A Novel Method for Fragmentation Studies in Particle Therapy: Principles of Ion Identification

Bernadette Hartmann, PhD\textsuperscript{1,2,3}; Carlos Granja, PhD\textsuperscript{4}; Jan Jakubek, PhD\textsuperscript{4}; Tim Gehrke\textsuperscript{1,2,3}; Raya Gallas\textsuperscript{2,3}; Stanislav Pospišil, PhD\textsuperscript{4}; Oliver Jäkel, PhD\textsuperscript{2,3,5}; and Mária Martišíková, PhD\textsuperscript{1,2,3}

\textsuperscript{1}Clinic for Radiation Oncology and Radiation Therapy, Heidelberg University Hospital, Heidelberg, Germany
\textsuperscript{2}Department of Medical Physics in Radiation Oncology, German Cancer Research Center (DKFZ), Heidelberg, Germany
\textsuperscript{3}Heidelberg Institute for Radiation Oncology (HIRO), Heidelberg, Germany
\textsuperscript{4}Institute of Experimental and Applied Physics (IEAP), Czech Technical University, Prague, Czech Republic
\textsuperscript{5}Heidelberg Ion-Beam Therapy Center (HIT), Heidelberg, Germany

Abstract

**Purpose:** In carbon ion beam radiation therapy, fragmentation processes within the patient lead to changes in the composition of the particle field with increasing depth. Consequences are alterations of the resulting dose distribution and its biological effectiveness. To enable accurate treatment planning, the characteristics of the ion spectra resulting from fragmentation processes need to be known for various ion energies and target materials. In this work, we present a novel method for ion type identification using a small and highly flexible setup based on a single detector and designed to simplify measurements and overcome current shortages in available fragmentation data.

**Materials and Methods:** The presented approach is based on the pixelated, semiconductor detector Timepix. The large number of pixels with small pitch, all individually calibrated for energy deposition, enables detection and visualization of single particle tracks. For discrimination among different ion species, the pattern recognition analysis of the detector signal is used. Fragmentation spectra resulting from a primary carbon ion beam at various depths of tissue-equivalent material were studied to identify different ion species in mixed particle fields. The performance of the method was evaluated quantitatively using reference data from an established technique.

**Results:** All ion species resulting from carbon ion fragmentation in tissue-equivalent material could be separated. For measurements behind a 158-mm-thick water tank, the relative fractions of H, He, Be, and B ions detected agreed with corresponding reference data within the limits of uncertainty. For the relatively rare lithium ions, the agreement was within $2.3 \Delta_{\text{ref}}$ (uncertainty of reference).

**Conclusion:** For designated configurations, the presented ion type identification method enables studies of therapeutic carbon ion beams with a simple, small, and configurable detection setup. The technique is promising to enable online fragmentation studies over a wide range of beam and target parameters in the future.

**Keywords:** carbon ion beam therapy; nuclear fragmentation; ion type identification; pixel; detector Timepix; pattern recognition analysis
Introduction

The number of clinical facilities offering radiation therapy with carbon ion beams has been increasing continuously in the past years [1]. The possibility of reaching deep-seated tumors with a high-dose conformation to the target volume and enhanced biological effectiveness in the target region are the main advantages of this radiation type compared with conventional radiation therapy with photon beams. At the same time, carbon ion beam therapy comprises its own characteristic challenges. In addition to technical demands, ion fragmentation processes represent one of the main physical intricacies. Upon their way through the tissue, the carbon ions interact inelastically with the target nuclei. Those interactions may lead to fragmentation of both the projectile and the target nuclei. Whereas the target fragments essentially stay at rest, the projectile fragments proceed traveling at a velocity close to that of the incident ions [2]. However, because of their lower charge and mass, they experience greater scattering and have a longer range in the tissue, leading to dose depositions beyond the Bragg peak. Moreover, the biological effectiveness of the fragments differs from that of the initial ion species [3]. Therefore, knowing about the characteristics and yields of the fragmentation processes and considering them within physical beam models used in treatment planning are important requirements for carbon ion beam therapy.

