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INVESTIGATION OF A FAST HYBRID SIMULATION APPROACH FOR DOSE CALCULATIONS IN HADRONTHERAPY

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Hadrontherapy is a pioneering technique adapted for the treatment of deep seated localized tumors while preserving healthy surrounding tissues. Ions present physical and radiobiological characteristics that differ from conventional radiotherapy beams (electrons and photons) : a depth dose distribution with a high energy dose delivered at the end of their track, a production of a high local density of electrons which contributes to the death of cancerous cells, a high RBE (relative biological effectiveness) compared to gammas and a weak scattering.

Developing efficient protocols to deliver high doses to tumors while preserving normal tissues requires joint efforts of experts from different special fields (biologists, physicists, engineers, computing experts, etc...). Prominent advances in computer technology have lead to a high interest in Monte carlo (MC) methods (with the GEANT4 toolbox for example). They are the best tools to model all the effects involved in ion irradiations but they are also too slow for an optimized application in clinical practice. Thus there are strong reasons to use analytical calculations, which are still faster and well suited to clinical practice. However they may be relatively inaccurate in highly heterogeneous regions.

The aim of our work is to develop tools for fast and accurate calculation of the dose deposited by a carbon ion beam in a patient described using previously acquired CT images. We propose a hybrid code combining the precision of MC simulation and the rapidity of a deterministic code based on MC generated data. The algorithm is based on the splitting of the fragmentation processes: for each inelastic hadronic collision several sets of secondary particles are created and subsequently processed to deposit their energy in a continuous deterministic way.

To build-up our hybrid simulation, some preliminary GEANT4 studies were carried out to determine the depth dose distributions of all the charged particles involved in an ion irradiation (these distributions constitute the input of the analytical dose deposition). The first dose calculations with a 250MeV/u carbon pencil beam impinging on a water box are validated against full MC simulation.

Real-time control imaging for ion therapy by means of prompt radiation

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We present two ongoing studies aiming at providing a real-time control of the dose distribution during ion therapy. These studies are undertaken in the framework of the National and Rhône-Alpes Regional Research Programs for Hadrontherapy to develop new methods for quality control in future hadrontherapy centers, such as the ETOILE centre in Lyon. The methods under study include in-beam prompt gamma imaging with time of flight and prompt emission of charged particles.

1. Time Of Flight-gamma camera with beam tagging

In order to improve the detection efficiency and the background rejection, we propose a prompt gamma detection method which uses time of flight information to discriminate between photons and massive particles delayed before reaching the photon detector, as compared to direct photons. The concept was tested on a carbon ion beam at GANIL. The photon profile is well correlated to the ion range, whereas that for neutrons steadily increases with depth. Further studies performed at higher beam energies at GSI confirm the correlation between prompt gamma yields and dose profile for carbon ions with longer ranges. This validates the method for the typical energies of carbon ion therapy.

The measured absolute photon yields are encouraging in view of designing a real-time control device during therapy. By increasing the solid angle by two orders of magnitude or more – which is made possible by minimizing the passive shielding against neutrons - enough contrast between the irradiated and non-irradiated zones should be observed within a few seconds exposure, thus allowing a real-time control during patient treatment.

2. Charged Particle Imaging with Vertex reconstruction

The analysis of charged particles, created in the ion interaction and fragmentation processes and emerging from the patient offer a potential complementary opportunity to determine the points of interaction of the primary beam. The principle, which resembles that of vertex identification in fixed target particle physics experiments, is to reconstruct trajectories of the particles emerging form the interactions by a precise charged particle hodoscope and extrapolate them back to their production point. The technique was originally proposed in the context of the CNAO-sponsored AQUA quality assurance program and it is being extensively studied on Geant-4 based simulation and accelerator-measurements carried out by IPN Lyon and TERA. A validation of the simulations using recent data obtained at GSI will be presented.

