Three dimensional reconstruction of therapeutic carbon ion beams in phantoms using single secondary ion tracks

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Abstract
Carbon ion beam radiotherapy enables a very localised dose deposition. However, even small changes in the patient geometry or positioning errors can significantly distort the dose distribution. A live, non-invasive monitoring system of the beam delivery within the patient is therefore highly desirable, and could improve patient treatment. We present a novel three-dimensional method for imaging the beam in the irradiated object, exploiting the measured tracks of single secondary ions emerging under irradiation.

The secondary particle tracks are detected with a TimePix stack—a set of parallel pixelated semiconductor detectors. We developed a three-dimensional reconstruction algorithm based on maximum likelihood expectation maximization. We demonstrate the applicability of the new method in the irradiation of a cylindrical PMMA phantom of human head size with a carbon ion pencil beam of \(226\) MeV \(u^{-1}\). The beam image in the phantom is reconstructed from a set of nine discrete detector positions between \(-80^\circ\) and \(50^\circ\) from the beam axis. Furthermore, we demonstrate the potential to visualize inhomogeneities by irradiating a PMMA phantom with an air gap as well as bone and adipose tissue surrogate inserts.

We successfully reconstructed a three-dimensional image of the treatment beam in the phantom from single secondary ion tracks. The beam image corresponds well to the beam direction and energy. In addition, cylindrical inhomogeneities with a diameter of \(2.85\) cm and density differences down to \(0.3\) g cm\(^{-3}\) to the surrounding material are clearly visualized.
This novel three-dimensional method to image a therapeutic carbon ion beam in the irradiated object does not interfere with the treatment and requires knowledge only of single secondary ion tracks. Even with detectors with only a small angular coverage, the three-dimensional reconstruction of the fragmentation points presented in this work was found to be feasible.

Keywords: MLEM, secondary ions, 3D beam monitoring, carbon ion radiotherapy, pixelized semiconductor detector Timepix

(Some figures may appear in colour only in the online journal)

1. Introduction

Compared to conventional irradiations with photons, heavy-ion radiotherapy offers a highly conformal dose deposition to the target volume. This is due to the fact that ions deposit most of their energy in a very sharp, well-defined peak at the end of the ion range, the so-called Bragg peak. With an active beam delivery that scans thin ion pencil beams over the tumour volume, the dose deposition can be precisely tailored to the target, and critical organs in the vicinity are spared. However, this strength of ion beam radiotherapy is also a challenge. Even small changes in patient geometry—such as tumour swelling or shrinking, organ motion, weight gain or loss—or small positioning errors can significantly distort the delivered dose distribution (Enghardt et al 2004). The precise dose localization thus requires a highly accurate beam delivery and quality assurance. While the primary beam parameters such as its direction and the particle fluence can be verified online by an external beam monitoring system, the final dose distribution within the patient is much harder to quantify. A live, non-invasive monitoring system for the beam delivery in the patient is therefore highly desirable.

In this study, we concentrate on carbon ion radiotherapy. Besides dose deposition through coulomb interactions with electrons, the ions also interact with the nuclei, and target and projectile fragments are created. While target fragments predominantly stay at rest, projectile fragments have a velocity similar to that of the primary ion. Thus, most projectile fragments have a longer range in tissue than the primary particles due to their lower mass and charge. This causes a dose tail behind the Bragg peak, which is in the first place an unwanted effect. On the other hand, these secondary charged particles partly emerge from the patient. In addition, photons are produced either in prompt processes or in the de-excitation of radioactive fragments. If any of these by-products of the irradiation can be detected and analysed, they offer additional information about the primary beam in the patient at no extra cost.

