Proton radiography and fluoroscopy of lung tumors: A Monte Carlo study using patient-specific 4DCT phantoms

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Purpose: Monte Carlo methods are used to simulate and optimize a time-resolved proton range telescope (TRRT) in localization of intrafractional and interfractional motions of lung tumor and in quantification of proton range variations.

Methods: The Monte Carlo N-Particle eXtended (MCNPX) code with a particle tracking feature was employed to evaluate the TRRT performance, especially in visualizing and quantifying proton range variations during respiration. Protons of 230 MeV were tracked one by one as they pass through position detectors, patient 4DCT phantom, and finally scintillator detectors that measured residual ranges. The energy response of the scintillator telescope was investigated. Mass density and elemental composition of tissues were defined for 4DCT data.

Results: Proton water equivalent length (WEL) was deduced by a reconstruction algorithm that incorporates linear proton track and lateral spatial discrimination to improve the image quality. 4DCT data for three patients were used to visualize and measure tumor motion and WEL variations. The tumor trajectories extracted from the WEL map were found to be within ~ 1 mm agreement with direct 4DCT measurement. Quantitative WEL variation studies showed that the proton radiograph is a good representation of WEL changes from entrance to distal of the target.

Conclusions: MCNPX simulation results showed that TRRT can accurately track the motion of the tumor and detect the WEL variations. Image quality was optimized by choosing proton energy, testing parameters of image reconstruction algorithm, and comparing to ground truth 4DCT. The future study will demonstrate the feasibility of using the time resolved proton radiography as an imaging tool for proton treatments of lung tumors. © 2011 American Association of Physicists in Medicine. [DOI: [10.1118/1.3555039](https://doi.org/10.1118/1.3555039)]

I. INTRODUCTION

The finite range of proton beams has long been hypothesized as advantageous in radiation therapy, and there is evidence of its effectiveness in a number of static treatment sites^{1,2} (choroidal melanoma,³ base of skull lesions,⁴ juxtaspinal tumors, and treatment of pediatric malignancies such as medulloblastoma⁵). For other sites where the tumor moves, irradiation of lesions is more challenging. This is because the radiologic pathlength from entrance to distal of the target may vary from moment to moment during respiration or over the course of days or weeks of treatment. Physical reasons for this range variation include changes in tissue density, tissue thickness, tumor size, or organ deformation. Temporal variations can also affect the pathlength along a specific ray varies when a structure of different density moves in and out of the ray path. The temporal variation may be magnified in the case of lung cancer treatment with proton beams. For example, a 5 mm water equivalent distal margin may expand to 25 mm in lung for a 0.2 g/cc lung density. These pathlength variations underscore the need for feedback and control of the proton beam to provide estimates of range variation on either a moment to moment or day to day time frame.

The need to measure beam penetration has been considered by others using a variety of techniques. One treatment

site under investigation is the prostate. Currently, lateral or nearly lateral fields are used to avoid uncertainties in the anterior range. The radiological pathlength from an anterior field is not constant from day to day due to soft tissue distribution or bladder filling. To cover the prostate from the anterior direction and yet spare the anterior rectal wall would require the beam be stopped reliably to ~ 2 mm. Without some feedback information on a daily basis, such precision would be unrealistic. Therefore, Melancon *et al.*⁶ proposed a liquid scintillation detector to be inserted into the rectum, combined with a wedge compensator to measure the range before treatment. Lu⁷ proposed to use a time-dependent dose consistent with a passively scattered beam. These devices are under development and may be suited for body sites where a detector can be inserted; such a device would not be feasible for lung or abdominal tumors. Investigators have also proposed the use of emission tomography of short lived positron emitters resulting from nuclear interactions of the protons.^{8,9} This method is only practical if a PET scanner is available in the treatment room and, due to the low positron production rate from proton irradiation, the image acquisition can be slow.

Another promising approach is to examine proton range variations as part of the image guidance process by using a real-time, in-room monitoring proton radiography system.