Previously, mainly large experimental setups were used for fragmentation studies [4–7]. For that reason, the available data, regarding, for example, initial ion energies in various target materials or setup geometries, are limited. Currently, most data available for carbon ions are based on measurements in water or polymethylmethacrylate (PMMA) phantoms and cover only restricted angles from the beam axis. For other ion species proposed for therapeutic use, such as helium ions, even fewer fragmentation data have been published [8, 9]. To overcome those limitations, we investigated the possibility of performing ion type identification in mixed ion fields with a small-scale and highly flexible setup using a compact detector. This new approach, based on the highly integrated technology of the hybrid semiconductor detector Timepix [10], is designed to allow extensive and flexible investigations of mixed ion field characteristics in terms of the ion type distribution over a wide range of experimental parameters. In the future, such studies will provide the input for benchmarking of Monte Carlo codes used for modeling the transport of therapeutic ion beams and, thus, will have the potential to improve treatment planning of ion beam radiation therapy.

In this work, the main principles and concepts of the novel approach to identification and quantification of primary carbon ions and nuclear fragments of various ion types in mixed fields are presented. The method was validated with reference data from an established ion identification technique, based on an array of scintillating detectors placed more than 3 m apart for time-of-flight and energy-loss measurements [7].

Materials and Methods

Measurements at the HIT Center

The measurements were performed at the Heidelberg Ion-Beam Therapy (HIT) center in Heidelberg, Germany. The HIT center provides radiation therapy with proton and carbon ion beams for, currently, up to 750 patients/y [10]. The ions are accelerated with a linear accelerator–synchrotron combination. For protons, energies of up to 221 MeV can be reached, whereas the maximum energy available for carbon ions is 430 MeV/u [12]. For both ion species, those energies correspond to particle ranges in water of approximately 30 cm.

An active beam application technology [13] in which thin pencil beams are scanned over the lateral extension of the target volume by magnetic deflection is used to enable tumor-conformal, homogeneous dose coverage. After acceleration, the highly energetic ions leave the vacuum pipe through a vacuum-exit window and pass the beam application monitoring system (BAMS). The BAMS, consisting of redundant ionization and multiwire–proportional chambers, controls the beam position and particle fluence for each irradiation spot. In experimental, nonclinical mode, the beam intensity (the number of ions emitted per second) can be adjusted manually. The lowest intensity level used for carbon ion therapy at the HIT center is $10^6$ s$^{-1}$. In this work, substantially lower intensities than those used therapeutically to restrict the number of ions detected per unit time and thus avoid a signal pileup in the detection system. Because the beam intensity used was out of the measurement range of the monitoring chambers, no exact intensity values are given here.

For patient treatment, 2 rooms with fixed, horizontal beam lines and 1 room equipped with a gantry allowing irradiations from 360° are available at the HIT center. Moreover, a room dedicated to quality assurance and experiments, also equipped with a horizontal beam line and equivalent beam scanning technology, is integrated into the facility. All experiments presented in this work were performed at one of those horizontal beam lines.
**Timepix Detector**

**Detector Design and Principles of Operation**

The Timepix detector [10], originally developed by the Medipix collaboration at the European Organization for Nuclear Research (CERN, Geneva, Switzerland) [14] for imaging applications with photon beams, provides dark current–free, quantum-counting sensitivity with a high spatial resolution and a wide dynamic range. Its design benefits from decades of experience in semiconductor detector development for particle physics experiments. The detector features a hybrid design, consisting of a semiconductor sensor layer bump-bonded to the Timepix pixel chip. The readout chip is subdivided into an array of 256 × 256 pixels with a 55-μm pitch, with each pixel containing highly integrated signal electronics. Each readout pixel contains its own preamplifier, a discriminator with a single energy threshold, and a digital counter. For the work presented in this article, the Timepix device was equipped with a 300-μm-thick silicon sensor with a sensitive area of 1.98 cm².

An externally applied shutter signal determines the measuring intervals of the adjustable duration (acquisition time) during which the signal is integrated. After the shutter closes, the accumulated data is read out as a frame. During the readout process, the detector is insensitive, resulting in dead time of the order of 10 ms.

Each pixel can be operated independently in 1 of 3 operation modes [10]. In the counting mode, the number of events registered during the acquisition time is counted. In the Timepix mode, the time of the interaction of the first event during the given measurement interval is registered. In this work, the third mode, the so-called time-over-threshold or energy mode was used. In this mode, the digital counter is incremented continuously, as long as the preamplifier signal stays above the preset threshold. The measured time-over-threshold is correlated to the deposited energy. Thus, in the time-over-threshold mode, the energy deposition of the ionizing radiation in the sensor layer can be estimated.