All main beam delivery monitoring techniques under development are based on the detection of secondary particles (Kraan 2015). The main treatment verification method currently clinically available is based on positron emission tomography (PET) (Enghardt et al 2004, Parodi et al 2008). Some of the created nuclear fragments are $\beta^+$ emitters and can thus be used for PET imaging. However, this technique suffers from several drawbacks (Knopf and Lomax 2013). If the patient is moved from the treatment position to the PET scanner, physiological processes during the transition time lead to a washout of the $\beta^+$-emitting nuclei (Knopf et al 2009). In addition, the fast signal decay results in long measurement times to achieve reasonable counting statistics. In-beam PET is not affected by these processes; however, it suffers from a high background, and its installation is technically challenging and cost-intensive (Shakirin et al 2011).
To overcome these drawbacks, beam delivery verification based on the detection of prompt gammas (Min et al. 2006, Testa et al. 2008, 2009, Testa et al. 2010, Smeets et al. 2012, McCleskey et al. 2015, Polf et al. 2015) and prompt secondary charged particles (Dauvergne et al. 2009, Amaldi et al. 2010, Henriquet et al. 2012, Agodi et al. 2012, Gwosch et al. 2013, Piersanti et al. 2014, Muraro et al. 2016) has been proposed and is currently being studied by several groups. These techniques potentially permit real-time monitoring of the dose deposition within the patient, since the relevant physical processes take place on short time scales in the order of $10^{-16}$ s (Kraft 2001). The first clinical use of prompt gamma based monitoring has recently been reported, and is undergoing further investigation (Richter et al. 2016). However, dedicated clinical detection systems for beam delivery verification based on prompt secondary charged particles are not available yet.

Previous studies (Agodi et al. 2012, Gwosch et al. 2013, Piersanti et al. 2014) have analysed two-dimensional projections of the beam image in the patient, thus losing information from the three-dimensional problem and increasing uncertainty. Gwosch et al. (2013), for example, considered the intersection points of the measured particle trajectories with the beam plane. This requires an a priori assumption of the position of the beam plane, and the neglected finite beam width smears out the distribution. A three-dimensional reconstruction of the fragmentation points does not suffer from these drawbacks. Two methods to gain 3D images were studied using Monte Carlo simulations in Henriquet et al. (2012), both based on the idea of reconstructing single fragmentation vertices. While vertex reconstruction based on two fragments originating from a single fragmentation event drops the detection statistics rapidly (by about one order of magnitude), finding an intersection point of a primary and secondary ion requires a primary ion detector in the beam, which deteriorates the treatment beam quality. Therefore, another method for 3D beam imaging in the patient, with high statistics, that does not interfere with the treatment, is desired.

Our research group focusses on carbon ion beam monitoring by secondary charged particle tracking with the pixelated semiconductor detector TimePix (Llopart et al. 2007). The technology of particle tracking originally developed in high energy physics is applied to medical physics, where such an approach is not yet common. The TimePix detector can successfully register single ion tracks in carbon ion radiotherapy (Jakubek et al. 2011, Martišňková et al. 2011). An initial study in a homogeneous polymethyl methacrylate (PMMA) phantom (Gwosch et al. 2013) showed that monitoring of the beam width and position with sub-millimeter precision, as well as the detection of changes in the beam range down to 1.3 mm, are possible.

The work presented in this article aims to improve the abovementioned 2D method. We developed a 3D beam image reconstruction based on single measured ion tracks and maximum likelihood expectation maximization (MLEM). This represents a new imaging modality of the beam in the irradiated object. The reconstruction process can be thought of as finding the point of origin of the measured secondary ion tracks. The resulting image, called ‘beam image’ in the remainder of this article, thus shows the fragmentation or interaction point distribution, convolved with the scattering in the patient body or phantom. Firstly, we present a proof-of-principle of this reconstruction in an irradiation of a homogeneous head-sized PMMA phantom with a therapeutic carbon ion beam. To demonstrate the capabilities of the novel method, we subsequently irradiated a phantom with inhomogeneities and investigated if the changes in the geometry are visible in the reconstructed images.
2. Materials and methods

