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Relativistic protons for image-guided stereotactic radiosurgery

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Abstract. Bragg-peak radiosurgery and proton radiography have been used in radiotherapy over the past few years. Non-Bragg-peak (plateau) relativistic protons ($E > 1$ GeV) can offer advantages both in terms of precision and target margin reduction, and especially thanks to the possible simultaneous use of high-resolution online proton radiography. Here we will present initial simulations and experiments toward image-guided stereotactic radiosurgery using GeV protons.

1. Introduction

Proton therapy is now a well established method in the treatment of cancer [1] and noncancer diseases [2]. The rationale of using protons with energies between 60 and 250 MeV is based on the favourable depth-dose distribution, so that the targets can be located on a spread-out Bragg peak while the normal tissue is exposed on the plateau region. However, the proton beam is broadened by multiple scattering in the beamline materials and in the patient's body. This broadening produces a "dose halo" in the treatment plan and worsens the dose contours [3]. For a charged particle with atomic number z and mass number A , the lateral scattering is roughly proportional to $z/A\beta^2$ (where β is the ratio of the particle velocity and the speed of light c), and therefore, the lateral scattering can be reduced either using heavy ions such as carbon [4], or by increasing the particle velocity. In the latter case, using protons in the GeV region the targets cannot be exposed on the Bragg peak (for instance, the range of 1 GeV protons is ~ 3.2 m in water), and then requires various beams cross-fired to the target from different angles, similarly to X-ray therapy.

The advantage of the "plateau" (non-Bragg-peak) radiotherapy will be a stable beam profile providing very sharp dose contours for sparing of critical organs. For this reason, relativistic protons were proposed for plateau stereotactic radiosurgery already in Berkeley [5]. The only clinical experience comes from St. Petersburg in Russia: more than 1,000 patients have been treated with 1 GeV protons at the Petersburg Nuclear Physics Institute (PNPI) since 1975, and results were reported in the present journal [6].

Even though the low scattering is appealing, the loss of the favourable dose-depth distribution provided by the Bragg curve is of course a major drawback compared to Bragg-peak radiotherapy. However, an additional advantage of relativistic protons is that the beam crossing the patient can be exploited for proton radiography. Proton radiography was investigated since the early 1970s because of its low radiation dose and high density resolution, but until recently the image blurring due to multiple Coulomb scattering was limiting its practical applications [7]. About a decade ago researchers

of Los Alamos National Laboratory (LANL) have introduced a magnetic lens after the object for imaging and chromatic aberration corrections. This allowed to reach unprecedented spatial resolution with high-energy protons, as proved by many dynamic experiments with 800 MeV beams at LANL [8]. A project for proton microscopy (PRIOR) at the new Facility for Anti-proton and Ion Research (FAIR) in Darmstadt plans to exploit a 4.5 GeV proton beam for radiography, reaching a spatial resolutions below 10 μm and a time resolution below 10 ns [9]. The high-precision in beam delivery combined with online high-resolution imaging and dose verification leads to reduced target margins and improved image-guided stereotactic proton radiosurgery (IGSpRS) for cancer (e.g. small brain metastasis, pituitary adenoma, vestibular Schwannoma) and noncancer (e.g. arteriovenous malformations, trigeminal neuralgia, epilepsy, intracranial aneurysm, macular degeneration) lesions [2] (figure 1).