The signal threshold for the Timepix detector was about 4 keV. This means that when the deposited energy per pixel was above that level, a signal was registered. The energy response for each pixel is calibrated individually, using x-rays of discrete energies from laboratory radioactive sources [15]. Additional response tests on the Timepix detector were performed in vacuum with radioactive alpha sources and low-energy light ions from the Van de Graaff accelerator at the Institute of Experimental and Applied Physics (Czech Technical University, Prague, Czech Republic). The calibration function can be described by a surrogate function, which is nonlinear in the low-energy region (from about 4 keV up to about 25 keV). For higher energies, the function maintains linearity up to approximately 900 keV [16]. Above that level, the pixel electronics start to behave nonlinearly, distorting and finally saturating the per-pixel signal, which needs to be accounted for when operating the detector in a high linear energy transfer (LET) radiation environment, for example, with heavy ion beams.

To operate the detector, the FITPix interface [17] is used. It can be connected to each standard personal computer or notebook via a standard USB 2.0 port. The FITPix interface provides power and the bias voltage to the sensor and controls the data readout. The overall size of the device, including the detector and the FITPix interface, is only about 150 × 50 × 20 mm³. The modular software package Pixelman [18] is used for detector operation configuration and control of the Timepix detector, as well as for data acquisition. Furthermore, it enables online response visualization of the measured signal during data acquisition.

**Single Particle Detection and Ion Type Discrimination by Pattern Recognition Analysis**

To distinguish single particle signals, the beam intensity was decreased below the values used therapeutically (see “Measurements at the HIT Center”). A typical particle rate recorded by the detector over the sensitive area was about 10 particles/ms.

When an ionizing particle traverses the semiconductor sensor, free charge carriers (electron-hole pairs) are released along the particle trajectory. The charge collection on the readout electrode is realized via an external voltage applied to the sensor, the so-called bias voltage. On their way to the pixelated electrode, the charge carriers are subject to electrostatic repulsion and diffusion [19, 20]. Because of that so-called charge sharing, the signal caused by a single ionizing particle can be collected in several adjacent pixels. All adjacent pixels showing a nonzero signal are referred to as a cluster [21]. Additional broadening of the clusters can be caused by a charge, which is induced at the collecting electrodes by the drifting free charge carriers during their collection. The processes described take place during the charge collection and depend on the radial dose distribution around the track in the silicon sensor [22], which is characterized by its radius and magnitude. The specific energy (energy per nucleon) determines the maximum range of the secondary electrons and, thus, the radius of the ion track [23]. The charge of the ion, together with its energy, determines the LET and, thus, the total energy deposited by the ion in the silicon sensor.
Therefore, in general even at the same specific energy, different ion types generally exhibit different microscopic dose distributions. Consequently, clusters corresponding to different ion types with the same specific energy can achieve sizes significantly different. Thus, the cluster size is not equal to the corresponding maximum range of the secondary electrons within a track. Descriptions of the charge sharing and its key processes, including the plasma effect, diffusion, and funneling, can be found in Campbell et al [22].

Examples of clusters observed in proton and carbon ion beams are shown in Figure 1, where the Timepix detector was operated in energy mode. For both ion species, the particles had equivalent residual ranges (approximately 2 cm in water) when passing the detector. A clear dependence of the cluster characteristics, such as per-pixel signal distribution, size, or shape, on the ion species is observable. These characteristics can be analyzed by pattern recognition algorithms and are the basis for the novel ion type identification approach presented in this work. Two cluster parameters are of particular interest: (1) the cluster size, referring to the overall number of adjacent pixels building the cluster; and (2) the cluster volume, provided by the sum of the energy-calibrated signal of all the pixels in the cluster, which is correlated to the total energy deposited by the given particle in the sensor. The discrimination among different ion species in this study was based exclusively on the analysis of the distribution of the measured clusters in those 2 parameters. To assign the single clusters to the different ion species, 2-dimensional (2D) histograms were used, as described in “Identification of Ion Species in 2D Parameter Distributions.”

**Experimental Setup**

Experiments designed to analyze the detector signal under ion irradiation and to identify different ion species, as well as measurements to verify that classification, were performed. In all experiments, the detector was placed perpendicular to the beam. The distance of the detector from the BAMS, depending on the particular experiments, is described in the respective paragraphs below. Water and PMMA phantoms were placed in front of the detector and irradiated with single carbon ion pencil beams.