2.1. Tracking of secondary ions with the TimePix detector

The image reconstruction requires directional information of the individual secondary particle tracks, which we register with the TimePix detector (Llopart et al 2007). The TimePix detector is a hybrid semiconductor pixel detector developed within the Medipix collaboration at CERN4. It can detect individual ionizing particles with a very high efficiency (Soukup et al 2011). The detector consists of a $14 \text{ mm} \times 14 \text{ mm}$ semiconductor detector chip, bump-bonded to a pixelated readout chip with $256 \times 256$ square pixels of $55 \mu\text{m} \times 55 \mu\text{m}$ pitch (Llopart et al 2007). In the measurements presented in this article, we used a sensitive layer of 300 $\mu\text{m}$ silicon. Different operation modes allow for the measurement of either the particle arrival time, the energy deposition or the number of hits in a pixel (Llopart et al 2007). In this work, we measured the particle arrival time. The signal is read out in so-called frames with a certain acquisition time that can be chosen by the user, followed by a detector dead time. A global shutter signal delimits the frames. The detector is controlled using the USB-based interface FITPix (Kraus et al 2011), and the software package Pixelman (Turecek et al 2011) is used for data acquisition.

Due to the charge-sharing effect (Jakubek 2009), multiple adjacent pixels register a non-zero signal for a single hit, forming a so-called cluster (Gwosch et al 2013). To guarantee a high quality of the data, we set constraints on the cluster parameters to exclude unwanted events. Only secondary ions are of interest in the reconstruction. At angles larger than $10^\circ$ from the beam axis—the smallest angle used in our experiments (see section 2.2)—the fragment spectrum is dominated by protons (Haettner et al 2013). This is confirmed by the small cluster sizes measured (Hartmann 2013). One-pixel events are attributed to photons or electrons, and hence excluded from further analysis. To exclude malfunctioning pixels or particles arriving just before the start of the frame, clusters with a time stamp at the beginning of the frame are not analysed.

In order to obtain information on the secondary particle trajectories, multiple detectors are combined to form a three-dimensional voxel detector (Soukup et al 2011). Coincident events in the various detector layers can be matched. For all measurements in this study, the coincidence time limit was set to 100 ns (one ADC count).

2.2. Experiments

All experiments were performed at the Heidelberg Ion Beam Therapy Center (HIT), Germany, with the experimental setups shown schematically in figure 1. A cylindrical PMMA phantom of approximately human head size ($\text{radius} = 16 \text{ cm}, \text{height} = 9 \text{ cm}$) was placed in the isocenter of the treatment room. A two-layered TimePix stack (see section 2.1) operated in time mode was mounted horizontally at distance $d$ from the center of the phantom to the surface of the first detector layer. Its vertical center was aligned with the center of the phantom, and the inter-layer distance was 3.6 mm. Measurements were taken at different angles $\theta$ of the center of the sensitive area from the beam axis. In order to facilitate the rotation of the detectors around the phantom, a remotely controllable rotation device was designed.

For the proof of principle, the new imaging modality was tested on a homogeneous PMMA phantom. The TimePix stack was placed at a distance $d$ of 10.3 cm from the center of the phantom, at angles $\theta$ of $-80^\circ, -60^\circ, -40^\circ, -30^\circ, -20^\circ, 10^\circ, 20^\circ, 30^\circ$ and $50^\circ$ from the beam.

4 http://medipix.web.cern.ch/medipix/
The cylindrical PMMA phantom was irradiated with a carbon ion beam with an energy of 226 MeV $u^{-1}$ and a focus of 4.6 mm. The beam intensity and the number of initial particles was adapted to the measurement angle to result in approximately $5 \times 10^5$ measured secondary particles. This corresponds to initial particle numbers of $5 \times 10^9$ particles for angles up to $30^\circ$, and $1 \times 10^{10}$ particles for all larger angles. The reconstruction method is described in detail in section 2.3.