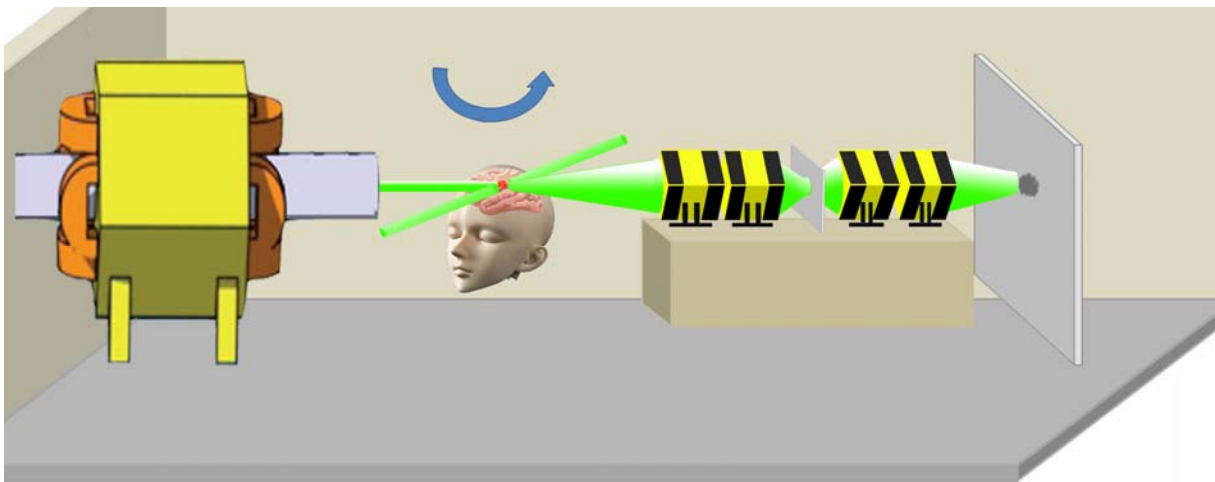


Figure 1. Proposed setup for IGSpRS using relativistic protons. Patient has to be rotated to allow cross-firing of the proton beam from different angles. A magnetic lens system is used for high-resolution radiography. This imaging system makes possible online guidance.

2. Lateral scattering

One advantage of plateau compared to Bragg-peak protons is the reduced lateral scattering. Dose halo due to scattering is indeed a major hindrance for treatment of small targets close to critical organs in protontherapy.

Proton scattering in treatment plans is generally well described by the Molière theory [10]. For small angles, the higher order terms in the Molière theory can be neglected and the beam profile at a depth d into a material of radiation length L_{rad} can be described as a Gaussian with standard deviation (p = particle momentum):

$$\sigma(rad) = 14.MeV \frac{z}{\beta pc} \sqrt{\frac{d}{L_{rad}}} \left[1 + \frac{1}{9} \log_{10} \left(\frac{d}{L_{rad}} \right) \right] \quad (1)$$

Figure 2 shows a beam's eye view of two protons beams going through 15 cm of water. The Monte Carlo simulation by SRIM2011 calculated the xy plane coordinates (in cm) of single protons with initial energy of 1 GeV (residual range in water 322 cm) or 150 MeV (residual range in water 15.6 cm) shot in the (0,0) central position. Clearly, relativistic protons in plateau (blue dots) are very sharp compared to the broad scattering of Bragg-peak protons (red dots).

The reduced lateral scattering is clearly shown in figure 3, where the beam FWHM in water was calculated using either equation (1) or the GEANT4 Monte Carlo code [11]. Beams at energies from 60 to 2500 MeV are simulated. Protontherapy of eye's tumor requires 60 MeV, while deep

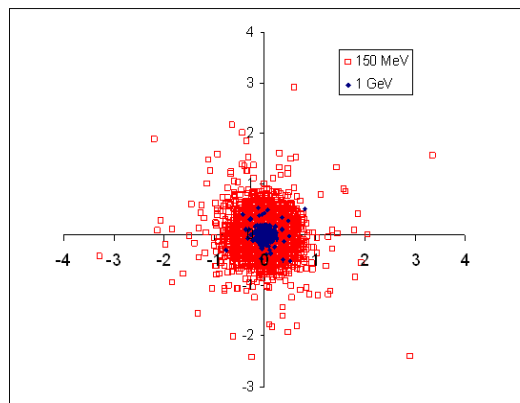


Figure 2. Lateral scattering of proton beams at two different energies after 15 cm in water. Each dot represents a single proton. Simulation by SRIM2011