The earliest literature on the use of protons for radiography was by Wilson¹⁰ in 1946. In anticipating the commissioning of a new proton accelerator at Harvard, he estimated that the penetration of 120–200 MeV protons through a thin part of the patient body would be feasible for generating a proton radiographic image. It was not until 1960s–1970s that researchers began to test protons in radiography and compared such images to the standard methods based on x rays. Koeher explored proton radiography on aluminum absorbers¹¹ and human brain specimens¹² using 160 MeV protons. He concluded that proton radiography was better than x-ray radiography in terms of density resolution. However, he also noted a poorer spatial resolution of proton radiography due to multiple Coulomb scattering (MCS). In 1980, Kramer *et al.*¹³ used a scanning proton beam at 205 MeV for imaging of medical specimens. They demonstrated a significant dose reduction and an improved mass resolution for proton radiography over the conventional x-ray radiography. Due to a strong dependence of the proton stopping power on tissue composition and density, image contrast of soft tissues was considerably greater with protons. These pioneers of proton radiography utilized integrating detectors such as film, and spatial resolution was still compromised when imaging thick samples.

Recently, interest in proton radiography as a quality assurance (QA) diagnostic tool has grown due to the proton therapy's rapidly increasing popularity.¹⁴ Furthermore, fast electronic detectors have enabled real-time data acquisition and analysis, outperforming the film used in the previous studies. Several studies have introduced modern electronic techniques to determine the radiologic pathlength and energy of protons. Johnson *et al.*¹⁵ used a pair of silicon detector modules to detect the position and energy loss of proton beams. The energy resolution was on the order of 20% in the 100–200 MeV energy range. Ryu *et al.*¹⁶ studied the density and spatial resolution of proton radiography using a range modulation technique. Seco and Depauw¹⁷ reported the use of a CCD to measure dE/dx of the protons. Sipala *et al.*¹⁸ used a calorimeter to measure the residual energy of the proton and reported range resolution to be greater than 3 mm.

The energy resolution of these techniques using planar detectors such as film is not sufficient for clinical applications until the emergence of electronic range telescopes. In 1995, Schneider and Pedroni¹⁹ reported a comprehensive study of proton radiography as a quality control tool for proton therapy. They produced proton water equivalent length (WEL) maps and WEL uncertainty maps by imaging an Alderson phantom and a sheep's head. With WEL information, treatment planning and positioning precision of the patient could, in principle, be improved. Pemler *et al.*,²⁰ for the first time, developed a detector system for proton radiography. The system consisted of two scintillating fiber hodoscopes and a range telescope of plastic scintillator slabs. This device was tested using a scanning pencil proton beam and various imaging phantoms. Based on experiments using water bath, the spatial resolution achieved for the residual range image is ~ 1 mm and the density resolution was 0.3%. In 2003 and 2005, Schneider *et al.*^{21,22} extended the test of their system to

a dog patient. Proton beams at 214 MeV were used and the range and range dilution information were analyzed. The spatial resolution was found to be ~ 1 mm and the range sensitivity of the images was reported to be ~ 0.6 mm. The dog received a very low dose of 0.03 mGy during the exposure time on the order of several seconds. As part of the Advanced Quality Assurance (AQUA) project, Sauli²³ built a proton range radiography system based on the range telescope concept, which we model for this study. Mumot *et al.*²⁴ proposed a range probe for pencil beam proton imaging and it was verified using Monte Carlo simulations. These studies did not address radiography as a tool for detecting time-dependent range variations due to intrafractional and interfractional organ motion.

In this article, we explore proton radiography/fluoroscopy as a means of providing information needed for image guidance with proton therapeutic beams. For brevity, we use the term proton radiography in this article to include both proton radiography and fluoroscopy. Image guidance has primarily been used to localize the position of the tumor on a daily basis.²⁵ We provide examples where proton radiography is used to (a) localize the tumor, (b) determine its trajectory, (c) detect changes in the total WEL during respiration, and (d) detect changes in WEL interfractionally, which may be indications of tumor shrinkage or weight loss. A “time-resolved range telescope (TRRT)” is modeled to create time-dependent proton WEL maps by reconstructing the range information. A Monte Carlo based performance study is described to demonstrate that such a device is clinically useful in image guided proton therapy. Image quality was optimized by choosing energy of particles, image processing, and image formation and was compared to the ground truth position. This is the first time a TRRT is systematically studied by Monte Carlo simulations using 4D (serial) CT. Our long term goal is to develop and provide image-guidance TRRT technology for the improvement of proton treatment of moving tumors caused by respiration and cardiac motion. In Sec. IV, we expand on some of the limitations of this technique.