After the successful proof of principle, we studied the possibility of visualizing phantom inhomogeneities. A PMMA cylinder of the same outer dimensions as the homogeneous phantom, but with a cylindrical cut-out with a diameter of 28.5 mm was used (see figure 1). Four different measurement sets were acquired. First, the cut-out (shown in red in figure 1) was filled with a PMMA insert to create a homogeneous phantom as reference ($\rho_{\text{PMMA}} = 1.19 \text{ g cm}^{-3}$). In the second measurement it was left empty ($\rho_{\text{air}} = 0.0012 \text{ g cm}^{-3}$), then filled with a Gammex SB3 bone surrogate ($\rho_{\text{bone}} = 1.82 \text{ g cm}^{-3}$) and lastly filled with a Gammex AP6 adipose tissue surrogate ($\rho_{\text{adipose tissue}} = 0.92 \text{ g cm}^{-3}$)$^5$. Two TimePix stacks were formed to speed up the experiment by measuring at two angular positions simultaneously. We placed the first stack at angles $-50^\circ$, $-30^\circ$, $-10^\circ$ at $d = 10.3 \text{ cm}$, and mounted the second stack at angles $40^\circ$, $60^\circ$, $80^\circ$ at $d = 10.6 \text{ cm}$. The beam energy of 226 MeV $u^{-1}$ and beam width of 4.6 mm were the same for all experiments, while the intensity and particle number were again adapted to compensate for the decreasing yield of secondary ions with increasing angle from the beam axis ($5 \times 10^9 - 1 \times 10^{10}$ initial particles).

2.3. Three-dimensional reconstruction algorithm

Compared to typical reconstruction problems, such as CT-imaging, the monitoring of ion beams using secondary particles as studied in this work poses additional challenges. First of all, no dedicated large-area detection system for the secondary ions is available. With the

\[ \text{Figure 1. Schematic illustration of the experimental setup. The incident ion beam (red) is directed along the z axis. The two parallel TimePix detectors are placed at distance d and angle } \theta \text{ from the center of the phantom. Two different phantoms were employed, a cylindrical homogeneous PMMA phantom and a PMMA cylinder of the same outer dimensions as the homogeneous phantom, but with a cylindrical cut-out with a diameter of 28.5 mm (red). The hole was either left empty or filled with PMMA, bone or adipose tissue surrogates.} \]
Timepix detector (see section 2.1) only a few detector positions can be measured in a reasonable time frame, leading to a small angular coverage of the forward hemisphere. The production of fragments is highly forward-peaked. This, combined with the small size of the detector, results in a limited number of events per detector position at larger angles away from the beam axis. In addition, the measured particle tracks can originate from the whole path of the beam in the patient and thus arrive at the detector from multiple directions. Therefore a re-binning to a parallel geometry or collimation is not feasible.

In a first approach, we investigated a simple volumetric backprojection method. This, however, resulted in prominent streaking artefacts. Due to the limited amount of data, analytical algorithms are not ideal for our purpose. Instead, iterative reconstruction algorithms were found to be better suited. We developed a three-dimensional reconstruction tool based on maximum likelihood expectation maximization (MLEM).

The following outline briefly describes the principle of an MLEM reconstruction, based on Buzug (2008). The reconstruction problem can be expressed as $p = A \cdot f^*$, where $p$ is a vector of the measured quantity, $A$ is a matrix corresponding to the imaging system, and $f^*$ the vector of pixel values of the image that is a priori unknown. The aim of the MLEM reconstruction is to find the most probable solution $f$. The reconstruction thus corresponds to the maximization of the likelihood $L(f)$. A global maximum of the likelihood is found if the derivative is zero and the respective Hessian matrix is negative semi-definite. From these conditions, the following iteration rule can be deduced:

$$f^{(n+1)}_j = f^{(n)}_j \cdot \frac{1}{\sum_{i=1}^{N} a_i} \sum_{i=1}^{N} p_i \cdot a_{ij} \cdot f^{(n)}_j$$

where $p_i$ are the $M$ measured values, $N$ is the number of voxels, $a_{ij}$ are the components of the system matrix, $f^{(n)}_j$ is the current image estimate and $f^{(n+1)}_j$ is the updated image, i.e. the new estimate (Buzug 2008).

