Purpose: In proton therapy a generic relative biological effectiveness (RBE) of 1.1 has traditionally been clinically applied, implying that protons are slightly more effective than photons. However, there exist large amounts of data, mainly from in vitro studies, demonstrating that the RBE is variable and dependent on a set of factors, including the radiation quality of the beam. Most of the phenomenological models made for estimating the RBE use the dose average Linear Energy Transfer (LET_d) as a parameter for the radiation quality. However, such a simplified description of the quality might lead to inaccurate RBE. In this work a new RBE model for proton therapy has been developed, utilizing the dose weighted LET spectrum ($d(L)$) to describe the radiation quality.
Materials/methods: A new formalism for RBE calculation is introduced, based on the concept of RBE_{max} and the usage of biological weighting functions. RBE_{max} is found by weighting the LET spectrum by $r_{max}(L)$, a smooth continuous function for the full LET range of protons (0-83 keV/µm). We assumed that $r_{max}(L)$ is nonlinear and symmetric around a turnover point (LET_u). A quantitative description of $r_{max}(L)$ was found by making a regression fit to the α/α_x of 96 data points, where the α and α_x are coefficients of the linear-quadratic model, for proton and photon irradiation respectively. These points were extracted from experiments with semi-monoenergetic proton beams found in literature. In our model we have assumed that $\beta = \beta_x$ and thus $RBE_{min} = 1$. A Fluka Monte Carlo simulation was done to check the new calculation method was benchmarked against a constant RBE of 1.1 and an existing LET_d based model for variable RBE (McNamara et al., 2015).
Results: By fitting $r_{max}(L)$ to the data, we found a peak at LET_u=34.5 keV/µm. The fit had a R^2 value of 0.634. In the simulated example, the new model estimated a RBE of 1.00-1.02 in the entrance region. The RBE rises from 1.05 to 1.6 along the SOBP. This indicates that a constant RBE of 1.1 leads to an overestimate of the dose to the normal tissue, as well to the proximal part of the tumour. Compared to the LET_d based model, the RBE is approximately 9-11% lower at all depths.
Conclusions: A dose and tissue dependent RBE model, based on the LET spectrum has been developed for application in proton therapy. Compared to LET_d–based model, this approach might give a better estimation of the biological dose in a mixed radiation field. The model could be further optimized, by adjusting the definition of $r_{max}(L)$ and introducing a term for $r_{min}(L)$, taking into account a variable LET dependent β parameter.

Keywords: RBE, dose average LET, LET spectrum

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DoPET: an in-treatment monitoring system for particle therapy

V.Rosso[1*],G. Battistoni[2], N. Belcari[1], N. Camarlinghi[1], G.A.P. Cirrone[3], F. Collini[4], G. Cuttone[3], M.Ciocca[5], A. Del Guerra[1], A. Ferrari[6], S. Ferretti[1], A.C. Kraan[1], A. Mairani[5], M. Pullia[5], S. Molinelli[5], F. Romano[3], P. Sala[6], G. Sportelli[1], E. Zaccaro[1]
[1] Department of Physics, University of Pisa and INFN, Pisa, Italy.
[2] INFN Milano, Milano, Italy
[3] INFN - Laboratori Nazionali del Sud, Catania, Italy
[4] Department of Physical Sciences, Earth and Environment, University of Siena and INFN, Pisa, Italy
[5] CNAO Foundation, Pavia, Italy
[6] CERN, Geneva, Switzerland

