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Nuclear physics and particle therapy

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Abstract

The use of charged particles and nuclei in cancer therapy is one of the most successful cases of application of nuclear physics to medicine. The physical advantages in terms of precision and selectivity, combined with the biological properties of densely ionizing radiation, make charged particle approach an elective choice in a number of cases. Hadron therapy is in continuous development and nuclear physicists can give important contributions to this discipline. In this work some of the relevant aspects in nuclear physics will be reviewed, summarizing the most important directions of research and development.

1 Introduction and basic principles

Charged particle therapy (CPT in the following), or hadron therapy, is an innovative cancer radiotherapy based on nuclear particles (protons, neutrons and light ions) for treatment of early and advanced tumors. In 1946, Robert Wilson proposed the therapeutic use of protons for treating cancer [1]. This is considered as the start of hadron therapy with charged particle. Proton therapy has now become an advanced clinical modality, and CPT with heavier ions (generally ^{12}C) is now becoming more and more attractive. The clinical interest in hadron therapy resides in the fact that it delivers precision treatment of tumors, exploiting the characteristic shape of the Bragg curve for charged hadrons, i.e. dose deposition as a function of depth of traversed matter. As compared to the standard X-ray radiotherapy, accurate and efficient irradiation of the tumor can be obtained reducing the dose to

the surrounding healthy tissue, thus achieving less complication probability. Especially for heavy ions, an increased relative biological effectiveness (RBE) in killing cancer cells can also be obtained, making this approach very interesting in a number of cases and in particular for radio-resistant tumors. After a rather long period in which hadron treatments were exclusively delivered in research laboratories, the first hospital-based treatment centre to be established was that of Loma Linda (USA) in 1990. Today proton therapy has grown into an advanced, cutting-edge clinical modality. According to recent statistics [2], more than 110,000 patients worldwide have been now treated with charged hadrons (about 10% with carbon ions), and the number of clinical centers dedicated to CPT is now rapidly increasing.

Hadron therapy represents a paradigmatic case of a topic in between research and actual clinical practice. It is a discipline in evolution and the contribution coming from nuclear physics has still a fundamental role to help CPT to reach in practice the high level of precision which would be in principle attainable. Several R&D projects are in progress with two main goals: to reduce the costs of infrastructures and treatments and reduce existing uncertainties, such those connected to radiobiology, the knowledge of particle range inside the patient and the monitoring of actual dose delivery during the treatment.

In order to reach these goals, nuclear physics can contribute to different items: i) optimization of treatment procedures and planning; ii) improvement of the present comprehension of radiobiological effects and of the related calculable models; iii) development of new detectors and imaging techniques to achieve specific and optimized monitoring; iv) development of accelerators and of related components; v) improving the knowledge of relevant nuclear processes, like fragmentation, and their modeling; vi) contribute to the development of new therapeutic beams using alternative ion species, like ^{4}He and ^{16}O.

The Nuclear Physics European Collaboration Committee has dedicate its 2014 report to the contribution of nuclear physics to medicine [3] where a comprehensive review of the key issues in CPT can be found. Here we limit ourselves to a few selected issues. In Section 2 the main aspects of nuclear physics relevant for CPT will be summarized. The topic of particle range uncertainties and the development of a specific imaging approaches will be presented in Section 3, while Section 4 will be dedicated to real time monitoring techniques based on the exploiting of nuclear interactions.

2 Nuclear Physics: what really matters

Several nuclear processes are relevant in hadron therapy. Inelastic interactions are responsible of beam attenuation along the longitudinal profile, while elastic scattering, especially in the case of proton therapy, contributes to the transversal profile of dose distribution. Fragmentation of both projectile and target is probably one of the most relevant processes to be studied in detail, since it affects the attenuation of primary beam and the biological effect. Compared to the radiation field of the primary ions, secondary fragments lead to an altered spatial dose distribution due to differing ranges and angular distributions of the fragments and to a modification of the linear-energy transfer (LET) spectra which results in a difference of RBE for the same delivered dose.

