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EDITORIAL

Ion and secondary imaging

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1. Introduction

Ion imaging is closely tied to the field of radiation therapy using protons or heavier ions, whose particular dose profile in depth can lead to highly conformal dose distributions. This allows for optimal tumor dose delivery while sparing organs at risk. The high conformity strongly relies on accurate volumetric images as input to the treatment planning software, precise patient positioning on the treatment couch, and information about anatomical changes at the time of the treatment. X-ray imaging can address these aspects (Kurz *et al* 2024, Peters *et al* 2024), but it requires a conversion procedure from photon attenuation coefficients to ion stopping power when used for dose calculation. Ion imaging, on the other hand, directly provides the ion stopping power without any conversion, which has spurred efforts to use ions for imaging in ion beam therapy (Gianoli *et al* 2024a), or their secondaries for beam or range monitoring (Gianoli *et al* 2024b).

Decades after Cormack proposed using ions for tomographic imaging (Cormack 1963), both radiography (2D) and tomography (3D) methods are now being developed, but the field is nascent and is still striving towards clinical implementation. Several areas of investigation have emerged, including tomographic reconstruction methods specific to the physics of ions and the nature of typical datasets; radiography-based imaging systems; tomography-based imaging systems; energy integrating vs ion counting approaches; development of dedicated detectors; small animal imaging systems making use of ions for image acquisition; imaging with heavier ions than protons; foreseen clinical impact of the use of ion imaging in treatment planning, and more. Closely related and of additional interest for this focus issue is the use of secondary particles emitted during photon and ion beam treatments to monitor dose delivery in real time. Such systems use similar detectors as ion imaging systems and share several aspects of the reconstruction process, and here we have seen the first steps towards clinical evaluation of systems based on positron emission tomography (PET) and prompt gamma (PG) imaging.

With this focus collection of Physics in Medicine and Biology, we have attracted original high-quality research that reflects the most recent advances in ion imaging. Several of the submissions collected in this focus collection stem from works presented at the third and fourth *Ion Imaging Workshops* held in Munich in 2022⁷ and in London in 2023⁸, respectively. The papers can be classified in four broad categories: imaging systems, establishment of acquisition protocols with existing systems, image processing methods and use of secondary particles. In the following, we summarize the contributions to the focus collection.

2. Systems

Since the early years of ion imaging research (Bélanger 1959, Koehler 1968, Steward and Koehler 1973a, 1973b), it became obvious that the development of fast, reliable and performant radiography and

⁷ <https://ionimaging2022.sciencesconf.org/>.

⁸ <https://ionimaging2023.sciencesconf.org/>.

tomography systems would be a major challenge and milestone towards clinical application. A variety of prototypes have been designed, built and tested, but a system that fulfills the specifications for clinical use is yet to be constructed.

The paper from Johnson (2024) is a topical review that outlines the system specifications of a (pre-)clinical proton computed tomography (pCT) system. It focuses on the concept of single-particle detection which, while increasing the system complexity, can fully exploit the potential of ion imaging. The paper first highlights the connection between the accelerator type used for creating the beam, especially its beam time structure, and the imaging system. The most complete design of a particle CT system would offer tracking of the protons before and after the imaged object. The paper presents the strengths and weaknesses of the different tracker detector technologies, such as solid state or gaseous detectors. Similarly, it discusses the different solutions for energy detection (calorimeter, range telescope, time-of-flight (TOF)). Besides listing the currently mostly used prototype scanners, it closes with an outlook of the requirements for a (pre-)clinical system: a few MHz acquisition rate, better than 1% relative stopping power (RSP) accuracy, calibration stability and turn-key simplicity of operation.

In Scaringella *et al* (2023), the INFN group presents the energy calibration of their pCT prototype scanner. The energy measurement is the dominant factor for an accurate RSP reconstruction. In the paper, the YAG:Ce scintillating crystal calorimeter was calibrated in a sequence of experiments conducted at the Trento Proton Therapy Centre. The authors first used the accelerator commissioning data and simulations to estimate the exact proton energy impinging on the calorimeter, ranging from 83 MeV to 210 MeV. They report the energy resolution of their system to be better than 1%. A set of tomographic acquisitions of water and polymethyl methacrylate (PMMA) phantoms of different sizes revealed that the achieved RSP accuracy was also better than 1%, thus satisfying one of the main requirements of a pCT system.

The same group investigated in detail the performance of their scanner, using several image quality metrics and comparing it to x-ray CT (Fogazzi *et al* 2023). They scanned, both with the pCT scanner and with a commercial x-ray CT scanner, a cylindrical phantom fillable with either air or water, which contains tissue equivalent plastic materials. The mean RSP accuracy was approximately 0.2%. They also showed that the background material (air or water) affected the spatial resolution of the pCT images. Matching the spatial resolution of the pCT to the x-ray CT system, at $(0.54 \text{ lp mm}^{-1})$ via application of the Hann filter and acquiring both with the same dose level (11.6 mGy), they concluded that pCT images turned out to be less noisy.

