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Control of the dose distribution in charged particle therapy

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The use of ions in radiation therapy aims at improving the selectivity of the irradiation thanks to a favourable depth-dose profile and, in case of heavy ions, to their enhanced radiobiological effect. The treatment modality employing actively scanned pencil beams provides highly conformal dose distributions but is sensitive to uncertainties in the dose calculation, delivery and measurement. During the treatment, the delivery of the beam has to be controlled in real time and monitored with high accuracy, including any effect due to patient positioning and motion. Based on the experience gained in the collaboration with the CNAO (Centro Nazionale di Adroterapia Oncologica, Pavia, Italy), this paper is intended to give an overview of recent techniques and trends for the delivery, measurement and verification of the dose distribution in charged particle therapy with scanned ion beams, focusing in particular on real time and online techniques.

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1. Introduction

What follows is a brief overview of the recent techniques and trends for the delivery, measurement and verification of the dose distribution in charged particle therapy with scanned ion beams. This will be partially focused on the CNAO facility (Centro Nazionale di Adroterapia Oncologica, Pavia, Italy), due to the close collaboration with the INFN (Istituto Nazionale di Fisica Nucleare), and particular emphasis will be given to real-time and on-line techniques, which are sometimes considered at the cutting edge of the actual research.

1.1 Rational for particle therapy

Nowadays, radiation therapy is one of the most successfully applied cancer therapy, second only to surgery, and, in the last few decades, there has been a growing interest toward the use of charged particles [1]. There are basically three main reasons that make particle therapy so appealing [2]. The first one is the favourable dose profile, that is the energy deposited by the radiation as a function of the depth in the patient body, which is characterized by an initial plateau followed by a steep peak (the Bragg peak) in the distal region. This allow to be more conformal in the dose distribution with respect to photon irradiation, especially when treating deep located tumours, lowering the dose to the healthy tissues. The second reason is a better beam collimation inside the target: in fact, the ion beam is mainly broadened by the multiple scattering, which effect is much lower than the one of the Compton effect on a photon beam. The third reason is the higher biological effectiveness of the charged particle, which result more efficient in cell killing with respect to photons. This means that the same level of cell survival is achievable delivering a lower dose to the target.

1.2 Accelerators

Currently there are two kinds of accelerators used in the clinical facilities: synchrotrons and cyclotrons (or synchro-cyclotron). These are far more smaller than the ones used in high energy physics, since the energy are lower, and the more compact the more appealing they are for the hospitals which often have a limited space to install them. The typical diameter of a clinical cyclotron [1] is about 4 to 5 meters and they are currently used only for protons, with maximum energies ranging from 60 to 250 MeV, while the diameter of a clinical synchrotron ranges from 8–10 meters for protons, up to 40 meters for carbon ions, with a maximum energy ranging between 220 to 250 MeV for protons and from 320 to 800 MeV/u in the case of carbon ions. To reduce the machine diameter, in the last years there is a growing interest toward superconducting cyclotrons to be used also for carbon ions [3].

1.3 Delivery systems

There are two techniques to deliver the beam, namely passive scattering and active scanning [4]. In passive scattering, the proton beam is spread by placing scattering material in its path. A single scatterer broadens the beam sufficiently for the coverage of small fields, while, in the case of larger fields, a second scatterer is needed to ensure a uniform dose profile; then a combination of custom collimators and compensators conforms the dose to the target volume. The active scanning,

instead, exploits the ion charge to deflect a narrow "pencil" beam through a couple of bending magnets. Hence the target is divided in monoenergetic layers, and for each of them the dose is delivered in a grid of spot, where the number of particle for each spot is defined by the treatment planning system (TPS). This is the best and most advanced technique since it offers a better conformity to the target [5], avoiding at the same time the need of field-specific hardware (i.e. collimators and compensators) which are responsible for a higher neutron contamination [6]. Nevertheless, besides its proved benefits [7], the so called intensity modulated particle therapy (IMPT), achieved with the active scanning, has also some drawbacks. In particular it is more sensible to patient positioning or moving [8, 9], range uncertainties [10, 11] and dose calculation [12]. Therefore, to preserve its high precision and ensure the stability and reproducibility of the treatment, pencil beam scanning (PBS) requires very accurate control and monitoring systems.