Nuclear reactions experienced by the primary and its possible fragments are also responsible of radioactive isotope production, which may be used for monitoring purposes, as mentioned in Section 4, in case of β^+ decaying radionuclides. Last, but not least, nuclear evaporation and de-excitation have to be considered, mostly for the production of lowest energy nucleons in the target. Prompt photon production from gamma–decay is a particularly interesting case, since they can also be used for monitoring. Of great interest, for the same reason, is the production of secondary fast charged particles.

Accurate modeling of all the mentioned processes is one of the most important contributions of nuclear physicists to the discipline of CPT, since an accurate knowledge of ion beam fragmentation is important for a precise description of biological effects inside and outside the treatment volume. Secondly, the precise prediction of nuclear particle interactions and resulting residual nuclei distributions are needed for imaging techniques which aim at in vivo dose monitoring. Important developments in Monte Carlo models have been produced in the last years but still there exist relevant uncertainties. Nuclear reaction models are continually evolving, but the amount of available experimental data and their limited precision (expecially in the case of nucleus–nucleus interaction in the relevant range of energies and masses) is not enough to provide a complete benchmarking. Devoted experiments aimed to measure nuclear cross-section are described in ref. [4, 5]. The relevance of existing discrepancies in numerical models (see for example ref. [6, 7]) should be discussed in the context of clinical applications. The detailed quantitative evaluation of biological dose distributions would require the simulation of a carbon ion treatment field including radiobiological modeling. Still, a simplified calculation for a single Bragg curve can give an estimate the degree of impact on the biological dose. It has been

estimated that, in the case of carbon ions, at maximum around 40% of the dose in the region in front of the Bragg peak is delivered by fragments and that a large fraction of this dose, about 15%, is delivered by protons. A discrepancy in predicted proton fluences of about 30% translates into a difference of 5% in dose delivered by protons. When taking generic values for the RBE of 1.1, 3.0 and 2.0 for protons, primary carbon ions and all other fragments, respectively, and assuming that the 5%dose which is not delivered by protons is delivered by primary carbon ions instead, one predicts an over-estimation of the biological dose of 4%.

3 Imaging for hadron therapy: proton Computed Tomography

The spatial precision of the dose delivered to the volume to be treated is one of the major specific advantages of CPT. However (see [3]) the precise knowledge of the position where particles deliver the maximum dose in the patient (*i.e.* the particle range), remains one of the most important uncertainties. In order to achieve the desired precision goals, the Stopping Power (SP) map of the patient should be reconstructed before the treatment to set up a detailed plan. At present the SP maps are extracted from 3-dimensional images obtained by X-ray Computed Tomography; here the photon attenuation coefficients are translated into SP using conversion tables. This intermediate step introduces an intrinsic uncertainty resulting into an error in the proton range calculation that can be of several millimeters [8]. To mitigate this effect the SP map could be directly determined using a proton beam with kinetic energy larger than the one used for treatment and reduced intensity. Such an imaging system should be able to determine the 3-dimensional SP map with a position resolution less than 1 mm and a density resolution of the order of 1%. A system which aims to fulfill these requirements should be able, at least, to partially overcome the problems introduced by Multiple Coulomb Scattering (MCS) on charged particles crossing matter. In fact typical objects under study could be as thick as 20 cm water equivalent: in this case a 200 MeV kinetic energy proton undergoes a r.m.s. MCS angle of the order of 40 mrad, which corresponds to an r.m.s. projected displacement of about 3.2 mm, considering a 8 cm minimum distance between the target and the detecting plane. The concept is to perform an imaging based on the use of proton beams with energies above 200 MeV.

An example of the research and development work for a prototype of proton Computed Tomography (pCT) is described in ref. [9, 10]. The scanner

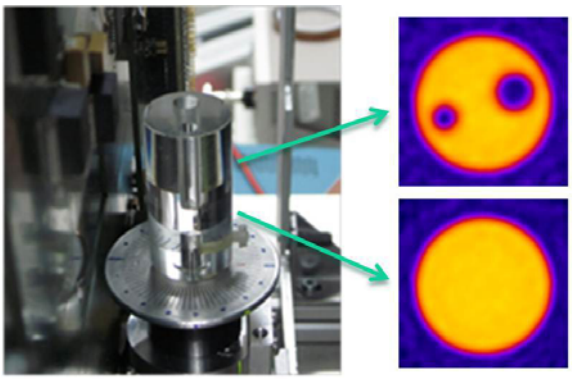

Figure 1: Example of pCT test results for inhomogeneous phantom [10].