Purpose: The growing interest in charged particle therapy has led to the development of dedicated systems able to monitor the dose delivered to the patient. Positron Emission Tomography (PET) is a non-invasive way for in-vivo verification of the dose delivery. In fact, during particle irradiation, various β^+-emitting isotopes (^{15}O, ^{11}C etc.) are generated in the patient and this activity distribution can be related to the delivered dose.
Materials/methods: A compact PET system was developed to be installed close to the patient. The PET system, DoPET, is based on two planar heads. Over the years the dimension of the heads was increased, from 5cm x 5cm, to 10cm x10cm and finally to the dimension of 15cm x 15cm per head. The heads result from the assembly of several detecting modules: in the present prototype there are 9 modules (3x3) per head. Each detecting module, (5cm x 5cm) consists of a segmented LYSO crystal matrix (2 mm pitch) coupled to a PSPMT. The readout is performed by custom electronics, and the data acquisition was designed to cope with the high fluxes present during the treatment plan (TP) delivery. The data reconstruction of the measured 3-D β^+-activity distribution, based on a MLEM-OSEM 3D algorithm takes less than one minute.
The system was mostly characterized for proton therapy applications: at CATANA, a cyclotron-based center(LNS-INFN Catania, Italy), and at CNAO a synchrotron-based center (Pavia, Italy). Preliminary characterization for carbon irradiations were also performed.
Results: The DoPET spatial resolution guarantees the reconstruction of the distal fall activity profile with a sensibility of 1 mm, operating in-treatment [1, 2]. The in-treatment data were useful. In fact, DoPET provided information on a whole protonTP and on its very early phases [3]. A study was done delivering only the proton TP Highest Energy Layer: thanks to the sharp shape of the mono-energetic activity fall- off profile, the shift due to the presence of a small air cavity was evident.
The experimental β^+-activity profiles were also compared to calculated data obtained with FLUKA Monte Carlo, with very satisfactory agreement [3].
Conclusions: DoPET represents a reliable and fast in-treatment monitoring system that could act as an image guidance in the case of hypo-fractionation scheme. The present head dimension allows studies with anthropomorphic phantoms that will be done before moving onto patients.

Keywords: Particle therapy monitoring, on-line PET
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Left: one head of the DoPET prototype. Center: the prototype ready for the data taking with an antropomorphic phantom at CNAO, Pavia, Italy. Right: a slice of the reconstructed activity after a 2Gy proton treatment plan

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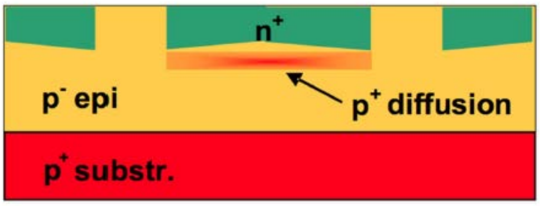
Design of an innovative beam monitor for particle therapy for the simultaneous measurement of beam fluence and energy

R. Sacchi[1,2], N.Cartiglia[1], F. Cenna[1], L. Fanola[1,2], M. Ferrero[2], S. Giordanengo[1], F. Marchetto[1], V. Monaco[1,2], A. Vignati[1], M. Varasteh Anvar[1,2], R. Cirio[1,2]
[1] Istituto Nazionale di Fisica Nucleare (INFN), division of Torino, Torino, Italy
[2] Department of Physics, University of Torino, Torino, Italy

Purpose: Monitoring the prescribed dose in particle therapy with the raster-scan method is equivalent to monitoring the correct delivery of the number of ions and the sequence of beam positions for every energy of the primary beam. The first task is typically carried out by using parallel plate ionization chambers working in transmission mode, where the number of particles is derived from the collected ionization charge with an accuracy in the order of 1%. The use of gas detectors has several drawbacks: they need to be calibrated daily against standard dosimeters and their dependence on beam quality factors need to be fully characterized and controlled with high accuracy. A detector capable of single particle counting is proposed which would overcome all these limitations. Combined with a gas ionization chamber, it will allow determining the average particle stopping power, thus providing an effective method for the online verification of the selected particle energy and range of the beam during the irradiation of the patient.
Materials and methods: Low-Gain Avalanche Detectors (LGADs) are innovative n-in-p silicon sensors with moderate internal charge multiplication occurring in the strong field generated by an additional p+ doping layer implanted at a depth of a few μm in the bulk of the sensor.