1.4 The CNAO facility

The CNAO medical center is a hospital-based particle therapy facility equipped with a custom synchrotron and dose delivery system (DDS) to provide actively scanned proton and carbon ion beams. The energy ranges from 62 to 228 MeV for protons and from 115 to 400 MeV/u for carbon ions, which correspond to a range in water of 3–32 cm and 3–27 cm respectively. The maximum beam flux is 10^{10} protons per second and 10^8 carbon ions per second, with a full width half maximum (FWHM) at the isocenter of 8–10 mm and 4–6 mm for protons and carbon ions respectively. Three treatment rooms are available, two of which are equipped with a horizontal fixed beam line and the third one has both an horizontal and a vertical fixed lines [13].

The patient treatment control flow starts from the TPS which creates a plan defining the spots, the energies and the number of particles per spot to be delivered. The plan is then extended and sent to the treatment console which dialogues with the synchrotron to set the energy layer by layer and to stop the irradiation when a layer is completed. During the delivery, the beam is extracted and steered by the scanning magnets (section 1.3). Between the magnets and the patient, the beam crosses the monitor chambers that monitor the number of particles and the beam position: if the detected position of the beam is wrong (out of 1 mm from the planned position) a warning signal is sent to the control system that applies an offset to the scanning magnets in order to correct on-line the beam position.

2. Detectors for beam control

2.1 Ionization chambers

The mainstream detectors used as beam monitors are the ionization chambers (IC). As an exemplary case, at CNAO the monitor chambers are enclosed in two independent steel boxes [14]. The first one contains an integral chamber, intended to measure the beam flux, and two strip chambers (128 strips, 1.65 mm wide) to measure the beam position or, better, the projection of the beam on the x and y axis respectively. The size of these detectors is 24×24 cm^2, to cover the maximum beam size. The detector front-end readout is based on custom designed boards, which host application specific integrated circuit (ASIC) electronics custom designed for this purpose [15, 16]. The readout frequency for the integral chamber is about 1 MHz, while for the strip chambers 20 and 10

kHz respectively for x and y strips. The second box is redundant, but required for the certification of the beam, and it is made of a back-up integral chamber and a pixel chamber (32×32 pixels, 6.6 mm wide) which can reconstruct the shape of the beam, which is lost by the strip chambers.

In the case of very high-intensity beams, such as the laser-driven ion beams [17], it may be necessary to correct for the recombination effect observed inside the IC. This could be done exploiting a multi-gap chamber [18, 19, 20] this device includes two or three parallel plate ionization chambers with independent anodes and cathodes separated by gaps of different thickness in order to have different charge recombination effects and therefore different charge collection efficiencies. The charge produced in the gas is proportional to the gap width. However, the charge collected by each chamber is expected to deviate from the gap width proportionality because of the inefficiencies due to charge recombination existing with high intensity beams. The deviation from proportionality can be used to determine the collection efficiency and to correct for it.

2.2 Ultra fast silicon detectors

At the moment, through the monitors chambers described above (section 2.1) it is possible to measure both the beam flux and position. Recently the INFN-Torino is working on a new kind of detectors to be put on the beam line which would be able to count directly the number of particles in the beam. If this would be possible, then this information could be used in combination with the IC measurements to get a direct measurement of the ion stopping power, hence to verify the ion energy. The challenging topic is that to have a maximum uncertainty on the particle range of 1 mm, which is the upper limit for the clinical practice, the number of particles should be measured with an accuracy of about 0.1%. Therefore, considering the high value of beam flux, very fast (i.e. thin) and segmented detectors (to avoid the pile-up effect) are required. To address this issue, we are investigating the possibility of using the so called ultra-fast silicon detectors (UFSD) [21], which exploit the same design of the low gain avalanche detectors for the charge multiplication: a gain of a factor 10 in the signal amplitude is obtained by adding to the silicon detector a layer with a really high doping concentration to reach an electric field of about 300 kV/cm, which is enough to have a good signal and not so much to have problems with the dead time. The time resolution obtained is about 20 ps. Currently, one of the biggest issue is the radiation resistance, because if the doping concentration is altered the gain results rapidly decreasing [22].