The Timepix detector settings were chosen according to the results of a systematic study on the detector response to therapeutic ion beams [24]. The acquisition time (frame duration) was set to 1 ms, with a bias voltage of 10 V.

**Data Analysis and Evaluation Parameters**

To evaluate the data obtained, self-written routines were implemented in MATLAB (MathWorks, Natick, MA, USA). In addition, subroutines, written in C++, were integrated to speed up part of the process. For each measurement frame, adjacent pixels with a nonzero signal were identified and defined as a cluster. In this way, the signals created by individual ions were separated and extracted. The cluster parameter sizes and volumes were derived as defined in the “Timepix Detector.”

Only clusters with a size larger than 3 pixels were included in the analysis. In that way, smaller clusters resulting from, for example, light secondary radiation (eg, electrons or x-rays) or noisy pixels, were removed.

Moreover, the cluster roundness was determined, as defined in Opalka et al [25]. To eliminate the signal of mainly light particles (electrons) traversing the detector nonperpendicularly or possible overlapping signals of 2 particles, a constraint on
the cluster roundness was used. Small clusters composed of only a few pixels exhibit naturally less roundness than do larger carbon ion–induced clusters. To account for that, cluster roundness distribution was analyzed for monoenergetic proton and carbon ion beams. Based on that, the following thresholds for cluster size were defined: (1) clusters with 6 or fewer pixels have a roundness of at least 0.6625, and (2) clusters of 120 pixels or more have a roundness of at least 0.7375. The threshold for any other cluster size in between 6 and 120 pixels was obtained by linear interpolation.

Experiments

Identification of Ion Species in 2D Parameter Distributions

The approach to ion type identification with the Timepix detector presented in this work was based on the simultaneous analysis of the clusters parameter size and volumes, as defined in “Detector Design and Principles of Operation.” The 2D histograms showing the distributions of the measured clusters in those parameters were evaluated. For measurements in mixed-particle fields, several areas showing a high concentration of events were visible in the histograms (see, eg, the respective figures in the “Results” section). To correlate them to the different ion species, a PMMA phantom was irradiated with a carbon ion beam, and the fragment distributions obtained from different material depths were compared, exploiting the fundamental knowledge that the lighter ions have longer ranges in tissue.

A carbon ion beam of $E = 271$ MeV/u was used. It was directed onto a PMMA phantom placed in front of the detector. For carbon ions of that energy, the beam range in PMMA was approximately 124 mm. To study fragmentation processes in the entrance region, the Bragg peak area, and the area far behind the peak, the thickness of the PMMA phantom varied between 50 and 448 mm. The results of these experiments are described in the “Identification of Ion Species” section below.

Verification of Ion Species Identification

To verify the identifications for the different ion species, the fragmentation of carbon ions was measured in water. The experimental setup was chosen in analogy to a reference measurement with an established technique based on scintillating detectors and time-of-flight as well as energy-loss measurements [7]. The measurement setup, including target and beam parameters, is depicted in Figure 2. To study the fragmentation spectra at various angles, different lateral detector positions, corresponding to angles of up to $7^\circ$, were used.

Minor differences between the reference measurement and the experimental setup shown in Figure 2 are in the beam width and in the phantom width, as well as in the distances between the vacuum exit window and phantom and the phantom and detector, respectively. However, all of those variations are expected to have only a minor influence on the fragment spectra obtained. The results of the experiments performed to verify the ion species identification are described in “Verification of the Ion Species Identification” within the “Results” section.

Results

Identification of Ion Species

The depth-dependent fragment distribution of the carbon ions ($E = 270$ MeV/u) in a PMMA phantom was studied, as described in “Identification of Ion Species in 2D Parameter Distributions.” In Figure 3, the 2D histograms show the distributions of the clusters by size and volume and were obtained at PMMA depths of 50, 118, 129, and 448 mm. The clear dependence of the
distributions on the material depth can be seen. Several areas showing high concentrations of events are visible. To assign those areas to the different particle species, a comparison was made between the measurements at the various PMMA depths.

As the lightest fragments have the longest ranges in matter, hydrogen ions were expected to be the only ions detected in the area far behind the peak. Based on that knowledge, the high signal area visible in the 2D histogram obtained from a measurement behind 448 mm of PMMA (Figure 3D) can be assigned to clusters created by hydrogen ions. Closer to the peak, at a PMMA depth of 129 mm, 2 further high-signal areas are visible (Figure 3C). Those areas correspond to events induced by helium and boron ions.

