Fig. 1: Time distribution of the fastest LORs. The lines correspond to the gaussian fits of the background (dotted line) and the peak (dashed line), while the continuous line corresponds to their sum.

The signal peak and the scattering distribution were modeled with two Gaussians and a fit was made. The single Gaussians and their sum have been superimposed. A peak value at bin -43.1 (1 bin = 25 ps) was found that corresponds to a difference of photons time of flight of 1.08 ns. This value, multiplied by the light velocity, corresponds to about 35 cm, the distance between the two detectors. The observed time resolution ($\sigma_{\text{obs}} = 150$ ps) includes the physics of the two detectors (σ_{MRPC}), the contribution of the electronics and channels synchronization ($\sigma_{\text{el\&ch}} \approx 20$ ps). Subtracting these contributions to the observed sigma we obtained $\sigma_{\text{MRPC}} \sim 145$ ps (FWHM ~ 340 ps). This value corresponds to the time resolution for a couple of photons and hence contains the time contribution of both detectors, while for a single MRPC the resolution is $\sigma_{\text{single}} \sim 103$ ps (that corresponds to a FWHM ~ 242 ps). However, the measured value does still not represent the achievable lower limit. The second experimental setup used for the measurement has been simulated through a full Geant4 simulation: detectors position, surrounding materials, kind of source, number of glass electrodes have been accurately reproduced. Both gamma propagation and electron scattering inside each detector have been studied, neglecting any contribution from the avalanches development in the gas gaps.

This contribution (of the order of about 70 ps) has to be added in quadrature to that due to the avalanche dynamics (50 ps). We consider the resulting value of 84 ps the achievable theoretical lower limit.

Future Development: The obtained result confirms that MRPCs have very good timing properties not only for charged particles but also in photons detection. This value is lower than that of the commercial crystals (FWHM ~ 500 ps) and close to that of LaBr_3 (FWHM ~ 300 ps).

Results with increasing number of MRPCs will be presented.

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DIFFUSING ALPHA-EMITTERS RADIATION THERAPY - A STANDALONE OR A COMPLEMENTARY TREATMENT MODALITY

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Solid tumor treatment by DART is based on a simple idea – sources containing ^{224}Ra atoms close to their surface are implanted in the tumor releasing their progeny by recoil into it. These alpha emitting atoms then disperse in the tumor by diffusion and by convection, delivering a therapeutically significant dose millimeters from the emitting source. The technological aspects of applying this modality have been developed so as to conform to the regulatory requirements governing clinical trials in humans. A series of preclinical experiments were conducted in vitro and in vivo on about 20 different cancer types, both of murine origin and human-derived (in athymic mice). In these experiments the relative sensitivity of individual cells to alpha radiation was investigated, as well as the response of real tumors to the applied treatment. This response ranged from total cure to tumor growth retardation, and depended consistently on tumor type. In another set of experiments the combination of DART with various chemotherapy agents were carried out on a number of cancer types. The metastatic load in the lungs of affected mice was investigated, as being the critical factor in determining the span of their survival. A comprehensive review of the status of this project will be presented.

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STRATEGIES TO OVERCOME HYPOXIA - A ROADMAP TO LET OPTIMIZED TREATMENT PLANNING FOR ION THERAPY

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Tumour hypoxia is one of the limiting factors in achieving tumour control in radiotherapy. High-LET radiation has been shown to be effective in reducing the Oxygen Enhancement Ratio (OER) in in-vitro systems. Furthermore, it has regularly been proposed for overcoming hypoxia in-vivo. However, high-LET radiation also means increased morbidity to healthy tissue, which limits the applicability of high-LET radiation. The high-LET region of a beam of heavy charged particles such as carbon ions is located in the distal part of the Bragg peak. A modulated or spread out Bragg peak (SOBP), however, results first, in a dilution of the dose-average LET in the target volume and second, in a distinct LET maximum beyond the target volume. In fact, the resulting dose-average LET in the target volume is usually insufficiently low for effectively reducing the OER in a tumour indicating that ions heavier than carbon may be required.

In this presentation, we would like to demonstrate two strategies to overcome the radioresistivity of hypoxic cells exploiting the radiobiological advantages of high dose-average LET distributions. In the first approach, which could be termed as LET painting, the radiation fields are optimized in such a way that the hypoxic compartments of the tumour are covered with high dose-average LET while keeping the dose in the entire target volume constant.

Alternatively, a second strategy could be utilized along with dose escalation, earlier referred to as dose and LET painting, in which hypoxic sub-volumes receive additional dose in form of high-LET radiation leading to a combined boost of dose and LET in the hypoxic compartments. Thereby, radiation with ions heavier than carbon could be harnessed to further increase the LET.

Following the general understanding of the relationship between hypoxia, LET and the OER, an additional therapeutic advantage can be achieved by confining the high-LET part of the radiation to the hypoxic compartments of the tumour and applying low-LET radiation, such as photon or proton irradiation, to the remaining normoxic tissue.

As a result of realizing the afore mentioned technique of LET painting, we were able to achieve optimized heterogeneous LET distributions in target volumes. Thereby, it was possible to obtain within a target volume several sub-volumes of macroscopic size ($>10 \text{ cm}^3$) in which the dose-average LET values were not below $100 \text{ keV}/\mu\text{m}$ using carbon ions. Despite of the inhomogeneously shaped LET distribution, we were able to keep the dose distribution relatively constant in the whole target volume.

The figure shows an example where this technique is applied to a patient CT (left column) in which hypoxic areas were identified with hypoxic tracer and were marked according to their oxygen level (lower row). The middle column shows dose and LET distributions for a treatment plan which is solely optimized on dose. This standard optimization is compared to a simple realization of LET painting, displayed in the right column, where regions with elevated LET (lower row) can clearly be identified.

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CANDIDATE THERAPEUTIC IONS: A PHYSICS ACCOUNT OF INTERACTIONS IN AND ESCAPES OUT OF THE BODY

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Modern therapeutic ion beamlines offer near-seamless switching from one type of ion source to another. This provides an array of ion types, so that selection may be driven by biological and clinical criteria rather than technological constraints. Candidates range from protons to neons. The biological effectiveness and clinical outcome are initiated by physical processes triggered in the body by the beam. As much as the biological effectiveness cannot be attributed solely to the total energy deposition, a full physics account goes well beyond what a Bragg curve can possibly contain. Whereas energy deposition is central to treatment planning, escapes pose not only issues for shielding and radiation protection but also prospects for patient dose reconstruction and treatment-time imaging. The latter is the key to the ENVISION (European Novel Imaging Systems for Ion Therapy) project. This work focuses on the physics, as an effort to lay out a detailed representation of the phase space, the energy balance-sheet, the dominating particle type(s) as well as contaminants, stable and unstable residual nuclei. Attention will be given even to characteristics populating the tail of statistical distributions. Ion therapy of the segmented VIP-Man was simulated using the FLUKA Monte Carlo code. At a resolution of 4 mm, tissue inhomogeneity in the anthropomorphic voxel phantom was represented by different proportions of materials from hydrogen to zinc - all of which differ considerably from water and PMMA (which are widely used as tissue-like phantoms) in terms of nuclear behaviour. Rather than relying on Hounsfield Units conversion ramps, the proportions and densities were defined according to ICRP and ICRU compositions for the respective tissue types. The simulation was repeated for different hypothetical clinical ion beams such as proton, carbon and oxygen. FLUKA simulates around 60 particle types and tracks