is based on a tracker and a calorimeter to measure single protons trajectories and their residual energy. The tracker is composed of four planes of silicon microstrip detectors to measure proton entry and exit positions and angles. Residual energy is measured by a calorimeter composed of YAG:Ce scintillating crystals. A first prototype of this pCT scanner, with an active area of about 55 cm^2, has been constructed and characterized with 60 MeV protons at the INFN Laboratori Nazionali del Sud. A first test to reconstruct the tomographic image of a 2 cm radius, 4 cm high PMMA cylinder has been performed. The phantom, mounted on a rotating platform, has been installed in the middle of the tracker (Fig.1) of the pCT prototype. A total of 36 data sets, each of them containing on average 9.5 10^5 events, have been acquired. The phantom has been rotated by 10^o each run. The 36 profiles have been used as input to a "Filtered Back Projection" tomographic reconstruction algorithm. Fig.1 displays two tomographic sections of the phantom: 4 and 6 mm diameter holes (top) and uniform part (bottom). The reconstruction algorithm has to be verified in a more clinical-like setting (*i.e.* higher proton energy and larger object thickness).

4 Real time monitoring

Beyond the question of Stopping Power determination, the need for a real time monitoring, *i.e.* during the treatments, of actual particle range in the patient is another important goal addressed in present research activity. The uncertainty on the position of the dose release in CPT treatments can be due to different factors, such as quality and calibration of the Computed Tomography (CT) images or possible morphologic changes occurring between

CT and each of the several irradiation sessions, operated in different days, that compose a treatment in CPT. Finally, also patient mis-positioning and organ motion during the treatment itself can be sources of uncertainty. All these effects can add up to give an overall uncertainty of the order of few millimeters [11]. A real time monitoring procedure can therefore increase the quality assurance of a CPT treatment. The techniques proposed for in-vivo range monitoring aim to exploit the secondary production coming from the hadronic interactions of the therapeutic beams. In ref. [12, 13] a discussion of range verification methods and of related physics can be found. Three are the nuclear processes that can yield a radiation suited for this purpose: production of β^+ emitters nuclei, excitation of nuclei and charged particle production in inelastic interactions. In order to make use of these processes, the comparison of measured and pre-calculated distributions of secondary particles is needed (see the discussion in Section 2 about Monte Carlo models).

4.1 In-beam PET

Nuclear β^+ decays produce positrons that can be traced exploiting their annihilation with electrons yielding almost back-to-back 511 keV photon pairs. Since organic tissue is mostly constituted of carbon, hydrogen and oxygen, the most likely β^+ emitting isotopes that can be formed are ^{10}C, ^{11}C, ^{15}O and ^{13}N. Positron Emission Tomography has proven to be the most mature technique for range verification. Original discussion and first investigations are reported in ref. [14–16]. An example of recent research and development activity to design a device to be used in real time during clinical operation is reported in ref. [17]. The proposed system consists of two planar detector heads [18] each having an area of 10×10 cm^2 based on the use of segmented scintillating LYSO crystal matrix. Measured activity results were compared with predictions from the FLUKA MC generator [19,20]. For PMMA phantoms the difference between the MC prediction and the data, considering the distance between the 50% rise and 50% fall-off position of the activity distribution is less than 1 mm [21]. The system showed to be able to detect the presence of inhomogeneities in the phantom.

4.2 Prompt photon detection

Nuclear interactions of the beam in the patient can also excite nuclei along particle path. De-excitation photons which are emitted in a very short (< 1 ns) decay times interval and have a useful energy range extending up to