The range of the primary particles was approximately 124 mm in PMMA. Therefore, in the measurements at 118 mm PMMA depth (Figure 3B), a signal from the primary particles was expected. A comparison between the distributions obtained behind 118 and 129 mm of PMMA shows an additional high signal area at the shallower depth, which can consequently be assigned to clusters induced by primary carbon ions. The extension of the carbon ion area to lower cluster volumes is due to primary particles arriving at the end of the respective measurement frame. Because the remaining acquisition time was not sufficient to digitize the full signal, a part of the cluster volume was cut. That effect is most prominent for carbon ions because they have the highest energy deposition in the sensor and thus the longest signal-shaping time. However, because, in this analysis, only the number of particles detected was evaluated quantitatively, rather than the corresponding cluster volume, that effect has no influence on the quality of the fragmentation data presented, as long as the signal in this tail area is also considered in the data evaluation.

Two additional high-signal areas are visible in Figure 3B. The area corresponding to very low cluster volumes (around 10–100 keV) and small sizes (around 4–10 pixels) can be assigned to secondary electrons. A further area at high-cluster volumes (around 1000–50 000 keV) with small cluster sizes (around 4–30 pixels) represents clusters containing the remaining signals.
from particles arriving during the detector dead time [24, 26]. For further quantitative evaluations, those events are of no relevance. Thus, they were excluded, exploiting the high average signal per pixel of the corresponding clusters. A constraint on the maximum average cluster signal of 200 keV was found to be appropriate for removing the artifacts.

According to the theoretical models, at 118 and 129 mm PMMA depth, lithium and beryllium fragments, with energy depositions in between those of helium and boron ions, were expected. However, because of their relatively low yield and the influence of energy-loss straggling, no distinct areas relating to those ion species could be identified in the respective 2D histograms.

Figure 3A shows the distributions obtained at the 50-mm PMMA depth, that is, well in front of the Bragg peak. In that depth, regions of clusters created by secondary hydrogen, helium, lithium, beryllium, and boron fragments, as well as primary carbon ions, are clearly distinguishable. These results demonstrate that the fragment species created from primary carbon ions can be detected and distinguished with the technique presented.

Verification of the Ion Species Identification

To verify the identification and separation of the ion species in the 2D histograms, a study of lateral-fragment distribution was performed in accordance to a reference measurement employing an established technique [7]. For example, the cluster size and volume distributions obtained along the beam axis and at an angle of 2° from the beam axis are shown in Figure 4A and B, respectively. High-signal regions related to primary carbon ions, all secondary fragment species expected, and a region of secondary electrons can be identified. As expected, the relative number of the different ion species varies among the positions. Please note the logarithmic scale in the color bar.
For larger angles (4°, Figure 4C), only a few primary carbon ions and heavy fragments were detected, whereas the incidence of light fragments observed was significant. At an even larger angle of 6° (Figure 4D), almost exclusively hydrogen and helium ions were detected.

To enable a quantitative comparison of the relative numbers of fragments detected, regions of interest were defined manually in the 2D histograms, as depicted in Figure 5 for the measurement at an angle of 2°. The definition of those regions of interest was based on 3 basic principles:

1. A detailed understanding of the characteristic detector response to ion beams in the energy ranges investigated. Explaining those characteristics in detail is beyond the scope of this article. The interested reader can find detailed background information in previous publications [24, 26].

2. A fundamental knowledge that, for carbon ions with the same initial energy penetrating the same target material, the lighter the evolving fragments are, the longer their ranges in this material, as described in “Identification of Ion Species in 2D Parameter Distributions.”

3. A comparison of cluster-parameter spectra obtained at various depths in the target material for identical, primary carbon ion beams as shown in the “Results” section.

This method is comparable to the approach used for extracting quantitative spectral data from the energy-loss and time-of-flight distributions in the referenced study [7]. To estimate the uncertainty related to this method, a determination of the regions of interest was repeated at least 3 times, and the mean value, as well as the smallest and largest values, were calculated. In this manner, the number of events registered for the various fragment species was determined for angles of 2°, 4°, and 6°. The measurement on the central beam axis was not included in the analysis because the reference data presented in Haettner et al. [7] are afflicted with large uncertainties for small angles, caused by the primary carbon ion signal screening the fragment data.