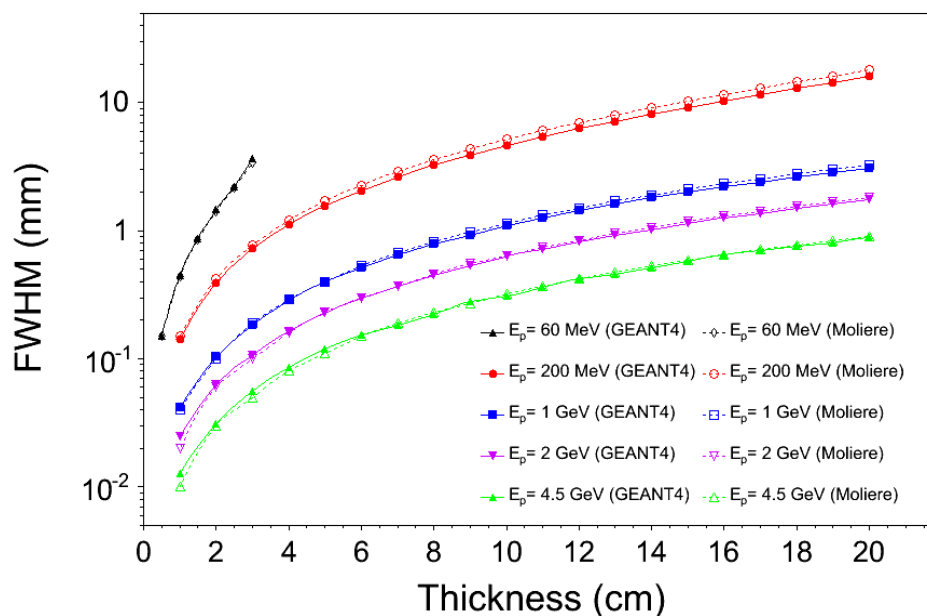


Figure 3. Simulation of the FWHM of proton beams in water at different energies using either a deterministic or a Monte Carlo calculation. Molière equation is shown in equation (1).

protontherapy of solid tumors exploits beams between 150 and 250 MeV. Energies close to 1 GeV (around 800 MeV) are available at Los Alamos National Laboratory (LANL) in USA and ITEP in Russia for proton radiography. These energies can also be reached by medical synchrotrons used to accelerate C-ions up to 400 MeV/n, such as those at HIT in Heidelberg (Germany) and CNAO in Pavia (Italy). Beams of 1-2 GeV are available at several high-energy accelerators with biomedical applications, such as the NSRL at the Brookhaven National Laboratory in USA and SIS-18 at GSI in Germany. Finally, the 4.5 GeV beam has been proposed for proton microscopy at FAIR, the facility under construction in Darmstadt that will exploit the SIS-18 as injector [12].

3. Depth-dose distribution

Although GeV protons must be used in the “plateau” region of the Bragg curve, the depth-dose distribution is not flat. This is caused by the production of secondary protons by nuclear reactions, particularly knock-out and evaporation hadrons. These effects have been carefully studied in the framework of shielding of relativistic protons for space radiation protection [13]. As shown in the Monte Carlo simulation in figure 4, the effect is important, and leads to a 30-40% increase of the dose with depth in a thick (~20 cm) tissue.