The increased signal-to-noise ratio allows designing very thin, few tens of micron, segmented LGADs, called Ultra Fast Silicon Detectors (UFSD) that, due to their large and very fast signal collection time, would be suitable for charged particle counting at high rates in particle therapy applications. We have finished the design of a sensor prototype, with a matrix of 100 pixels which will provide first indications on the particle rate capability and count accuracy. The sensors are expected in early spring 2016.
Results: Different LGAD diodes have been characterized both in laboratory and beam tests, and the results compared both with those obtained with similar diodes without the gain layer and with a program simulating the signal in the sensors. The signal is found to be enhanced in LGADs, while the leakage current and the noise is not affected by the gain. Additional results, as the information on the doping profiles, extracted from the study of CV curves and radiation tolerance studies, are also shown. Possible alternative designs and implementations are also presented and discussed.
Conclusions: Thanks to their excellent counting capabilities, UFSD detectors are a promising technology for future beam monitor devices in hadron-therapy applications. Studies are ongoing to better understand their properties and optimize the design in view of this application.

Keywords: Particle Therapy, Beam Monitoring, Silicon Detectors

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Variance Reduction of Monte Carlo Simulation in Nuclear Medicine
P. Saidi
Nuclear Engineering Dept., Science and Research Branch, Islamic Azad University, Tehran, Iran

Purpose: A method, which has had a great impact in many different fields of computational science,is called "Monte Carlo".The range of Monte Carlo application is enormous, from the Nuclear medicine, Radiation therapy, Reactor design, Quantum chromo dynamicsto Traffic flow and econometrics.One of the difficulties associated with Monte Carlo simulations is the amount of computer time required to obtain results with high precision. To shorten the calculation time and also improve the efficiency, there comes the idea to use the variance reduction techniques.
Method: There are many ways in which a user can improve the precision of a Monte Carlo simulation. In this study several of the more widely used variance reduction techniques such as: Splitting/ Russian Roulette, Energy cut off, Time cut off, Weight window, Implicit capture, Forced collision and Exponential transformation are presented. Application of variance reduction and guideline for these techniques in simulation are described.
Results: In Splitting/ Russian roulette technique each region is classified as important and unimportant. If the selected region is unimportant the Russian roulette has been used and in contrary if the important region is selected Splitting is used.
The energy cutoff and time cutoff are similar but more caution is needed in energy cut off because low energy particles can produce high energy particles.
The weight window technique is space energy dependent and can control weight fluctuation by define upper and lower energy bounds. Weight window technique is used to avoid following very low weight particles which causes reasonable computer timer during the simulation.
The main advantage of implicit capture is that a particle always survives a collision. It means when a particle reaches near the tally region would not be absorbed just before a score is made.
The exponential transformation is designed to enhance efficiency for deep penetration problems, but it should be noted that due to the large weight fluctuation that can be produced by this technique, it should be used accompanied by weight controls.
Conclusion: Variance Reduction techniques are used to produce more accurate and precise estimation in Monte Carlo simulations. There is a problem that these techniques may lead to results not being analyzed correctly but it should be noted that experience will lead the users to find the tricks for using these techniques to obtain the more accurate results.

Key words: Variance reduction, Monte Carlo, Simulation

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Simulation of cell survival for proton broad and minibeam radiotherapy with hexagonal and square minibeam alignment
M. Sammer[1,*], S. Girst[1], C. Greubel[1], J. Reindl[1], C. Siebenwirth[2,1], J.J. Wilkens[2], T.E. Schmid[2], G. Dollinger[1]
[1] Universitaet der Bundeswehr Muenchen, Neubiberg, Germany;
[2] Klinikum rechts der Isar, Technische Universitaet Muenchen, Germany;
*Corresponding author: matthias.sammer@unibw.de

Purpose: Proton radiotherapy using so-called minibeams of sub-millimeter dimensions allows to additionally enhance the advantages of proton therapy by spatial fractionation. This leads to a lower fraction of cells suffering from direct radiation damage and thus to reduced side effects compared to conventional proton therapy, which has been shown in a human skin and a mouse ear model [1,2]. Tumor control is maintained via homogeneous irradiation of the tumor due to minibeam widening with increasing depth. The minibeam distances need to be maximized for improved tissue sparing while generating a homogeneous tumor dose. Here, the required distances for quadratic vs. hexagonal minibeam arrangement are analyzed (see Figure 1). The resulting dose distributions are simulated in a water phantom with clinically relevant energies leading to different cell survival fractions and side effects.
Figure 1: *Minibeam arrangement on a quadratic lattice (left) and on a hexagonal lattice (right).*