In Figure 6, for each measurement angle, the relative fractions of the various ion species detected are compared with the reference measurement [7]. As shown, both methods follow similar trends. Moreover, the relative fractions of hydrogen, helium, beryllium, and boron fragments determined using the novel ion type identification method agree with the reference data within the limits of uncertainty. For lithium, a lower fraction was obtained in the measurements at angles of 2° and 4° compared with the reference study. The relative deviations were 19.7% ± 19.7% –8.5% (2°) and 28.1% ± 14.0 –22.9% (4°).

Discussion

Despite using fundamentally different detection technologies, good agreement was obtained between the results from the novel ion type identification approach presented in this study and the reference measurement. Deviations outside the limits of the measurement uncertainty were observed only for the rare lithium ions. Considering possible imperfections in the experimental setup and variations in the beam parameters could possibly improve the agreement for the relative number of lithium ions detected. Based on these results, the identification of the different ion species in the 2D histograms can be considered correct. Furthermore, quantitative evaluation of the data using regions of ion species defined manually, comparable to the reference method, was found, at first approximation, to be suitable.

As described in “Timepix Detector,” in principle, a direct energy-deposition measurement of each pixel is possible with the Timepix detector. For heavy-charged particles, leading to high-ionization densities, however, values above 1 MeV/pixel can occur. In that case, the response of the electronic chain of the pixels saturates gradually with an increasing charge per pixel [16].
That effect can lead to an underestimation of the measured energy loss of the particle. For that reason, in this article, the signal introduced by an ion was not considered equal to the particle energy loss. Despite possible signal-quenching effects, the distinction of the various ion species, using the cluster parameters of volume and size, was shown to be feasible.

The method presented was designed for the distinction of ion types in mixed ion fields. As discussed above, at present, the method does not provide quantitative measurements of LET or residual energy of the particles in the mixed ion field. However, ion type distributions can be used to improve benchmarking of Monte Carlo codes, which are presently used for modeling nuclear fragmentation processes in tissue. If the distribution of ion types in 3-dimensional space agrees with the Monte Carlo calculations, then the distributions of the residual energies from the ions can also be considered correct.

The analysis of the cluster size and volume distributions at different PMMA depths was shown to provide the resolving power and selectivity among various ion species. Although, in the entrance region, all expected ion species were clearly distinguishable, at increasing PMMA depths, the regions of the various ion species smear and overlap. Those findings correspond to increasing energy-loss straggling of the secondary particles. The effect is of particular significance when the signal of a frequent fragment species overlaps the signal of a rare ion species in the spectra, as, for example, observed for the helium and lithium ions in Figure 3B. The possible overlaps of the regions corresponding to different ion species represent a limitation of the method presented. Therefore, the method can not currently be applied universally but should be restricted to designated ion energy and target configurations, for which the influences of the overlap of the regions are sufficiently low with respect to the required accuracy of the measurements.

The minimum spread of the measured clusters over their volume is given primarily by the energy-loss spread of the mixed ion spectra to be measured. The distance among the regions corresponding to single ion types might further decrease because of detector-related effects, such as the signal quenching discussed above, which might lead to an increase in the overlap for the region of single particles. Consequently, in general, the resulting uncertainty in the results can differ from the values presented, which were valid for the particular combination of the water-equivalent thickness of the target and the beam energy. Therefore, the uncertainty of the method must be evaluated for every case in which the beam energy or the water-equivalent thickness is different. If the resulting uncertainty is larger than the desired accuracy, one option is to divide the target lengthwise to several pieces and perform experiments with correspondingly decreasing carbon ion beam energies. That approach would lead to lower energy-loss spread after each target part and, thus, to the increased accuracy of the measurement.

Because this method is based on a single, small detector, which can be placed close to the target, the resulting spectra are expected to be less influenced by scattering processes in the air behind the target, when compared with data available from previous studies. Therefore, studies with this setup allow separation of the influences of interaction kinematics in the fragmentation processes themselves and scattering thereafter, which is of particular interest in modeling fragmentation processes.
processes in treatment-planning systems and in Monte Carlo simulations. In addition, the technique and the setup can be used at irradiation sites with limited space, as is often the case in clinical treatment rooms.

A further advantage of the method presented can be found in the small pixel size of the detector employed, which enables the detection and analysis of the signal from individual ions in 2D with high spatial and angular resolution. Moreover, the straightforward and easy handling of the detector allows a fast, time-sparing setup of the measurement equipment.