We aim for a spatial resolution of 1 mm$^3$ in the reconstructed image (resulting in $2.2 \cdot 10^6$ voxels for the phantom used). In addition, the small pixel pitch of the TimePix detector allows for a very high resolution in the track direction. However, this increases the size of the reconstruction problem to a system matrix with approximately $n \cdot 10^{16}$ entries ($n$ detector positions $\times 256^4$ possible tracks $\times 2.2 \cdot 10^6$ voxels), which is in practice not computable within reasonable computation times. We therefore developed a modified reconstruction method. To reduce the size of the problem, we optimized the data organization. We list all tracks instead of all possible pixel combinations, which reduces the size of the problem by a factor of $10^3 - 10^5$. Additionally, it allows the computation to be carried out subsequently for each measurement position and track, leading to the new iteration rule:

$$f^{(k+1)}_j = \frac{f^{(k)}_j}{\sum_{i=1}^{m} a_{ij}} \cdot \sum_{\text{angles}} \left\{ \sum_{\text{tracks}} \left[ \sum_{i \in \text{track}} \frac{1}{a_{ij} \cdot f^{(k)}_j} \cdot a_{ij} \right] \right\}$$

We implemented the algorithm outlined above in a C++ program. To further decrease the computation time, the normalization to the system geometry, $1/\sum_{i=1}^{m} a_{ij}$, is precalculated. Under the given iteration rule, the likelihood is monotonously increasing. However the images tend to become noisy, since a noisy image corresponds best to the noisy measurement. Therefore, a termination criterion different from simple convergence is chosen, depending on the application.
3. Results

3.1. Proof of principle

The main objectives of this work are to demonstrate the general feasibility of a three-dimensional reconstruction of a beam image in the phantom through the fragmentation points as well as a first analysis of inhomogeneity visualization. For the first application of the reconstruction algorithm to experimental data, the homogeneous phantom was irradiated with a carbon ion pencil beam, and the emerging tracks were registered at nine discrete angular positions between $-80^\circ$ and $50^\circ$ (see section 2.2). The three-dimensional image of the beam in the phantom was reconstructed as described in section 2.3. The projections of the image volume onto the $yz$-, $xz$- and $yz$-planes are shown in figure 2. The colour scale corresponds to the probability of the measured signal originating from each voxel, which is related to the production frequency of secondary particles. Figure 2 depicts the reconstructed image volume after five iterations. This number of iterations was chosen based on visual judgement as the best compromise between limited streaking artefacts and reduced noise.

In all three images, the course of the primary carbon ion beam in the phantom is clearly visible. The signal is most prominent on the central axis of the phantom up to the phantom center. This corresponds to the expected beam region, since the ions were directed at the phantom center along the $z$ axis and stopped in 91.6 mm of PMMA. Only a few traversing tracks behind the beam area can be seen. The limitation of the signal to the phantom volume is an intrinsic property of the algorithm, since the initial image estimate is set to zero outside of the object. The arising noise is on the one hand due to the iterative algorithm itself. In addition, the normalization to the detection geometry results in an increase of the noise. The detectors only cover a small part of the forward hemisphere, and the normalization image is a back projection of all possible tracks. Thus, the fields of view of the individual detector positions overlap partially, and interferences and border effects can occur. Especially patterns such as the prominent points in the lower center of the $yz$-projection (figure 2(a)) are artefacts of the normalization image.

The shape of the beam area is not perfectly symmetric (see figure 2). This can be explained by the choice of the detector positions. The detector was placed, amongst others, at small angles from the beam axis with overlapping fields of view, $10^\circ$ and $20^\circ$. This results in the slightly curved form of the beam area and the signal tail in the center of the phantom.

It can also be observed that the reconstructed beam area does not lie exactly on the central axis of the phantom. This is likely caused by detector setup imperfections. Even small misalignments between the detector layers, in the order of three pixels, or a small rotation of the detector stack by $3^\circ$ can noticeably distort the reconstructed image.
It stands out that more signal in peripheral areas can be seen in the vertical projection (see figure 2(b)) than in the horizontal projection (see figure 2(a)). This can be traced back to the setup geometry. The detectors were placed on a horizontal ring around the cylindrical phantom. Therefore, the precision is better in the horizontal direction, also resulting in lower noise.

The projections onto the three coordinate planes already contain much information about the incident carbon ion beam. However, since they depict the sum of the three-dimensional image along one axis, small structures may be lost in the analysis. To further evaluate the performance of the modified MLEM algorithm, the 1 mm thick $yz$-, $xz$- and $xy$-slices through the center of the beam are given in figure 3. Even though they show only a small portion of the available data, the beam area is clearly visible. As expected, the images appear noisier than the respective projections, but all features of the 3D image are preserved.