In Fogazzi *et al* (2024), the same scanner was utilized for the derivation of a HU to RSP x-ray CT cross-calibration. First, the authors developed biological phantoms (bovine or porcine) and tested their stability. These phantoms were imaged with the pCT prototype and a commercial x-ray CT scanner. Using a stoichiometric calibration, the x-ray CT images were converted to RSP maps. As expected, significant discrepancies were observed between x-ray and proton derived RSP, especially for bone tissues (larger than 3%, accounting for the 5th to 95th percentile of RSP values per 1 HU interval of the calibration). These discrepancies were reduced to less than 2%, when the pCT derived cross calibration was applied to the x-ray CT images. Thus, the authors demonstrated that it is feasible to utilize proton imaging as a calibration tool in the current, x-ray based, imaging workflow for RSP determination.

Energy measuring devices are not the only detector concepts that can lead to accurate measurement of the water equivalent thickness (WET) (which is equivalent to energy loss), required for the determination of the RSP. In Ulrich-Pur *et al* (2024), it is shown that the energy loss of protons in an object can be measured by means of the TOF information. When ions traverse an object, their energy and thus velocity progressively decreases, which leads to an increase of their TOF, as compared to traversing air. This principle was utilized for building the so-called Sandwich-TOF ion imaging prototype. The authors first calibrated their device for TOF to WET, using a set of PMMA slabs of known thicknesses. Subsequently they used their calibrated device for obtaining a proton radiography of an aluminum stair-shaped phantom. Although the WET accuracy was larger than the current pre-clinical goals, the group demonstrated experimentally that TOF-based pCT is technically feasible and also identified the main aspects of the calibration that require improvements.

In the context of the OPTIma project, Winter *et al* (2024) present a new method for registering and interpreting the residual energy of individual protons. To simplify the setup while accelerating data acquisition, they used a calorimeter that sums up all residual energies of all protons that reach it within the duration of one cyclotron cycle (10–14 ns). The single-particle information is not maintained in this type of acquisition, but can be retrieved by posing this as an inverse problem called de-averaging: every proton's trajectory, which is recorded via the tracker, is correlated to its energy loss. Therefore, by reconstructing the trajectories, the single-particle contribution to the summed energy of the calorimeter can be retrieved. The authors simulated the data acquisition of different phantoms and concluded that the RSP accuracy can be better than 1%, as long as the beam flux is not too high (beam current not exceeding 30 pA, noting that minimum cyclotron operation currents are of order 100 pA at the nozzle).

3. Acquisition protocols

Each of the existing ion imaging prototypes has its own limitations, e.g. the range at which it can measure the residual energy of ions traversing the patient. Several authors had previously proposed to modulate the ion beam energy during scanning depending on the WET of the scanned object to acquire ion CT data in the best possible range for the energy detector. Metzner *et al* (2024) describe their first experimental realization at the Heidelberg ion-therapy (HIT) center on several phantoms using the prototype scanner of HIT based on Timepix detectors. Five initial beam energies were calibrated and combined to produce ion radiographies with higher precision, thus improving 2.5 times the single-particle WET precision and reaching values similar to or better than other prototype systems for ion imaging. The technique could also be applied to these other systems to improve their precision since all systems have a precision which depends on the residual energy.

For carbon therapy, the treatment beam can be mixed with lighter helium ions which would fully cross the patient for imaging if the treated target is sufficiently deep. Hardt *et al* (2024) developed a software based on the matRad toolkit for treatment planning and motion verification for this mixed beam approach which includes the parameters of the beam delivery system at HIT and a commercial radiography system. They investigated two clinical scenarios for this mixed approach using Monte Carlo (MC) simulations: inter-fraction setup errors of a prostate patient and intrafractional motion of a lung patient. The developed software is able to predict the dose contribution of helium ions. Interfractional setup errors were estimated with a submillimetric accuracy and intrafraction motion of the patient, freely breathing or breath-holding, were detected. This software is another step towards the clinical implementation of mixed carbon-helium beams for image-guided carbon therapy.

4. Image processing/reconstruction

In the paper from Simard *et al* (2024), a novel method for acquiring and reconstructing proton radiographies in an integrated mode imaging setup was presented. The authors describe an advanced way of reconstructing radiographies, by using a CCD camera to record the signal created by the protons stopping in a scintillator, after having traversed the imaged object. The conventional way of radiographic acquisition is placing the CCD camera at the distal end of the scintillator, integrating the optical signal along the beam's axis. An alternative way would be to place the CCD camera on the side of the scintillator (lateral), thus acting as a range telescope. The authors show that a setup consisting of two lateral cameras can significantly improve image quality, compared to distal or single-lateral views. To utilize the acquired information, they propose a probabilistic, likelihood-based reconstruction method and apply it to simulated as well as experimental data. They quantified a 30%–50% improvement of the spatial resolution and of the reconstructed WET, when using their method.