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Laser-controlled Proton Beam for Medical Imaging

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Proton radiography has not been developed despite international focus on proton therapy as a preferred modality for treating many types of cancers and the increasing number of proton therapy facilities. Proton radiography has long been known to be capable of producing superior radiographic images, but required an innovation in extraction, safety, and control to be commercially feasible in present proton therapy accelerators. Development has been hampered by technical limitations in conventional sweeping systems which draw excessive power and overheat, for example, at a rate appropriate for cardiography (20 images/sec). Although in principle slow extraction from a synchrotron can be gated for cardiography, proton beam radiography remains a prohibitively expensive and almost unused imaging technique under current technology. A new technique would

employ a laser to perform selective extraction of a proton beam from a larger, parent H- beam through the photodetachment process (removing an electron from H-) and separating the neutral species in a fixed, magnetic field followed by foil-stripping of the last electron. The laser beam would thus define the end proton beam and provide powerful control over, including spot size, of the extracted proton beam. Laser beams can further, be rapidly rastored producing a scanned, pencil beam for radiography. The H- solution proposed here can be supported and applied in many existing and certainly future facilities, enabling proton radiography at these facilities. This new technique also addresses targeting, dose control, size and other problematic control issues in proton therapy. A proof of principle experiment has been proposed using the 400-MeV H- beam from the Fermilab linac (in the Mucool Test Area facility). Fast spatial, temporal and intensity modulation of the beam as required for proton radiography would be demonstrated, all under the control of na Nd:YAG laser (the system proposed for this application.)

On the transport of β* production and range modulation for prescribed beam parameters in biological optimized inverse light ion treatment planning.

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The use of light ions for radiation therapy increases the possibility to deliver tumour suicidal doses almost without normal tissue injury, not least in cases where the target is unresectable, radio resistant and located near organs at risk.
The β* projectile beams such as 8B, 9C, 10C, 11C, are clinical very interesting in many aspects, not least due to their reduced fragmentation in relation to the heavies stable isotopes, their potentially enhanced therapeutic efficiency in the Bragg peak region as well as for treatment verification. Since these ions are unstable in their nature, a careful handling of their production is of key importance for realizing their high potential in their clinical application. Futhermore, in the case when the beam energy of the generated β* ions not easily can be varied, such in the use of cyclotrons, there is a need to adjust the energy of and thus the range of the particles. The present study focuses on an analytical transport of β* production and range modulation in the case when a high energy 11C beam are produced in a secondary beam line through projectile fragmentation. The analytical transport was compared with the Monte Carlo code SHIELD-HIT + . in which the fluence distributions, differential in energy and angle, were used to calculate the depth variation of quantities such as the planar fluence, energy fluence of all particle species.
The analytical results illustrate a good description of the build up of the physical quantise of the produced β* fragments in the given target as well as their transport in use of range shifter. The optimal media properties, such as target thickness, can thus be analytically determined so that the prescribed beam parameters in the patient are obtained.

TRACK STRUCTURE EFFECTS IN A STUDY OF CELL KILLING IN NORMAL HUMAN SKIN FIBROBLASTS

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To study track structure effects in cells irradiated by heavy ions, we have performed a model analysis of an extensive data set published by Tsuruoka *et al.* [1] of over 40 survival curves of normal human skin fibroblast cells irradiated *in vitro* by energetic carbon, neon, silicon and iron ions measured in track-segment conditions. This data set which refers to an experiment performed in a single laboratory covers an unusually broad range of track-segment LET values from different ion species with considerable overlap of their LET values. We have fitted four parameters of the cellular track structure theory (Katz model) [2] and demonstrate a systematic interpretation of this

data set, highlighting effects specific to track structure. In particular, we model the dependence of RBE and "single-particle:" and "extrapolated" cross-section on LET or Z^{*2}/β^2 and suggest that the biological effects of charged secondary particles generated by degrading the energy of the primary ion beams by Lucite absorbers cannot be ignored, especially at the highest values of LET.

