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NUCLEUS–NUCLEUS INTERACTIONS AND THEIR APPLICATION IN MEDICINE

G. Battistoni
INFN, Sezione di Milano, Italy

Abstract

The use of charged hadrons (protons 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 therapy an elective choice in a number of cases. Hadron therapy is in continuous development and nuclear physicists can give important contributions to this discipline. The physics of proton–nucleus and nucleus–nucleus interactions plays a fundamental role but there are still important uncertainties. In this work some of the basic elements of Charged Particle Therapy will be summarized in connection to the relevant aspects of the underlying nuclear physics.

1 Introduction

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 [1)]. The original proposal dates back to 1946, when Robert Wilson proposed the therapeutic use of protons for treating cancer [2)]. 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 precise treatment of tumors, exploiting the characteristic shape of the Bragg curve of charged hadrons, *i.e.* dose deposition as a function of depth of traversed matter, exhibiting a sharp peak (the Bragg peak) at the end of the particle range. 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 tissues, thus achieving less complication probability. Especially for heavy ions, an increased biological effectiveness 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, today CPT has grown into an advanced, cutting-edge clinical modality. According to recent statistics [3)], more than 130,000 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. Nuclear physics is still playing a fundamental role to help CPT to reach in practice the high level of precision which would be in principle attainable. The Nuclear Physics European Collaboration Committee has dedicated its 2014 report to the contribution of nuclear physics to medicine [4)] 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 we summarize the basic principles of CPT, while Section 3 will be focused on the relevant nuclear physics for CPT. Section 4 will be dedicated to real time monitoring techniques based on the exploitation of nuclear interactions.

2 The Basic Facts of Charged Particle Therapy

Therapeutic beams are accelerated by cyclotrons (especially for protontherapy) or synchrotrons. The useful energy is determined by the amount of material that has to be penetrated in patients. Typically from 3 to 27 g/cm^3 and this roughly corresponds to 50÷250 MeV for protons and 60÷400 MeV/u for ^{12}C ions. As an example, Fig. 1 shows the synchrotron in operation at CNAO (Pavia, Italy) [5] and capable of accelerating different particles and nuclei, from protons to ^{16}O.

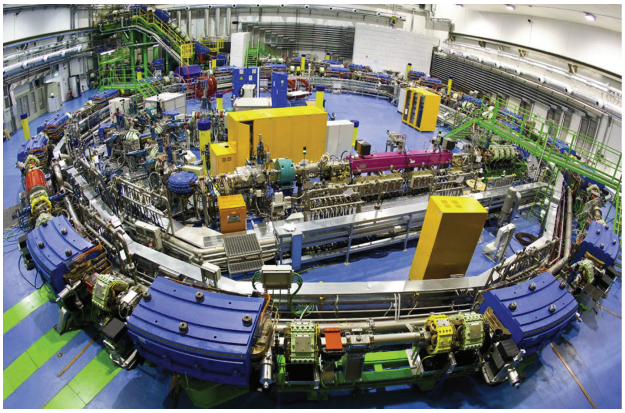

Figure 1: *The CNAO synchrotron* [5].

CNAO is designed for a fully active dose distribution system. This means that the tumor is ideally divided into "slices", *i.e.* in regions that are reached by particles of the same energy. The energy is varied by the synchrotron so as to choose the slice and within the slice the beam moves horizontally and vertically thanks to the finely laminated scanning magnets. Each slice is thus irradiated by "painting" it with a pencil beam. Typical currents can be as high as 10^{10} protons/s or 10^8-10^9 ^{12}C ions/s.

Charged particles loose energy primarily by inelastic collisions with the atomic electrons, resulting in ionization and atomic excitation, while the amount of energy lost due to Coulomb interactions with the material nuclei is instead very small. For charged particles other than electrons the mean ionization en-

ergy loss (or electronic stopping power) can be described by the Bethe-Bloch equation [6]: the growing energy loss with decreasing particle velocity causes the characteristic Bragg peak. The Bragg peak is not perfectly sharp due to energy loss fluctuations (range straggling) and energy spread of the accelerated beams. An example of actual longitudinal dose deposition in water is given in Fig. 2, where we show a comparison of experimental data and simulation for different proton beam energies [7] as measured at CNAO [5].

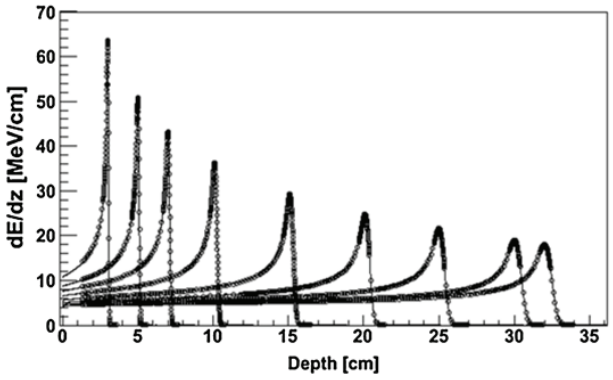

Figure 2: *Comparison of experimental data (dots) and simulation (continuos lines) for ionization energy loss in water at different proton beam energies* [7].