II. MATERIAL AND METHODS

To explore how proton radiography can be applied to image guided proton radiotherapy, three lung cancer patient cases with various tumor sizes, locations, and motion are studied. The 4DCT datasets and the TRRT system were modeled and simulated by a Monte Carlo code to construct proton WEL maps. Both intrafractional and interfractional WEL variations are analyzed and correlated with the ground truth derived from the 4DCT data. The accuracy and effectiveness of the TRRT system are estimated.

II.A. Range telescope description

In this study, we modeled a range telescope designed by Sauli.²³ Figure 1 illustrates the schematics of the TRRT system. A 20 cm $\times$ 20 cm planar proton beam with energy of 230 MeV with 0.5% energy spread and 60 mrad angular spread is used for imaging. This initial source energy is sufficient to pass through a typical patient in the AP direction.

FIG. 1. Conceptual design of the time-resolved proton range telescope system consisting of two position detecting GEM chambers and a range telescope that measures the residual range of protons.

The entry and exit coordinates of each proton are tracked by a pair of position-sensitive gas electron multiplier (GEM) chambers with a spatial uncertainty of $<200\ \mu\text{m}$ that are placed proximal and distal to the patient with a distance of 35 cm. The residual range of each proton after traversing the patient is measured by a proton range telescope consisting of a stack of 3-mm-thick plastic scintillators. Electronics limits the count rate of telescope system currently to $\sim 1\ \text{MHz}$, and the source beam intensity is tuned down to allow particle by particle tracking. Improvements in electronics are anticipated to increase the data acquisition eventually by a factor of 10, which will advance the use of proton radiography to faster cardiac motion and irregular respiration.

II.B. Monte Carlo simulations

Computer simulations of a proton radiography in terms of WEL maps were performed using Monte Carlo N-Particle eXtended (MCNPX) code version 2.5.0 (Ref. 26) with the PTRAC feature activated to record every particle interaction and associated tracks. The modified Rossi model was used to model the MCS. In our previously published study,²⁷ MCNPX simulation results of scattering and displacement of a proton pencil beam in water were compared to GEANT4 (Ref. 28) simulation results as well as theoretical calculations. The good agreement ($<0.27^\circ$ scattering angle and $<0.15\ \text{mm}$ displacement) shows that MCNPX is sufficiently accurate for a proton radiography study. In addition, the proton energy straggling was treated with the Vavilov model.²⁹ Inelastic nuclear interactions were modeled with the default option of MCNPX, which includes the pre-equilibrium model after Bertini³⁰ intranuclear cascade treatment. The sensitive area of the two GEM chambers is $200\ \text{mm} \times 200\ \text{mm}$. To ensure adequate range resolution in the WEL maps, we simulated enough proton histories in the MCNPX code to accumulate ~ 50 particles per $2\ \text{mm} \times 2\ \text{mm}$ pixel, according a study by Schneider and Pedroni.¹⁹ Given that approximately 20% of the protons would undergo nuclear interactions inside the patient, a total of 5×10^6 source protons were simulated for each WEL map. Simulations were performed on a Linux server computer with two quad-core Intel Xeon CPUs and 8 GB RAM. A typical simulation for a WEL map from ten

respiratory phases required 2–3 h of run time without special computational acceleration.

In this Monte Carlo study, we used CT data to create patient phantoms from which radiographic images are simulated. Each patient received one or more 4DCT scans in the course of radiotherapy, and the breathing cycle was equally subdivided into ten phases (T00–T90) providing ten volumetric CT scans evenly spaced over the nominal breathing period. Phase T00 represents the peak inhalation of a breathing cycle. CT images were reconstructed on a voxel grid of $0.9766\ \text{mm}$ transaxial pixel size and $2.5\ \text{mm}$ axial thickness. CT image datasets at each respiratory phase were converted into mass density and elemental composition on a voxel-by-voxel basis for input into Monte Carlo simulations. The mass density was determined using an interpolation method based on Hounsfield units (HUs). Twenty-four bins with different elemental compositions according to 71 human tissues³¹ were used to account for the variations of proton stopping power in different tissues.