3.2. Visualization of target inhomogeneities

In the next step, we applied the new data reconstruction method to a phantom with different inhomogeneities (see figure 1). We aimed to investigate whether the method can directly visualize changes in the geometry. The resulting $yz$-slices through the phantom along the beam axis for all four inhomogeneities are presented in figure 4. On a first glance, the air gap is by far the most obvious. Furthermore, an increase in signal in the region of the inhomogeneity with respect to the reference image figure 4(a) can be clearly seen for the bone insert, while slightly less signal can be observed for the adipose tissue surrogate. These tendencies are in accordance with the density differences and thus the differences in the fragmentation probability between PMMA and the inhomogeneities.

Furthermore, we analysed the signal along the beam axis. To increase statistics, we summed over the central region in $y$-direction, from 70 mm to 90 mm. The curves are normalized to the entrance point, since the entrance material and beam energy are equal in all four cases and hence no differences in the entrance regions are expected. In the plot given in figure 5, the four phantom configurations are well distinguishable.

The signal intensity within the inhomogeneity follows the material density, the highest signal being in the bone surrogate with 1.82 g cm$^{-3}$, followed by PMMA with 1.19 g cm$^{-3}$, adipose tissue surrogate with 0.92 g cm$^{-3}$, and air with 0.0012 g cm$^{-3}$. The early decrease of signal in the bone insert is due to the shorter residual range of the primary particles. The non-zero signal in the air cavity is a result of smearing due to the algorithm, the cylindrical shape of the cavity, and scattering of the secondary particles in the phantom.
Figure 4. Horizontal, 1 mm thick slices through the phantom for the full PMMA phantom (a) and the phantom with air (b), bone (c), and adipose tissue (d) inserts. The region of the inhomogeneity is marked by the small grey circle. Differences from the full phantom can be observed for all three cases.

Figure 5. Projections of the reconstructed images onto the beam axis for different inhomogeneities. Changes in the area of the inhomogeneity (delimited by the grey lines) and the distal edge of the curves are clearly visible. The curves are normalized to the signal at a depth of 0 mm.
4. Discussion

In this article, we have presented a novel method for carbon ion beam radiotherapy monitoring based on single emerging secondary ion tracks. A three-dimensional reconstruction of the beam image from single secondary ion tracks was investigated. A homogeneous cylindrical PMMA phantom of human head-size was irradiated with carbon ion beams, and the secondary particles emerging from the phantom were tracked with a stack of parallel TimePix detectors. We developed a MLEM-based data reconstruction algorithm and showed its general applicability to this data. In addition, we demonstrated the possibility of visualizing phantom inhomogeneities.

Since this method only requires single tracks, the statistics is significantly higher than in interaction vertex reconstruction, which requires two measured tracks from a single fragmentation event (Henriquet et al 2012, Rescigno et al 2014). Compared to investigations of beam monitoring employing a monitoring detector (Agodi et al 2012, Henriquet et al 2012), the presented approach offers the advantage that no material is placed in the beam path in front of the patient. Scattering and fragmentation of the primary particles in this additional material would diminish the beam quality. In previous studies within our group (Gwosch et al 2013), the 2D distribution of intersection points of the secondary particle trajectories with the beam plane was analysed for treatment verification. This introduces uncertainties due to the reduction of a three-dimensional problem to a two-dimensional plane, such as signal smearing due to the neglected finite beam width. Measurements at large angles from the beam axis, as presented in Agodi et al (2012) and Piersanti et al (2014), limit the influence of smearing due to the beam width in 2D approaches. However, this goes hand in hand with a loss of statistics by orders of magnitude. Our three-dimensional approach does not introduce smearing, and allows the use of the forward peaked production of secondary ions. In contrast to beam delivery verification with PET, this new method offers the advantage that no extra time beyond the standard treatment work flow is required.