Highly ionizing particles, such as fully ionized nuclei, give rise to an energy deposition in matter with a higher spatial density with respect to protons (and photons). Most of the induced secondary electrons deposit the dose in the center of the primary tracks, within a typical radius of the order of nanometres. This leads to a larger probability of producing complex DNA damages, difficult to repair, resulting in an increased killing capability of cells. This is expressed by means of the concept of *Relative Biological Effectiveness* (RBE) which is defined as the ratio between the absorbed dose of a reference radiation (typically X-rays) and that of the test radiation (for example heavy ions) required to produce the same biological effect. Typically, RBE is determined considering the dose needed to achieve a 10% survival probability of cells in the irradiation. RBE is a very complicated radiobiological concept, which depends on several factors and variables. While in proton therapy a single RBE factor can be

applied throughout the entire radiation field (1.1, *i.e.* they are in average 10% more effective than photons), the situation for the mixed field in heavier ion therapy is much more complex, since RBE is ion-dependent and varies along the ion path.

3 Nuclear Physics and Particle Therapy

Several nuclear processes are relevant in hadron therapy. Inelastic interactions are responsible for 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. Indeed, the most frequently occurring nuclear reactions are peripheral collisions where both beam particles and target may lose one or several nucleons or clusters of nucleons. Those emitted from the projectile fragmentation appear forward peaked in the laboratory frame due to the high velocity of the projectile. The projectile-like fragments continue traveling with nearly the same velocity and direction, and contribute to the dose deposition until they are completely slowed down or undergo further nuclear reactions. Neutrons and clusters from target-like fragments are emitted isotropically and with much lower velocities. The particles ablated from the fireball cover the range between the projectile and target emission. Nuclear fragmentation reactions lead to an attenuation of the primary beam flux and the build-up of lower–Z fragments with increasing penetration depth. These fragments are responsible of the tail beyond the Bragg peak, as shown in Fig.3.

These lighter fragments in general have a RBE factor different from that of primaries, even for the same delivered dose, and Treatment Planning programs for heavy-ion therapy must take into account these effects and their validation against experimental data is mandatory. In order to study such secondary fragments, many experiments have been performed with thick targets made of water or tissue–equivalent materials. The most recent measurements of this kind were performed for carbon ion collisions with water [12, 13, 14, 15]. Devoted experiments aimed to measure nuclear cross-sections have also been designed [16].

Accurate modeling of all the mentioned processes is one of the most im-

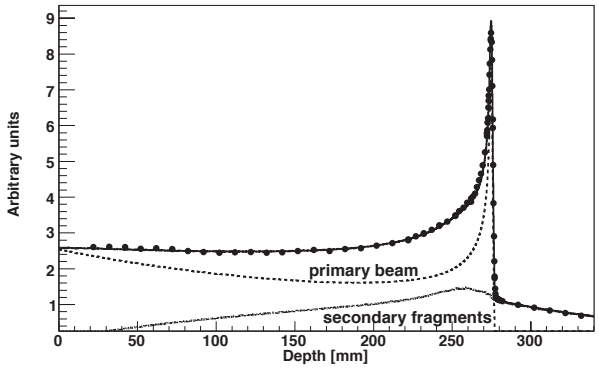

Figure 3: *Bragg curve as a function of depth in water for a 400 MeV/n carbon beam. The points represent experimental data and the solid line represents Monte Carlo calculation (FLUKA code [8, 9, 10]). The calculated dose contribution from primary ^{12}C ions and secondary fragments is shown [11]*

portant contributions of nuclear physicists to the discipline of CPT. The level of accuracy that present Monte Carlo codes exhibit in the description of nuclear reaction models and the level of accuracy in the comparison of predictions with experimental data are encouraging, but there is still ample room for improvement. However, the amount of available experimental data is not enough to provide a complete benchmarking.

4 Nuclear Interactions and Real Time Monitoring

There are uncertainties on the position of the dose release in CPT treatments which are 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 [18]. A real time monitoring procedure can therefore increase the quality assurance of a CPT treatment. Nuclear reactions experienced by the

primary and its possible fragments can be exploited to achieve the goal of in-vivo range monitoring. A discussion of range verification methods and of related physics can be found in the literature [19]. Three are the main nuclear processes that can yield a radiation suited for this purpose: production of β^+ emitters nuclei, gamma de-excitation of nuclei and charged particle production in inelastic interactions. A sketch of the possible useful reactions is shown in Fig. 4. In order to make use of these processes the comparison of measured and pre-calculated distributions of secondary particles is needed. This is a further motivation to push for a continuous upgrade of available Monte Carlo models.

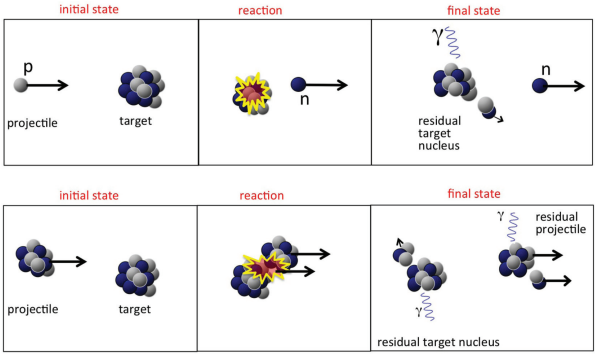

Figure 4: *Sketch of possible nucleon-nucleus reaction in proton therapy (above) and in ion therapy (bottom [19]).*

5 Conclusions

The contribution of nuclear physics to the development of CPT is still fundamental. The study of nuclear fragmentation is one of the most important issues and further work is needed both at experimental level and in model development. Furthermore new nuclear species are under study as therapeutic beams, ^{4}He and ^{16}O being the most important [20]. Important developments are in progress also on the technological side in order to build specific particle detection systems to be used for real time range monitoring.

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