For the purpose of recording the entry and exit positions of each proton, two planes were defined in the Monte Carlo simulation to represent the GEM chambers. Realistic modeling considered design details in Sauli's range telescope.³² The energy response of the plastic scintillator (Saint Gobain BC-408) stack was simulated in MCNPX by incorporating vendor-provided information on the light output for various energy depositions. For each proton, the light output in each scintillator slab was calculated. The signals in the last five slabs [~ 2 full width half maximum (FWHM)] in the Bragg peak region are important because they were used to estimate the residual proton range using the Gaussian fitting method. To benchmark the modeling, the simulated light output result for a 99.7 MeV proton beam incident on the scintillators was compared to the experimental result from Paul Scherrer Institute (PSI) obtained by Sauli.³²

II.C. Proton WEL map image reconstruction

For each proton, the simulated entry (x_1, y_1) and exit (x_2, y_2) positions, and Gaussian fitted residual range (R) were recorded to construct a proton residual range map. Figure 2 shows two proton histories from a MC simulation: Track 1 underwent small lateral scatter, while track 3 experienced larger lateral scatter. Protons undergoing nuclear scattering or large angle MCS (track 3 in Fig. 2) tend to pass through more tissues and their tracks are difficult to predict even using information such as entry and exit positions. The residual range of these particles relates to neither the geometry behind the entry pixel nor the geometry in front of the exit pixel, and thus introduced noise into the image. To improve the spatial resolution, such particles should be rejected in the reconstructed range map. At the same time, to achieve real-time proton fluoroscopy, we need to balance rejection with practicality of limited protons that can be processed at a time. More acceptable protons accumulated in each pixel provide more statistics and thus better image. In previous pCT studies,^{33–35} linear, cubic spline and the most probable tracks were used to improve the spatial resolution by improv-

FIG. 2. (a) Illustration of the linear track assumption algorithm with event rejections. (1) The actual track of a proton exits at point B. (2) The approximated linear track of the proton in track (1). (3) The actual track of a proton exits at point C. (4) The approximated linear track of the proton in track (3). G1 and G2 represent the two GEM chamber planes upstream and downstream. (b) Illustration of the linear path algorithm for WEL map reconstruction. The total pathlength ($L_{tot,i}$) is divided into segments that correspond to 5 pixels that are affected by the proton's path. The segment ($L_{2,i}$) is the segment that corresponds to pixel 2.

ing image reconstruction. In this study, a linear track approximation algorithm with event rejection was tested and explored to construct proton WEL map. For proton that scatters less than a specific lateral distance, linear track from entry point to exit point is accepted to construct the WEL map. For instance, the proton (track 1) shown in Fig. 2(a) scattered 5 mm laterally and was accepted. The dashed straight line 2 was the approximated proton track for this proton. Figure 2(a) also shows another proton in track 3 that scattered 15 mm laterally. It underwent larger angle MCS and the linear track 4 (dashed line AC) was no longer an accurate approximation. Thus, i proton in track 3 was rejected in the reconstructed WEL map.

The i_{th} proton, as shown in Fig. 2(b), traverses through the tissue at an angle before reaching the imager (GEM2) pixel 5. The total pathlength ($L_{tot,i}$), as shown in Fig. 2(b), and the energy loss associated with it, is divided into segments that correspond to 5 pixels that are affected by the proton's path. The segment ($L_{2,i}$) corresponding to pixel 2 is illustrated. By analyzing the paths of all protons, the WEL values of all pixels are calculated using the formula:

$$R(\text{pix}) = R_{\text{source}} - \frac{\sum_{i=1}^n R_i \times L_{\text{pix},i} / L_{\text{tot},i}}{\sum_{i=1}^n L_{\text{pix},i} / L_{\text{tot},i}},$$

where R_{source} is the range of source proton and R_i is the residual range of the i_{th} proton.