In this work, a three-dimensional beam image within the phantom was reconstructed from single measured secondary particle tracks. It mirrors the expected fragmentation point distribution, and provides information on both the beam extension and the phantom structure. In clinical applications of this monitoring technique, no extra dose to the patient would be required since the exploited secondary radiation is a by-product of the therapeutic irradiation. Dedicated detectors for this method are not yet available, but the presented results are very encouraging for further development and the application of trackers developed for high energy physics experiments. The TimePix detector proved to be a valuable tool in this approach, due to its high detection efficiency for charged particles and high resolution combined with its small size, straightforward employment and the versatile application possibilities due to the different operation modes and stacking options. Even with the limited number of detectors available, the new modified MLEM algorithm shows promising results. Due to the significant influence of minor positioning uncertainties, thorough positioning and calibration of the detection system is important to fully realize the benefits of the new method.

We demonstrated the ability to detect inhomogeneities with the new data reconstruction algorithm. Materials with a large difference in density of $\Delta \rho \approx 0.6 \text{ g cm}^{-3}$ can be visualized directly. Materials with a smaller density difference of $\Delta \rho \approx 0.3 \text{ g cm}^{-3}$ could be clearly identified in the projection of the data onto the beam axis. In the presented experiments, the density changes were therapy-realistic, but the inhomogeneities were rather large in size, with a diameter of almost 3 cm. In future studies, the achievable spatial resolution of patient-realistic structure changes will be investigated.
Previous studies for beam range monitoring (Agodi et al 2012, Gwosch et al 2013, Piersanti et al 2014) focussed on the distal edge of the distribution projected onto the beam plane. This shift in the distal edge due to the different carbon ion ranges in the inhomogeneities is also clearly observed in our 3D method (see figure 5). The behaviour of the reconstructed beam image with changes in the beam energy will be investigated in future work, but the current results are promising for use in carbon ion beam monitoring.

The results presented above were achieved with measurements at only six defined angular positions of the detector around the phantom, irradiated with a single pencil beam. An increase in image quality and resolution is expected with a ring- or helmet-like detection system covering a larger solid angle in a single measurement. In addition, the third-generation TimePix detectors have a negligible dead time (Poikela et al 2014), which would increase the measurement statistics significantly, approximately by a factor of 150. For this proof-of-principle study we used $5 \cdot 10^9$–$10^{10}$ primary particles. Considering the highly forward peaked production of secondary fragments, this would be reduced to approximately $2.5 \cdot 10^6$ primary particles for a horizontal, semi-circular strip of TimePix3 detectors. Compared to typical beam spots with $10^5$–$10^6$ primary ions, this suggests that monitoring of scanned pencil beams could be possible with such a system.

The very satisfactory results in the visualization of phantom inhomogeneities give rise to a number of possible applications of this novel method. With a larger angular coverage of the detectors and a larger radiation field, prominent structures within the patient could potentially be visualized. These landmarks could be registered to CT images and used as reference points for the beam delivery monitoring, thus leading to a combined patient imaging and beam delivery monitoring system. Previous studies with two-dimensional signals use relative measurements, requiring a calibration of the observed signal, e.g. the distal edge position, to the known particle range in tissue. Possibly, the registration to CT images could eliminate the need for this type of calibration of the range monitoring method, and hence turn the approach into an absolute, real-time measurement technique. The results presented here are a first step towards the feasibility of such an approach. Detailed studies with more patient-realistic setups are planned for the future.

5. Conclusion

We have presented the successful reconstruction of a three-dimensional image of a carbon ion beam image in a phantom. We developed a modified MLEM algorithm to reconstruct the fragmentation point distribution from single secondary ion tracks measured behind the phantom. As a proof-of-principle, the reconstructed image in a homogeneous phantom corresponds well to the distribution expected from the beam energy and shape. In addition, density changes in the phantom down to $\Delta \rho \approx 0.3 \text{ g cm}^{-3}$ could be visualised. Future work includes the investigation of more patient-realistic phantom setups and a thorough calibration of the positioning system. The method would benefit from larger area detectors, but the results with the TimePix detector presented in this work are already promising for carbon ion radiotherapy monitoring.

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