imaging will experience increased scattering, leading to decreased spatial resolution. Additionally, the image resolution phantom used in this study used thick sheets of metal in its line pair features. We expect this high-Z material to increase proton scatter, which may have been detrimental to the spatial resolution measurements. Future studies will include a customized low-Z phantom with additional line-pair pattern frequencies to evaluate a definitive spatial resolution for the system.

Image artifact correction—In this work, certain imaging artifacts, such as background noise, stray radiation and lens-induced image blurring, which are related to the optical components of the imaging system, were accounted for. The MTF plot constructed from proton radiographs (see figure 5b), especially the plot indicating MTF after removing the lens-induced blurring, demonstrated that artifact corrections led to improvement in image resolution. However, the system's inability to resolve relatively denser line patterns in regions C and D (see figure 5a) suggests that system images are still impacted by proton scatter. Our results demonstrated that image blurring from optical artifacts exert only a marginal influence on the overall proton image resolution. This finding is in agreement with Zygmanski et al (2000), who estimated that the contribution of optical artifacts to image blurring is only a small percentage of the total blurring in proton radiography systems. Other imaging artifacts investigated as part of proton and photon dosimetry studies were previously reported by the author's group and include light refraction at the air-scintillator interface, and change in image perspective as a function of depth inside the scintillator volume (Robertson et al 2014). These artifacts were not included in this work, but their impact on the overall image resolution will be investigated in future studies.

4.3 Stopping power measurement accuracy

Image noise—The inter-image noise in calculating phantom WETs from the recorded pixel intensities was determined to have a mean uncertainty of 0.81 mm. It is therefore necessary to minimize this noise in order to calculate phantom WETs with greater accuracy. One approach to reducing this noise is by choosing a better sensor technology such as electron-multiplying CCDs that possess low read noise. Another option is to use CCD sensors with greater active area pixel well depth to increase the dynamic range of captured images. These detector options will be explored for the next imaging system prototypes.

Contrast non-linearity—The image contrast plot (see figure 3b) showed a non-linear response. This non-linearity was a combined result from non-linear dose deposition by protons and due to collection of the scintillation light by integrating it along the z-axis, as explained in Results section. It was found to impact the sensitivity of the imaging system when providing contrast for larger WET phantoms. For example, a second-order polynomial fit to the contrast plot,

$$(-2.439 \times 10^{-5})x^2 + (0.009)x + (0.003), \quad (8)$$

was used for determining a relative percentage change in contrast for a unit WET step. A relative contrast increase of 9.5% was determined for a 1 mm WET interval when stepping from 9 mm to 10 mm. On the other hand, the system sensitivity dropped to a relative contrast increase of only 0.6% for an equivalent 1 mm interval when stepping from 109 mm to 110 mm WET. Thus, the sensitivity to the imaging contrast was found to vary as a function of the phantom WET.

4.4. Imaging dose and contrast

SNR and dose—The system SNR was plotted using a 0.008 cGy dose which is one of the lowest doses that the synchrotron at the Proton Therapy Center at The University of Texas MD Anderson Cancer Center typically delivers. From figure 3a it can be observed that the calculated SNR for this dose was 26.2 dB implying that the mean pixel intensity for the radiograph was 20 times above the noise level. Thus, the chosen image sensor is capable of imaging under low-light conditions that are available for low dose levels. The SNR for the images further increased to 34.23 dB or approximately 50 times above the noise level for 6.6 cGy dose. One of the key design criteria envisioned for a clinical proton CT scanner was its ability to produce a scan using low dose levels (< 5 cGy) (Schulte et al 2004). The range of doses and their corresponding SNRs mentioned above suggest that the radiography system presented here is capable of imaging at clinically acceptable dose levels. The maximum SNR dose (15.73 cGy) was selected such that it drove the CCD sensor into saturation. Most experiments in this study were conducted by exposing the phantoms to 4.72 cGy dose that was calculated proximally to the Bragg peak. This dose was calculated for the Bragg curve at a depth of 5 cm. Thus, there is potential to significantly reduce the proton dose for future imaging studies. The impact of noise on proton images for these reduced dose levels will however have to be carefully evaluated.

5. Conclusion

We report the first proton radiograph measurements using a beam-integrating liquid scintillator detector ($20 \times 20 \times 20 \text{ cm}^3$) at a clinically-relevant proton energy (180 MeV). The advantage of the volumetric scintillator detector is its ability to utilize a single passive beam irradiation to capture and measure a wide distribution of residual beam energies (range distribution up to 20 cm). The system was able to calculate WETs for a set of phantoms with a maximum error $< 2.5\%$. Image blurring induced by system optics was accounted for, resulting in image sharpening. The spatial resolution of the system was determined to be 0.19 lp/mm. Finally, a FBP algorithm was used for proton CT reconstruction and was found to be accurate enough to provide the phantom WET to within 0.3% of the MC simulated WET.

Acknowledgements

The authors thank Dr. Narayan Sahoo and Archana Gautam for their help with proton beam measurements. We would also like to acknowledge Amy Ninetto from the Department of Scientific Publications at UT MD Anderson Cancer Center. The research reported in this publication was supported by the National Cancer Institute/National Institutes of Health under award number R01CA182450 and an Institutional Review Grant from MD Anderson Cancer Center. The authors have no relevant conflicts of interest to disclose.

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Figure 1.

A schematic of the proton imaging system. The dotted arrows indicate the physical dimensions of the setup (dimensions are not drawn to scale).

Figure 2.

(a) An image of a uniform system-generated proton radiograph captured by the CCD by integrating scintillation light intensity within the scintillator volume along the beam axis. (b) An energy-specific calibration curve used for converting the recorded camera pixel intensities of the radiograph into equivalent integrated water-equivalent thicknesses (WETs).

Figure 3. Plots of (a) signal-to-noise ratio (SNR) measured in absence of any intervening phantom, and (b) image contrast measured using plastic water phantom slabs as described in section 2.2.

Figure 4.

(a) A picture showing physical dimensions (diameter 2.8 cm, length 7 cm) and orientation of the three Gammex inserts (solid water, acrylic, and cortical bone) with respect to the beam direction. (b) A WET proton image for the 3 inserts. (c) Line profiles across the 3 phantoms were obtained from (b) and show the 1-dimensional WET distribution.

Figure 5.

(a) An image of the MV-QA phantom radiograph used in this study. The inset shows a picture of the phantom placed in the x-y plane and touching the left tank surface. The highlighted ROIs contain line-pair patterns with varying spatial densities (A (0.09 lp/mm), B (0.19 lp/mm), C (0.49 lp/mm), D (0.98 lp/mm)). (b) A plot of modulation transfer function (MTF) is plotted as a function of increasing line-pair densities both before (dashed line) and after (continuous line) deconvolving the radiograph using the measured lens PSF in order to remove lens-induced image blurring.

Figure 6.

(a) A picture of the position and orientation of the Gammex solid water insert with respect to the left tank surface. (b, c) Proton radiographs and (d, e) proton SPR distributions for the reconstructed proton CT slices obtained from measurement (left column) and MC-simulation with TOPAS (right column) datasets.

Figure 7.

A comparison of WET profiles along the x-axis (see figure 1 for system orientation) obtained from the reconstructed proton CT slices for the solid water insert for Monte Carlo-simulated (solid line), system measured before (dashed-dotted line) and after deconvolving the PSF for the objective lens (dashed line).