Conclusions

The novel approach to ion type identification presented enables fragmentation studies in mixed-particle fields typical for ion beam radiation therapy. The method provides results comparable to those of conventional methods. In contrast to established techniques, which are mostly based on scintillating detectors and time-of-flight measurements, the new approach relies on a single, compact device, the pixelated, semiconductor-detector Timepix. The main advantage of this method in comparison to previous techniques lies in its simple, small, and highly flexible setup. Consequently, fast and easy sampling of data over a wide range of beam and target parameters is possible. The method is particularly advantageous for ion type identification measurements with ion energy and target thickness combinations for which the influences of energy-loss straggling are low, but for which current methods based on time-of-flight measurements are afflicted with large uncertainties. Therefore, the approach presented is promising to enable different, clinically relevant investigations, complementing existing ion spectroscopy techniques. Among the possible applications for this new method are studies of fragmentation in various materials, as will be presented in a forthcoming publication.

ADDITIONAL INFORMATION AND DECLARATIONS

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

Acknowledgments: This research was performed within the framework of the Medipix Collaboration. The authors would like to thank the Heidelberg Ion-Beam Therapy Center for the beam time and support provided. B.H. was funded by the Virtual Institute ‘Heavy Ion Therapy’ of the Helmholtz Association of German Research Centres, under contract VH-VI-303. M.M. was funded by the Olympia Morata Program of the University of Heidelberg and by the German Cancer Aid. Calibration tests of the pixel detector Timepix were performed at the Van de Graaff light ion accelerator of the IEAP CTU in Prague under the MSMT Grant Research Infrastructure LM2011030 of the Ministry of Education, Youth and Sports for the Czech Republic. The results presented in this article were part of Hartmann, B. A Novel Approach to Ion Spectroscopy of Therapeutic Ion Beams Using a Pixilated Semiconductor Detector [PhD thesis]. Heidelberg, Germany: University of Heidelberg; 2013.

References

1. Particle Therapy Cooperative Group. Particle therapy facilities in operation 2016. https://www.ptcog.ch/index.php/facilities-in-operation. Accessed February 17, 2018.
2. Serber R. Nuclear reactions at high energies. Phys Rev. 1947;72:1114–5.
3. Chu WT. Overview of light-ion beam therapy. In: Hendry J, Vatnitskiy S, eds. Dose Reporting in Ion Beam Therapy: Proceedings of a Meeting Jointly by the International Atomic Energy Agency and the International Commission on Radiation Units and Measurements, Inc. and Held in Ohio, United States of America, 18–20 March 2006; Vienna, Austria: IAEA; 2007:5–28.
4. Golovkov M, Aleksandrov D, Chulkov L, Kraus G, Schardt D. Fragmentation of 270 MeV/u carbon ions in water. In: Amaldi U, Larsson B, Lemoigne Y, eds. Advances in Hadron Therapy: Proceedings of the Second International Symposium on Hadrontherapy, PSI, and CERN, Switzerland, 9–13 September 1996; Amsterdam, the Netherlands: Elsevier Science; 1997.
5. Matsufuji N, Fukumura A, Komori M, Kanai T, Kohno T. Influence of fragment reaction of relativistic heavy charged particles on heavy-ion radiotherapy. Phys Med Biol. 2003;48:1605–23.
6. Gunzert-Marx K, Iwase H, Schardt D, Simon RS. Secondary beam fragments produced by 200 MeV u⁻¹ ¹²C ions in water and their dose contributions in carbon ion radiotherapy. New J Phys. 2008;10:075003.
7. Haettner E, Iwase H, Krämer M, Kraft G, Schardt D. Experimental study of nuclear fragmentation of 200 and 400 MeV/u ¹²C ions in water for applications in particle therapy. Phys Med Biol. 2013;58:8265–79.
8. Rovituso M, Schuy C, Weber U, Bröns S, Cortés-Giraldo MA, La Tessa C, Piasetzky E, Izraeli D, Schardt D, Toppi M, Scifoni E, Krämer M, Durante M. Fragmentation of 120 and 200 MeV u⁻¹ ⁴He ions in water and PMMA targets. *Phys Med Biol.* 2017 Feb 21;62:1310–26.

9. Marafini M, Paramatti R, Pinci D, Battistoni G, Collamati F, De Lucia E, Faccini R, Frallicciardi PM, Mancini-Terracciano C, Mattei I, Muraro S, Piersanti L, Rovituso M, Rucinski A, Russomando A, Sarti A, Sciuumba A, Solfaroli Camillocci E, Toppi M, Traini G, Voena C, Patera V. Secondary radiation measurements for particle therapy applications: nuclear fragmentation produced by ⁴He ion beams in a PMMA target. *Phys Med Biol.* 2017 Feb 21;62(4):1291–309.