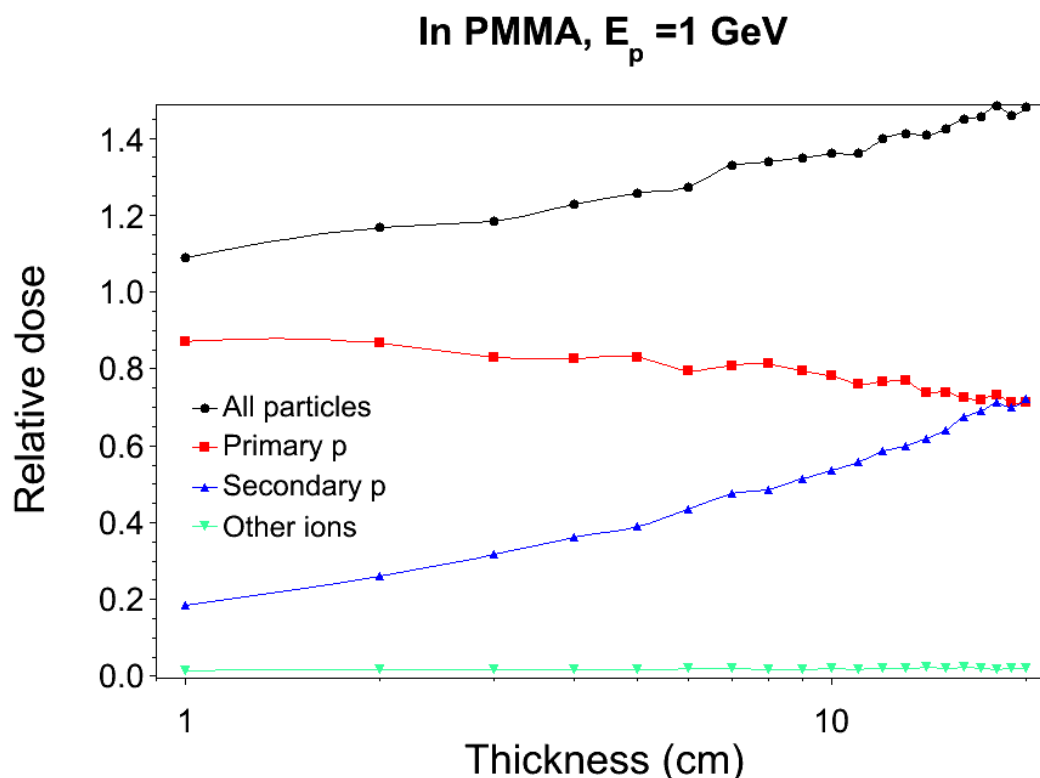


Figure 4. GEANT4 simulation of the dose of a 1 GeV proton beam as a function of the thickness in a plastic (Lucite, PMMA) phantom. Dose is normalized to the entrance value. The contributions of primary protons, secondary protons, and other ions (neutrons, deuterons, tritons, helium, and lithium) are plotted in different colours and symbols.

The increase as a function of the depth is mostly caused by fast knock-out protons. These results and simulations show that in the treatment planning for IGSpRS a careful calculation of the nuclear interaction at relativistic energies is necessary. This will be done within the analytical and Monte Carlo methods developed at the Frankfurt Institute for Advanced Studies (FIAS) [14].

4. Proton radiography

The original idea [15] of proton radiography was to exploit the different ranges of protons crossing structures with different mass thickness, and is indeed now used for quality control in protontherapy [16]. However, a strong image blur is caused by multiple Coulomb scattering. Morris and colleagues in LANL had the idea to compensate the imaging blurring using magnetic lenses (figure 5). Using high-energy protons, optical aberrations are greatly reduced, since both the object scattering and the detector blur are proportional to p^{-1} . The excellent results at LANL [8] for spatial resolution and mass thickness (areal density) measurements led to further plans for high-resolution proton radiography, including the PRIOR at FAIR [9], where 4.5 GeV protons will be used. The PRIOR theoretical spatial resolution is only 20 μm , thus clearly marking a switch from radiography to microscopy. However, these proposals are mostly focused on shock waves, while in our plans (figure 1) we propose to image biological structures, such as tumors, nerves or blood vessels.