Single-particle ion CT acquisitions require dedicated processing to reconstruct radiographies and CT images with the highest possible spatial resolution, including the estimation of the ion paths and their use in the reconstruction algorithm. Several algorithms had proposed to reconstruct multiple radiographies for a given beam angle, each with a focus on a different depth of the object. Volz *et al* (2024) investigated a new approach, *focus stacking*, which aimed at processing such a stack of radiographies to obtain a single radiography with the best depth for each visible feature in the projections. Focus stacking uses a combination of elementary image processing such as smoothing and Laplacian filters. They also demonstrate that the selected depth corresponds to the depth of the feature, thus providing a 3D feature detection from a unique single-particle ion CT radiography.

Like all computer-aided scientific fields, machine learning is being increasingly used for processing and reconstructing ion and secondary images. One of the key tools of machine learning is algorithmic (or automatic) differentiation (AD) to automatically calculate the derivatives of a function implemented in a computer program with respect to (some of) its parameters. This is crucial for computing the numerous unknown parameters with respect to the loss function of a given model. Aehle *et al* (2023) studied AD in the specific case of pCT. They investigated specific software parts: the MC simulation of pCT data, the reconstruction of proton tracks from the tracker measurements and model-based iterative reconstruction of the RSP map from single-particle pCT data. They closely analyze the differentiability of these functions by evaluating the variations of the output value(s) with small variations around one of the input parameters. They observe piecewise differentiability with some discontinuities and propose some solutions to mitigate some of them.

5. Secondary emissions

Range monitoring by detection of secondary emissions has a long history in particle therapy, as well summarized in the book chapter by Gianoli *et al* (2024b). Early efforts focused on the use of PET scanners to measure the distribution of β^+ emitters generated by the treatment beam, and subsequent developments seeking to exploit PG emitted by the de-excitation of nuclei. Recently, the use of secondaries such as protons or neutrons that exit the patient has also been proposed and commonly called vertex imaging.

In the paper by Toramatsu *et al* (2023), it was hypothesized that the β^+ emitter biological washout rate may correlate with related washout rates as estimated by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI), which is itself predictive of tumor response to radiotherapy. Six tumor bearing rats were irradiated with a ^{12}C ion beam at the Chiba facility, and the PET prototype of Akamatsu *et al* (2019) was used to perform in-beam measurements, with PET acquisitions lasting 30 minutes. A single tissue pharmacokinetic model was used to extract biological washout parameters, and these were found to correlate linearly with those obtained from DCE-MRI at 7 T. This paper well exemplifies the long running expertise with PET range monitoring, which allows novel applications of the technique.

The second paper related to PET focused on modelling nuclear fragmentation in MC simulations, specifically with the Geant4 framework (Chacon *et al* 2024). That work again made use of the prototype PET scanner of Akamatsu *et al* (2019) to measure β^+ emitter distributions (^{11}C , ^{10}C and ^{15}O) following carbon ion and oxygen ion irradiation of PMMA, polyethylene or gelatin targets. They found variations in performance with different versions of Geant4 and with different physics list settings. It was reported that performance did not necessarily improve with subsequent versions. They finally recommend the use of different versions and models for prediction of total positron yield and the distribution of fragmentation products, the depth of maximum positron yield and the distal 50%-of-peak point.

The PG contributions to the focus collection all relate to MC simulation. Létang *et al* (2024) propose to accelerate such simulations when predicting PG yields by using a track length estimator, which is a common scoring technique to accelerate MC simulation. Their proposed approach includes time tagging to allow keeping track of the emission time for application making use of such information, such as PG timing. Their developments are made available in the latest version of the GATE framework (9.4).

The paper from Werner *et al* (2024) is also on the topic of PG timing. In a simulation study, they propose determining the RSP of protons from PG timing measurements. Such determination relies on an optimization procedure with hyperparameters selected manually for each energy layer. The paper in the focus collection aimed at automating this selection, which led to a reduction of maximum errors.

In their simulation study, Borja-Lloret *et al* (2023) focus on PG detection using Compton cameras. Their work is based on the Medical Applications CompAct COMpton camera developed in Valencia and sought to evaluate the impact of background signals on PG distribution reconstruction. They conclude that time resolutions below 1 ns would be needed.

Finally, the study by Schilling *et al* (2023) is based on the digital tracking calorimeter of the Bergen pCT collaboration for detection of secondary neutral particles for range verification. By analyzing the detection of charged particles created in the digital tracking calorimeter with an uncertainty-aware machine learning algorithm, they could predict the Bragg peak location and its uncertainty. This allowed rejecting treatment plan spots with high uncertainties, leading to a hypothetically more robust plan in terms of range verification.

6. Conclusion

The healthy submission volume to this focus collection highlights the vitality of research in ion and secondary imaging. This is further exemplified by the yearly Ion Imaging Workshop (2024 edition took place in Vienna). This focus collection has made clear that the number of ion imaging systems has been increasing. Nonetheless, clinical implementation remains to be realized. The development of systems of varying complexity may allow determining which approach is the more likely to see clinical usage. We have also seen the positive interplay between ion imaging, which would be done before treatment, and secondary imaging, often proposed as a verification method during treatment.

Data availability statement

No data were used to prepare this editorial. The data that support the findings of this study are available upon reasonable request from the authors.

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