2.3 Gas electron multiplier

Recently, there is a new interest in the application of gas electron multiplier (GEM)-based detectors as beam monitor for the daily quality assurance at CNAO. Very preliminary results have been actually published about this topic [23] but they seems to be very promising, and the possibility to use them as substitutes of the strip chambers has to be investigated.

3. Online imaging and range verification

As mentioned in section 1.3, one of the main issues in IMPT is the range uncertainty, since the more conformal is the dose distribution the more sensible is the outcome to deviations from the prescriptions. Imaging techniques play a fundamental role in facing this problem. Moreover, on-line imaging could really improve the control and quality of the particle therapy treatment.

Here I will briefly mention three of the main and most promising imaging techniques, for the characterization of the Bragg peak and control of the dose distribution (a detailed review of this technique is beyond the scope of this paper: for a detailed description see for example [24]).

3.1 Prompt-gamma imaging

The prompt-gamma imaging is based on the idea to reconstruct the position of the Bragg peak exploiting the photons emitted in the wake of the inelastic interaction between the particles of the beam and the nuclei of the target. Currently, there are several methods under development to exploit the prompt-gamma emission [24], but the slit camera [25, 26] is the only system which has been successfully applied in a real patient treatment [27]. This is basically a knife-edge shaped slit collimator which projects the prompt-gamma ray emission profile onto an array of 40 individual scintillation detectors, arranged in two rows and optimized for detecting gamma rays of 3–6 MeV energy, resulting in a spatially resolved gamma profile.

3.2 Ionoacustic characterization of the Bragg peak

One of the emerging imaging techniques which aims at reconstructing the deposited dose profile inside the target is the ionoacustic tomography (IAT) [28] which exploits the so called ionoacoustic effect: when the particle beam crosses the target, a great amount of energy is deposited in correspondence of the location of the Bragg peak. This energy deposition induce a local heating and consequently a fast thermal expansion which generates a pressure wave. Hence, by detecting and mathematically inverting the ultrasound waves, it is possible to reconstruct the deposited dose profile. Recently, it has been published an *in-vivo* proof of this technique [29], used in combination with traditional ultra sound and optoacoustic clinical imaging to reach a submillimiter precision in the localization of the Bragg peak.

3.3 In-beam PET

When traversing the tissues, a small fraction of ions create β^+ emitting isotopes (e.g. ^{11}C, ^{13}N and ^{15}O) through nuclear interactions. The recombination of the emitted positrons with an electron of the surrounding tissue, results in two coincident gammas that can be observed with a positron emission tomography (PET) camera. Details of this technique can be found in references [24, 30], but it is worth to mention that *in-vivo* PET range verification has, in some institutes, moved from a research tool to clinical implementation, such as the case of the OpenPET scanner [31] tested at HIMAC or the INFN-INSIDE project [32] which has been recently tested at CNAO. These systems represent a powerful tool toward a possible image guided particle therapy, which would strongly improve the quality of a particle therapy treatment.

4. The RIDOS system

To address the issue of real-time control of the dose delivered to the patient, a new system, named RIDOS (Real-time Ion DOse planning and delivery System), has been developed by the INFN-Torino group. The goal of RIDOS is to calculate on-line the delivered dose distribution, using the measured data of the beams from the DDS and of the patient's movement, and to compare

it with the planned dose in order to be able, in principle, to correct on-line the treatment in case of deviation from the original plan. This system runs on a dedicated Workstation with a NVIDIA-TeslaK40c and it has been fully integrated in the CNAO DDS. It exploits the duty cycle of the CNAO synchrotron, which has a spill of 1 second and a dead time of 3–4 seconds during which RIDOS is able to evaluate a fast forward planning and a fast gamma index [33] to compare the actual delivered dose with the original planning. This is made by a deep exploitation of the graphic processing unit (GPU) calculation, which allows, in our case, to gain a factor 800 with respect to the existing single core CPU calculation [34]. Moreover, RIDOS is also able to manage the patient 4D-CT together with the information of the real-time respiratory phase, in order to account for intra-fraction target deformation.

5. Conclusion

This paper aimed at giving a brief overview of the main trends for the dose delivery and monitoring in charged particle therapy, with a particular focus on the real-time and on-line techniques which highlight the increasing demands on the accuracy of dose calculations, delivery and measurement. A lot of work is still to be done to achieve a full clinical exploitation of the promising features offered by scanned ion beams.

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