FIG. 3. Axial scan at T50 phase of patient 1's 4DCT data with the tumor circled. The radiologic pathlength passing through the tumor center at T50 is divided into five anatomical regions: (1) Anterior chest wall, (2) proximal lung, (3) tumor, (4) distal lung, and (5) posterior chest wall.

II.D. Patient-specific case studies

Three patient cases were studied to explore and optimize the TRRT analysis approach in detecting intrafractional and interfractional organ motion, tumor regression, tumor trajectories, and implications of weight loss. Each patient received one or more 4DCT scans in the course of radiotherapy, under free breathing conditions using a commercial multislice CT scanner (Discovery ST, General Electric Healthcare, Waukesha, WI; MX8000-IDT). Patient respiration was monitored by tracking a reflective block placed on the patient's abdomen (RPM, Varian Medical Systems, Palo Alto, CA).

II.D.1. Patient case 1

Patient 1 had a tumor in the right lung, ~2 cm in diameter. This case is used to illustrate the application of proton radiography/fluoroscopy in quantifying WEL variations during respiration. The axial scan at T50 is shown in Fig. 3. The gross tumor volume (GTV) is outlined by the red circle; a line that passes through the tumor center at T50 along the AP axis indicates an example ray along which we quantify the radiologic pathlength. During inhalation, the tumor moves inferior to the sample ray and tends to reduce the WEL along the sample ray. The chest wall thickness and the density changes can also influence the radiologic pathlength. Therefore, along this ray, the radiologic path is divided into five specific anatomical regions: The anterior chest wall, proximal lung, tumor, distal lung, and posterior chest wall. The variations in WEL in these regions were calculated in order to study their relation to the total pathlength. To reduce the variations due to placement of the sampling point, the ROI region was set 5 mm diameter from the ray in the coronal plane. We simulated 4DCT in MCNPX and generated ten phases of WEL maps. The outline of the tumor and the cranio-caudal tumor motion were studied. The tumor trajectory was extracted from WEL maps and compared to the ground truth from 4DCT. The WEL profile from instrument simulation was also validated against true radiologic pathlength calculated from Aqualyzer.³⁶

FIG. 4. CT images of patient 2: Sagittal views of the respiratory phase at (a) T00 and (b) T50. Lesion located at the lower left lung shadowed by the heart. To clearly illustrate the chest wall thickness variation (circled region), two constant length rulers were indexed to the moving anterior entrance surface.

II.D.2. Patient case 2

Patient 2 had a tumor in the lower left lung partially shadowed by the heart. This case is used to study the effectiveness of proton WEL maps under more complicated geometry with respiration and cardiac motion. Figures 4(a) and 4(b) show the sagittal views of the respiratory at T00 and T50. Lesions in the heart shadow may not be clearly imaged due to cardiac motion. Lesions near the mediastinum also may be difficult to image. This case is illustrative of the limitations of proton radiography when tumors are in a location unfavorable for proton radiography. Furthermore, by analyzing patient 2's 4DCT data, we observed a ~ 5 mm variation in the chest wall thickness during respiration. Hence, it is interesting to study this chest wall thickness variation by the time-dependent proton WEL maps. The overall WEL variations in the lung can also be estimated using WEL difference maps relative to phase T50.

II.D.3. Patient case 3: An example of interfractional proton radiography

The interfractional WEL variations in patient case 3 were assessed, where a lung cancer patient took eight weekly serial 4DCT scans. After the initial planning CT scan (week 0), weekly serial 4DCT (repeat CTs: From week 1 to week 7) scans were acquired. Figure 5(a)–5(c) are coronal views of phase T50 at week 0, week 3, and week 7. The proton WEL maps at T50 of all eight serial 4DCT scans were generated. The tumor regression and motion during different treatment fractions were visualized and quantified.

FIG. 5. Coronal views of patient case 3's at T50 for week 0 (a), week 3 (b), and week 7(c). The tumor located in the upper right lung (white arrow). The images were registered relative to each other with respect to bony anatomy.