10. Llopart X, Ballabriga R, Campbell M, Tlustos L, Wong W. Timepix, a 65k programmable pixel readout chip for arrival time, energy and/or photon counting measurements. *Nucl Instrum Methods Phys Res A.* 2007;581:485–94.

11. Heidelberg Ion-Beam Therapy Center (HIT). facts and figures. https://www.klinikum.uni-heidelberg.de/index.php?id=124447&L=1. Accessed February 14, 2017.

12. Parodi K, Mairani A, Bröns S, Hasch BG, Sommerer F, Naumann J, Jäkel O, Haberer T, Debus J. Monte Carlo simulations to support start-up and treatment planning of scanned proton and carbon ion therapy at a synchrotron-based facility. *Phys Med Biol.* 2012;57:3759–84.

13. Haberer Th, Bechner W, Schardt D, Kraft G. Magnetic scanning system for heavy ion therapy. *Nucl Instrum Methods Phys Res A.* 1993;330:296–305.

14. [CERN] European Organization for Nuclear Research. Medipix. http://medipix.web.cern.ch/medipix/. Accessed February 17, 2017.

15. Jakubek J. Precise energy calibration of pixel detector working in time-over-threshold mode. *Nucl Instrum Methods Phys Res A.* 2011;633(suppl 1):262–6.

16. Granja C, Jakubek J, Köster U, Platkevic M, Pospišil S. Response of the pixel detector Timepix to heavy ions. *Nucl Instrum Methods Phys Res A.* 2011;633(suppl 1):198–202.

17. Kraus V, Holik M, Jakubek J, Kroupa M, Soukup P, Vykydal Z. FITPix — fast interface for Timepix pixel detectors. *J Instrum.* 2011;6:C01079.

18. Turecek D, Holy T, Jakubek J, Pospišil S, Vykydal Z. Pixelman: a multi-platform data acquisition and processing software package for Medipix2, Timepix and Medipix3 detectors. *J Instrum.* 2011;6:C01046.

19. Jakubek J. Energy-sensitive X-ray radiography and charge sharing effect in pixelated detector. *Nucl Instrum Methods Phys Res A.* 2009;607:192–5.

20. Bouchami J, Gutierrez A, Houdayer A, Jakubek J, Lebel C, Leroy C, Macana J, Martin P, Platkevic M, Pospišil S, Teyssier C. Study of the charge sharing in silicon pixel detector by means of heavy ionizing particles interacting with a Medipix2 device. *Nucl Instrum Methods Phys Res A.* 2011;633(suppl 1):117–20.

21. Jakubek J, Cejnarova A, Holy T, Pospišil S, Uher J, Vykydal Z. Pixel detectors for imaging with heavy charged particles. *Nucl Instrum Methods Phys Res A.* 2008;591:155–8.

22. Campbell M, Heijne E, Holý T, Idárraga J, Jakůbek j, Lebel C, Leroy C, Llopart X, Pospišil, Lüstos L, Vykydal Z. Study of the charge sharing in a silicon pixel detector by means of α-particles interacting with a Medipix2 device. *Nucl Instrum Methods Phys Res A.* 2008;591:38–41.

23. Scholz M, Kraft G. Track structure and the calculation of biological effects of heavy charged particles. *Adv Space Res.* 1996;18:5–14.

24. Hartmann B. A Novel Approach to Ion Spectroscopy of Therapeutic Ion Beams Using a Pixelated Semiconductor Detector [dissertation]. Heidelberg, Germany: Ruperto-Carola University; 2013. http://www.ub.uni-heidelberg.de/archiv/15690. Accessed March 29, 2017.

25. Opalka L, Granja C, Hartmann B, Jakubek J, Jaekel O, Martisikova M, Pospišil S, Solc J. 3D measurement of the radiation distribution in a water phantom in a hadron therapy beam. *J Instrum.* 2012;7:C01085.

26. Hartmann B, Soukup P, Granja C, Jakubek J, Pospišil S, Jäkel O, Martišiková M. Distortion of the per-pixel signal in the Timepix Detector observed in high energy carbon ion beams. *J Instrum.* 2014;9:P09006.