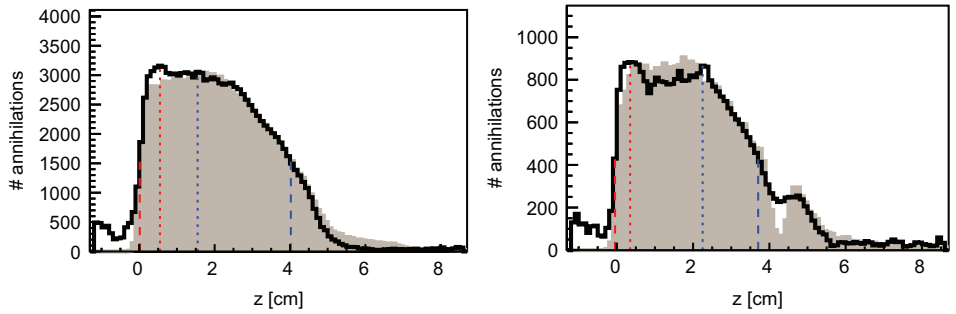

Figure 2: Experimental 1-D activity profiles along the beam direction at 180 s from the beginning of the irradiation, for a homogeneous PMMA phantom (left) and for the same phantom with an air cavity (right). The experimental data, black line, are superimposed to Monte Carlo simulation profile, light brown area. The profiles are normalized. The vertical segmented lines represent: in red the 50% positions for the activity rise and the local maximum of the considered interval; in blue the local maximum of the fall-off used interval and the 50% fall-off positions [18].

about 10 MeV. A review of results on the yields of photons emitted during irradiation with proton and Carbon beams can be found in [22]. At phantom entrance, the average number of detected prompt γ's was found to be of order 10^{-4} per incident carbon ion and 10^{-5} per incident proton. The energies of these prompt photons are too high for standard single gamma detection devices, like SPECT, to be efficient, and dedicated detectors are needed. There are different system at present under investigation. Among them the Compton Camera and the Collimated Camera approaches [23]. A Knife-edge-shaped slit camera [24] is now being developed for clinical application. Promising measurements with a collimated slit-camera prototype, tested with clinical proton beams, have recently been presented in ref. [25]. A precision on single spot range determination of 2 mm is achieved.

4.3 Detection of charged particles

The detection of charged particles can be a promising alternative approach, mostly in the case of CPT performed with ions heavier than protons. Recent studies have been focused on the possibility of exploiting particle production (and in particular the high penetrating proton component) for monitoring purposes, since it can be used to estimate the position of the distal edge of the dose profile. Experimental studies of carbon ion collisions with water reported in refs. [26–29] showed that fragmentation products are peaked in the forward region and mostly contained within few degrees of the beam

axis, apart from protons, that represent the largest sample and show tails at large emission angles and energies. Other measurements performed at small angle [30, 31] suggested that, using solid state tracking devices at 30^o with respect to the beam direction, the distal edge of the beam could be estimated with an accuracy of 1.3 mm. In addition, variations in the beam width could be measured with a precision of 0.9 mm. In principle, due to obvious geometrical considerations, production at large angle is the most interesting case. The quality of the reconstruction of the trajectory of the single charged particle compensates for the reduced statistics expected at large angle.

Experimental data about charged particle emission under irradiation by a therapeutic ion beam can be taken by ref. [32], in which a a $20\times5\times5$ cm^3 PMMA target was irradiated with a 220 MeV/u ^{12}C beam at GSI. Charged particles were identified with tracks reconstructed in a Drift Chamber and a LYSO crystal detector providing Time-of-Flight and scintillation light output information, so to allow particle identification. Measurements were performed at 90° and at 60° with respect to the beam direction. The resulting flux of secondary p per incident ion, measured for the 90° experimental configuration, is

$$\Phi_p(\theta = 90^\circ) \quad = \quad (1.83 \pm 0.02_{\rm stat} \pm 0.14_{\rm sys}) \times 10^{-3}\ sr^{-1}$$

The production region of charged secondary particles has been studied extrapolating backwards the reconstructed tracks, demonstrating the possibility of correlating the spatial profile of emitted particles with the longitudinal dose profile. New preliminary results using ^{4}He and ^{16}O primary ions have been reported at this conference [33].

5 Conclusions

The contribution of nuclear physics to the development of CPT is still fundamental and this review could cover only a very limited part of the research items relevant in this discipline. Several groups in the world, in collaboration with physicians, biologists and medical physicists, are in scientific competition in this area, searching for solutions which can be actually implemented in the clinical practice. An example is the multi-modal system for real time monitoring developed by the INSIDE collaboration [34].

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