References

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Premature cellular senescence in normal human endothelial cells as a non-lethal effect of low doses of ^{12}C ions: implications for hadrontherapy

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Non-cancer biological effects of ionising radiation exposure are of relevance for predicting normal tissue damage arising from radiotherapy. As ^{12}C ion-based radiation treatment of cancer is looking increasingly promising, it is necessary to investigate its late effects, which are largely undetermined. Stress-induced premature senescence (SIPS) is attracting interest as a cellular response to sublethal stimuli including ionizing radiation (IR). Its underlying molecular mechanisms are not clear. Furthermore, *in vivo*, accumulation of prematurely senescent cells in a normal tissue can impact its performance and accelerate its degeneration. On the other hand, the efficacy of sublethal doses to impair tumour vasculature is much desirable. Therefore, we exposed a model system (HUVEC or human vein endothelial cells) to the GSI carbon ion beam used for therapeutic purposes, at both the LET values incurred by normal (plateau region) and tumour (spread-out Bragg Peak) cells. X-ray irradiation was used as a reference. The onset of cellular senescence was studied by beta-galactosidase expression in the progeny of irradiated or control cells and related to measurements of telomere length. The latter was performed by means of an automated system that allows recognition of interphase cells labelled by a pan-telomeric fluorescent probe and a centromere-directed probe (IQ-FISH). Relative telomere length was obtained by the fluorescence intensity ratio between the two markers. In our hands, the senescent phenotype was found to occur at early times post irradiation and was efficiently induced by doses as low as 0.1-0.5 Gy of carbon ions from the plateau region of the Bragg curve. A significantly higher fraction of senescing cells compared to sham-irradiated cells was also found to occur following SOBP irradiation despite the incidence of lethal damage being associated with the higher SOBP LET. Mean telomere length reduction was shown to accompany both physiological and radiation-induced senescence. However, telomere shortening was more pronounced after low-LET irradiation, whereas carbon-irradiated senescent cells showed a telomere shortening similar to that measured in controls. This suggests telomere length attrition as a driving molecular mechanism for SIPS after low LET-irradiation but of no apparent relevance for carbon ion-induced senescence. Telomere temporal stability is critical for maintenance of genomic stability and suppression of carcinogenesis. These results may bear important implications for normal tissue adverse effects as well as for desirable tumor vasculature impairment following hadrontherapy.

Interlacing arrays of parallel carbon microplanar beams: ablating a target in the rabbit brain

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Radiation therapy and radiosurgery have limitations in controlling certain types of CNS tumors including high grade gliomas and pediatric brain tumors. The limitations come in part from a) the radioresistance of the gliomas, requiring high tumor doses, and b) the risk for delayed radiation effects in the CNS tissues surrounding the tumor, which not only limits the deliverable tumor dose but also prevents re-treatment of recurring tumors. The method "interlaced carbon microbeams", being developed at the NASA Space Radiation Laboratory (NSRL), Brookhaven National Laboratory (BNL) addresses both these limitations. The method rests on the remarkable tissue-sparing effect of arrays of parallel, thin planes of radiation, called microplanar beams or microbeams. This sparing effect, which was originally observed with synchrotron-generated x rays beams of about 25 µm thickness (Slatkin et al, PNAS 1995), was later confirmed to a limited extent with 0.37-0.68 mm-thick x-ray beams, and very recently with heavy ion beams of 0.3 mm. The other component of the method, namely interlaced microbeams, was also developed first with x rays (Dilmanian et al, PNAS 2006). Here the tumor is exposed to two arrays of horizontal microbeams aimed at the tumor from 90º angles. The thickness of each microbeam is equal to the gap between then beams and one array is vertically shifted with respect to the other by the thickness of the microbeams. In this way the two arrays interlace at the tumor, producing a non-segmented radiation field there. As a result the target can receive a lethal dose of unsegmented radiation while the surrounding normal tissues are spared because they are exposed to single arrays of microbeams, which are safe at the dose where unsegmented radiation ablates the tumor. To examine the sparing effect of heavy ion microbeams in the CNS we irradiated the brains of adult rats with four parallel 0.3-mm thick 12 mm wide iron microbeams of 600 MeV/nucleon, spaced 3.5 mm on-center at up to 20 Gy physical dose (and substantially higher "Gy equivalent (GyE)" dose). H&E histology three months later showed no damage. Next, we examined the extent of beam broadening, i.e., angular straggling, of carbon microbeams in a Bang-gel phantom using arrays of 148 to 250 MeV/nucleon 0.3 mm-thick carbon beams spaced 0.9, 1.0., 1.1, 1.2, and 1.3 mm on-center and imaged them optically. The results showed that the beam broadening does not pose a problem at least for targets of about 10 cm depth. Finally, two rabbits were irradiated in their cerebrum with interlacing carbon microbeams 0.3 mm thick, spaced 1.0 mm on-center, over a target volume of 6.5 mm in diameter. The irradiations were administered from four directions. The target dose was 45 physical Gy that, together with the RBE of 3.0 for carbons make its photon equivalent dose 135 GyE. Gd-enhanced MRI of one of the rabbits 65 days after the irradiations showed only a focal lesion in its brain. Now, four months after the irradiations, the rabbits behave normally and gain weight normally, which also indicate that there is no major damage to the tissues around the target. We conclude that interlaced carbon microbeams show promise as a method of treating high grade gliomas and pediatric brain tumors with better tumor control, less damage to the surrounding CNS tissues, and potential for use in re-treatment. We thank I Hung Chiang, Joseph Gatz III, Maryann Petry, and Michael Sivertz for assistance. This research was supported by grants Musella Brain Tumor Foundation, Brain Tumor Foundations of "Lauren's First and Goal" and "Have a Chance", Stony Brook Foundation (Allen G. Meek MD, PI), Stony Brook's School of Medicine and the Office of Vice President for Research, and Stony Brook's Targeted Research Opportunities program.