FIG. 6. Benchmark test of simulated and measured light outputs, normalized by the peak in each curve, for a 99.7 MeV proton beam incident on 3.7 mm slabs of the range telescope. The signals for the last five slabs (~ 2 FWHM) in the Bragg peak region are used to deduce the residual range of the proton by Gaussian fitting.

III. RESULTS

III.A. Instrument modeling and simulation

Figure 6 illustrates the results of the benchmark test comparing the measured and simulated relative light outputs of a 99.7 MeV proton beam in the telescope. This energy represents a typical exit energy of a 230 MeV source proton traveled through the lung in the AP direction. For depth up to 5.5 cm, there is a relatively flat region, which is not used in range determination. The light output in the last five scintillators are related to the Bragg peak and a Gaussian fitting was performed. Then, the residual range of the proton beam was identified by the depth that corresponds to 90% of the distal falloff. The range deduced from the simulation and the experiment exhibits an agreement within 0.5% of the total range and the curves follow almost identical trend as shown. Gaussian fit to the deduced range has a standard deviation of 1.7 mm, which is a combined effect of the energy distribution of proton source, range straggling of each proton, and range uncertainty in the detector. Given the $\sim 0.5\%$ FWHM of the source range distribution and $\sim 1\%$ range straggling, the range uncertainty due to the detector specification is estimated to be ~ 1.5 mm. This uncertainty in the detector is mainly determined by the energy-light response, light transfer efficiency, and slab thickness of the scintillator stack. By reducing the slab thickness, the density resolution tends to be improved but the trade-off effect is less light generated in each scintillator slab. In future study, we will analyze this effect and optimize the slab thickness thus to reduce the uncertainty in the detector.

III.B. Patient case 1

Patient case 1's 4DCT data were simulated in MCNPX and the WELs along the example ray (specified in Fig. 3) in all ten phases were calculated. The radiologic pathlength variations in all five anatomical regions relative to T50 during the entire breathing period were quantified and are plotted in Fig. 7(a). The maximum WEL variation was 14.98 mm mostly due to the tumor motion. The WEL variations in other

FIG. 7. MCNPX simulation results of (a) patient case 1's WEL variations of different parts of the body along the sample ray penetrating the tumor center at T50 (Fig. 2.) (b) Energy spectra of pixels at tumor center and lung region (just outside the tumor edge). Protons scattered greater than 8 mm laterally were rejected.

anatomical regions along the analyzed ray were less than 2 mm. This case illustrates that for the tumor in the middle or lower lung when the tumor moves with respirations, the AP WEL map is a good representation of the WEL changes from entrance to distal of the target.

The energy spectra of protons in a range map pixel that geometrically passes through the tumor center and lung region (just outside the tumor edge) is shown in Fig. 7(b). By rejecting the large lateral scattering protons (>8 mm), the mean energies of the protons are 153.8 and 174.4 MeV, respectively, with standard deviations of 2.3 and 2.4 MeV. The mean WEL of two sample rays are 176.8 and 136.7 mm with the standard deviations of 4.3 and 4.8 mm, respectively. The 20.1 mm WEL difference between these readings is consistent with the craniocaudal motion of the 20 mm diameter tumor.

Monte Carlo particle tracking data suggest that protons scattered a lateral distance less than 8 mm result in acceptable ~ 1.26 mm mean lateral displacement between actual track and approximated linear track. Around 10% of imaging protons were rejected. Applying the spatial cut of 8 mm and linear track approximation algorithm to the data from simulations for the patient case 1, the reconstructed WEL maps of all phases are shown in Fig. 8. With appropriate color-map windowing, the tumor in the right lung is identified and displayed throughout the entire respiratory cycle.

The accuracy of the WEL map from MCNPX simulations was estimated by comparing to the WEL line profiles' ground truth as calculated from 4DCT. The results of this comparison are shown in Fig. 9. With the spatial cut of 8 mm and linear track approximation algorithm, the largest discrepancy between the simulation and 4DCT is 5 mm WEL in highly heterogeneity region such as the tumor edge.

The trajectory of the tumor was extracted from WEL maps using normalized cross-correlation techniques. From the trajectory, we determined the craniocaudal tumor motion to be ~ 1 cm. The tumor trajectories, as defined from ground truth established 4DCT analysis and from MCNPX simulated radiographs, are shown in Fig. 10. Their difference in this exploratory study is less than 1 mm, suggesting that the information obtained from the TRRT was possible to use for adjustment to the fractionated treatment delivery.