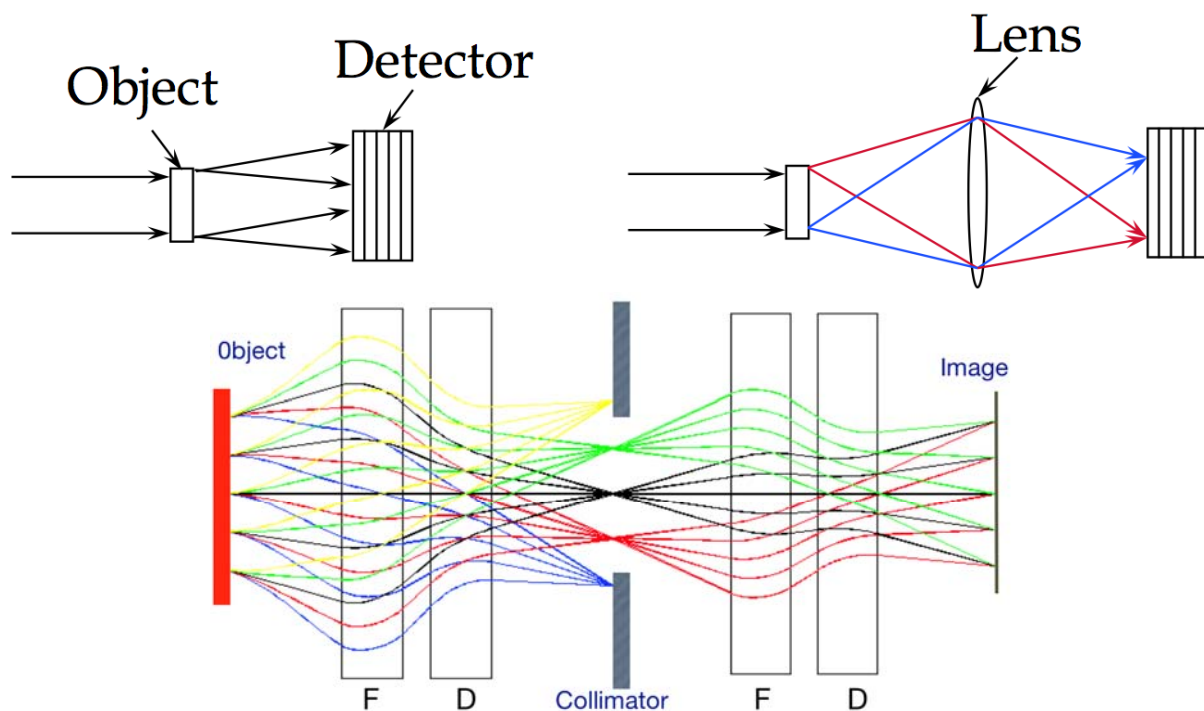


Figure 5. Correction of image blurring in proton radiography using magnetic lenses. The idea was originally proposed by Morris and Zumbro (LANL Technical Report LA-UR-974172, 1997).

The question is therefore whether the novel high-resolution optically-compensated proton radiography can be used for imaging biological objects. A first test has been performed at ITEP in Moscow (Russia), where a proton radiography setup is installed on the 800 MeV beamline. Although the performance was much lower than that expected at PRIOR (e.g. spatial resolution about 0.15 mm), we were able to generate a first image of a zebrafish fixed in paraffin and exposed in a vacuum chamber (figure 6) [17].