Application of the Probabilistic two stage model: cellular repair study and description of inactivation effect of different types of ions

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To analyze in detail the cell inactivation effects of different ions at various energies, damage induction and repair processes in several hamster and human cell lines have been studied. Published survival curves for Chinese hamster CHO-K1 cells and their radiosensitive mutants xrs5 irradiated by carbon ions and normal human fibroblasts irradiated by several light ions have been analyzed using the Probabilistic two-stage model. Detailed characteristics of damage induction and repair-success probabilities will be established. The difference in response will be quantified in dependence on physical parameters of radiation and biological characteristics of given cells. High attention is paid especially to the cellular repair processes. The comparison with two common used radiobiological models, the Linear-Quadratic model and the Local Effect Model, will be presented, too.

First systematic in vitro cell irradiation experiments with laser accelerated particles

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The novel technology of particle acceleration based on high intensity laser systems promises accelerators of compact size and reasonable costs and may significantly contribute to a widespread use of high precision hadron radiotherapy. Although some basic properties of laser acceleration are reasonably well known from theory, simulations and fundamental physical experiments, several further requests have to be fulfilled for its medical application such as supply of a stable and reliable particle beam with reproducible properties and precise delivery of dose in an appropriate irradiation time with required exposure of a desired irradiation field. Moreover, the ultra-short pulsed (in the region of 100 fs) particle beams with resulting high pulse dose-rate (in the order of 10^{12} Gy/min) have to be characterized with regard to their radiobiological properties.

First *in-vitro* cell irradiations with laser accelerated electrons have been performed at the Jena Titanium:Sapphire (JeTi) 10 terawatt laser system and dose-effect-curves were obtained for four cell lines and two endpoints. Laser pulses (80 fs duration, 2.5 Hz repetition rate) were focused into a helium gas jet, accelerating electrons to energies of up to 20 MeV. Before irradiation, the JeTi system was optimized for cell experiments: the electron spectrum was limited to a minimum energy of 3 MeV, the beam spot size was adjusted and the dose rate and homogeneity were improved. Each cell sample was equipped with two Gafchromic EBT radiochromic films, one in front and one behind the cell monolayer, used for retrospective precise dose determination. A Roos ionization chamber and a Faraday Cup monitored the beam providing on-line dose information necessary for irradiation control. Moreover the energy spectrum was measured both with an electromagnetic spectrometer and by analyzing film stack measurements. Following to the irradiation the cell survival fraction was determined using clonogenic survival assay. In addition, DNA double strand breaks present in cell 24 h after irradiation were analyzed.

Normally used for physical single-shot experiments, the JeTi was customized for a long-time cell irradiation. 163 Samples were irradiated at 13 experiment days over a period of 10 weeks with doses between 0.3 and 10 Gy. A reasonably stable and reproducible beam was achieved. Dose homogeneity was examined for all samples within the target area and the inhomogeneity obtained was less than 10 % for all days and all applied doses. Although still preliminary, the dose-effect-curves obtained show in general a lower biological effectiveness for the laser accelerated electron beams in comparison with conventional x-rays.

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