FIG. 8. Proton WEL maps are windowed and leveled to visualize tumor at each of the ten respiratory phases of patient 1's (beginning at peak inhalation). The tumor is clearly seen in all phases.

FIG. 9. WEL line profiles from right to left through the tumor center. The dashed line is the ground truth WEL as calculated from CT and the solid line is extracted from the MCNPX simulated proton radiograph.

III.C. Patient case 2

Patient 2 had a tumor in the lower left lung partially shadowed by the heart. The WEL variations between phases T00 and T50 were quantified from proton radiographs. The WEL difference map (Fig. 11) shows the variation in the WEL from peak inhalation to peak exhalation. Although determination of the tumor location is more complicated with respiration and cardiac motions, a red region and a dark blue region clearly indicate the WEL variation due to the motion of the tumor and show the effectiveness of proton WEL maps. Note the entire lung region (except tumor), indicating a uniform WEL change of ~ 5 mm. Further 4DCT analysis shows that in this patient, the chest wall thickness varied during respiration. Two constant length rulers were indexed to the moving anterior entrance surface in Fig. 4. The variation in the chest wall thickness can be clearly visualized. Soft tissue in the chest wall is seen to redistribute itself during breathing.

III.D. Patient case 3

In patient 3, we analyzed and quantified range changes using serial CT over an 8 week treatment course. The pre-treatment scan (week 0) was followed by seven serial 4DCT scans until the end of treatment (week 7). Proton WEL maps at T50 over the 8 week period were simulated to study WEL variations with the goal of documenting tumor size regres-

FIG. 10. Tumor trajectory from CT and from MC simulated proton WEL map. The difference is less than 1 mm.

FIG. 11. WEL difference map (T50-T00). The regions (with greater than 40 mm WEL variations) in the left lung are due to the tumor motion. Over the entire lung, there is a uniform time varying WEL change of ~ 5 mm.

sion and trajectory changes. The mean WEL in the tumor region and GTV volumes are plotted in Fig. 12. The mean WEL decreased 3.7 mm during the first two weeks of treatment but increased 6 mm in the third week. Over the entire 8 weeks, the mean WEL decreased 15.9 mm. The WEL variation follows the trend of the change in the tumor volume during the course of treatment. The exception between weeks 4 and 5 is possibly cost by patient positioning error or miscalibration of the CT machine. Simulation results of this patient suggest that proton radiography can be useful in detecting and quantifying interfractional WEL changes.

IV. DISCUSSION

We have simulated acquisition of proton radiographs from a TRRT system and applied it to sample patients' 4DCT datasets using MCNPX. Time-dependent WEL range maps were reconstructed. The linear track algorithm in combination with spatial cut method was used to optimize the image

FIG. 12. Variations in WEL (tumor region) and GTV volume over 8 weeks for patient case 3. The WEL decreases over 8 weeks, which follows the trend of the change in the tumor volume during the course of treatment. The exception between weeks 4 and 5 is possibly cost by patient positioning error or miscalibration of the CT machine.

reconstruction. Tumors for all three cases were accurately located and the intrafractional tumor trajectory in patient case 1 was in good agreement with the ground truth 4DCT data to 1 mm. The spatial resolution was estimated to be ~ 1 mm by fitting an error-function to the edge of WEL map. It is agreed with Schneider's estimation of spatial resolution when two coordinates were used.³⁷

Range resolution was estimated by studying three key factors. The first is the statistical fluctuations of proton interactions such as range straggling. It is Gaussian distributed and typically $\sim 1\%$ of the total proton range. The range straggling can increase if the track passes through more heterogeneities. The second factor is the energy spread of the proton source. The scanned proton beams at Massachusetts General Hospital (MGH) and PSI can achieve 0.5% FWHM Gaussian distribution of total nominal energy. The third factor is the inherent range resolution of the telescope. As we described, with Gaussian fitting of the last five signals in Bragg peak, the range resolution of the detector was ~ 1.5 mm, in spite of a 3 mm scintillator slab thickness. Therefore, the total range resolution for one detected proton is $\sim 1.3\%$ of total range greater than 200 mm. With ~ 36 protons in each pixel, the density resolution can be reduced to $\sim 0.2\%$. However, the use of passive scattering proton beam with more energy and angular spreads compromises the range resolution.