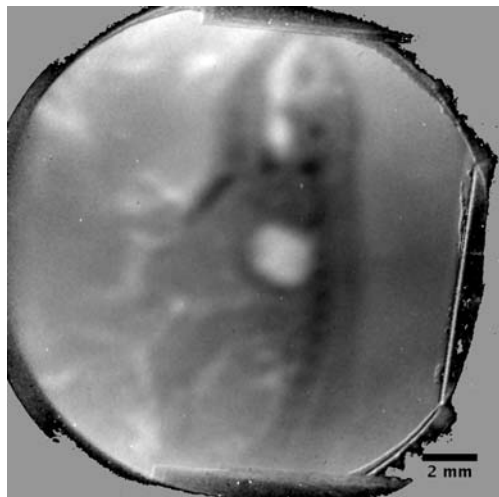
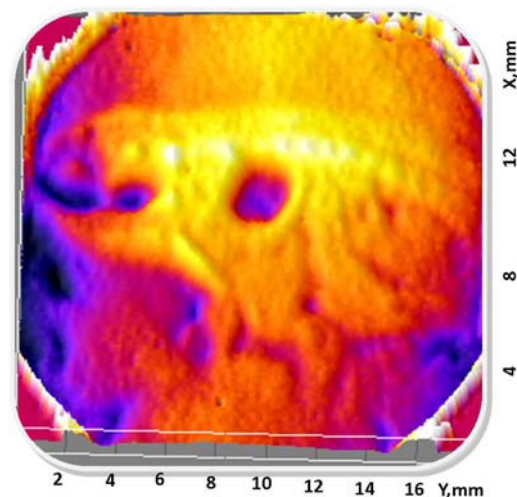
**A****B****C**

Figure 6. First tests of proton radiography at ITEP, Moscow. A zebrafish (*Danio rerio*) fixed in paraffin (**A**) was exposed in vacuum to 800 MeV protons from the TWAC accelerator using the PUMA-x4 microscope. A 7 mm-diameter, 38 mm long collimator has been used for all the measurements at an intensity of about $1\text{--}3\cdot 10^{10}$ protons/image. The images at the scatterer (the position right before the matching triplet upstream the microscope) were analyzed. The beam origin and the beam intensity were determined and the shots with largely different beam positions or beam intensities were excluded from the processing (subjective selection). Then, all the remaining images at the detector plane were summed up for each target irradiation sequence, normalized to the shot intensity. While averaging, a 3 or 5-pixel wide median filter has been applied to each individual image to illuminate the dead pixels due to the neutron background. The same procedure has been applied to the white field measurements. All the intermediate image processing steps have been performed storing the data in the 32-bit float TIFF format, in order to avoid information losses. The resulting averaged target images were divided by the corresponding averaged white fields. The 2D image is shown in panel **B**, and a 3D color- reconstruction in panel **C** (rotated 90° with respect to **B**). The white spot in panel **B** (in false-purple-color in panel **C**) corresponds to the fish's empty swim bladder. Details in reference [17].

Images show both the actual 2D imaging accumulated with 100 pulses from the synchrotron of about 10^{10} protons/pulse, and a 3D color reconstruction of the areal density of the sample. Although this should be considered only as a preliminary test, clearly imaging of biological objects is feasible and can provide quantitative information on the areal density of the target [17].

5. Discussion

We presented a proposal for IGSpRS using relativistic protons (figure 1). Thanks to the low lateral scattering (figure 3) and simultaneous online imaging using the high-resolution proton microscopy setup (figure 5), this setup allows reduction of target margins, sparing of critical structures, and target dose escalation, thus potentially leading to improved clinical outcomes. The first step will be the implementation of a treatment plan for IGSpRS, based on the TRiP98 code developed for heavy-ion therapy at GSI [18]. This development will require careful analysis of relativistic nuclear collisions, which contribute significantly to the dose at high energy (figure 6), in a region where medical physics measurements are absent. Mathematical models developed at FIAS [19] will be used for the implementation of relativistic molecular dynamics in the treatment plan. *In silico* trials will then be run comparing IGSpRS to X-ray stereotactic radiosurgery and heavy-ion therapy. In parallel, proton radiography will be tested at GSI and at other accelerators, based on the first encouraging preliminary results (figure 6). Finally, first tests with animal and anthropomorphic phantoms will be performed at GSI in preparation of the final setup. The encouraging clinical results obtained at PNPI with 1 GeV protons [6] without target imaging, support the rationale for IGSpRS for future clinical applications in radiosurgery at FAIR. This prototype could eventually be adopted by other facilities equipped with high-energy proton and heavy ion synchrotrons in clinical environments.

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