Estimation of temporal resolution of the TRRT system is also important. A typical respiratory cycle is ~ 4 s in length. In order to achieve comparable temporal resolution as 4DCT in one breathing cycle, WEL maps of each phase need to be reconstructed based on protons acquired in 0.4 s (or 2.5 frames/s). Given the current count rate of 1 MHz electronics speed, the histories of 0.4×10^6 protons can be recorded during each of ten breathing phases. Hence, for a 200 mm $\times$ 200 mm WEL map with 2 mm $\times$ 2 mm pixel size, there are 50 source protons (~ 40 exit protons and ~ 36 protons after rejection) per pixel in average, which result in a density resolution of $\sim 0.2\%$. In more complex situations such as tumor under the shadow of the heart or near the mediastinum, higher density resolution can be achieved using a gating technique similar to RPM in regular breathing scenario. Using these settings, the effective dose to patient was estimated using the RPI-adult male and female phantoms.³⁸ These computational phantoms, consisting of more than 140 organs and tissues, were designed to match internal and external anatomical features of the Reference Man as defined by the International Commission on Radiological Protection (ICRP). The estimated effective dose was ~ 1 μ Sv for one proton radiograph or one frame of fluoroscopy.

The WEL map acquired by TRRT system consists of pixels, each related to protons that have traversed the body, covering both tissues proximal and distal to the tumor. Based on our exploratory study, the total WEL variations are mostly attributed to tumor motion and proximal density and anatomical changes. The WEL of the distal chest wall in our example cases were relatively stable, which makes AP WEL maps adequate range verification tools for proton treatment. However, the effectiveness of the TRRT system was limited. If treatment angles are near the AP direction, depending on

tumor location, WEL range maps still may provide some useful information. However, for lateral fields, given the possibility of rays that traverse the heart, cardiac motion and other factors along the ray path may limit usefulness. Nevertheless, our exploratory study does suggest that location and trajectory can still be quantified from projection/transmission images.

Using the same radiation for treatment and image guidance suggests a possibility of guidance during irradiation. In the initial scenario, a proton radiograph would be acquired prior to treatment to establish tumor position, trajectory, and total range through the patient. A high energy beam would be used to penetrate through the patient for the imaging purpose. In future scenarios, it may be feasible to acquire proton fluoroscopy during treatment if the therapeutic beam (high dose rate, limited range) is interleaved with diagnostic pulses of protons (very low dose rate, long range). This requires a proton beam control system which would be robust enough to accurately control beam to the required therapeutic/diagnostic beam properties and is likely a complex challenging task. Additional studies show the value of image guidance with proton imaging is critical, developments along this line may be warranted.

The exploratory study consisted of three case examples. We are currently studying the target registration error and feasibility of proton radiography in multiple cases, with different locations and motion, and the impact of motion on the dose delivered to the tumor and normal lung. This study will provide a more convincing argument to continue or not, in the development of proton imaging for image guided proton radiotherapy of lung tumors.

V. CONCLUSION

This exploratory study used Monte Carlo methods to optimize the TRRT system as an in-room image guidance for real-time sensing of proton range perturbations during proton treatment. Various proton radiographic/fluoroscopic images have been simulated and their usefulness in providing feedback on proton range fluctuations due to intrafractional and interfractional tumor motions and regression has been analyzed. The tracking of individual proton in Monte Carlo simulations allowed large angle lateral scattering and nuclear events to be rejected, resulting in an improvement in the image quality to a clinically useful level. The quantitative analysis of the 8-week serial 4DCT data provided evidence that the TRRT system is useful in daily QA, image guidance, and adaptive radiotherapy applications. Future work will further compare this method with other in-room imaging methods in terms of patient exposure, sensitivity, treatment planning dosimetry, and signal processing software involving a physical detector system.

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