simulated dataset mimicking real data characteristics, but provided with a ground truth for performance assessment. **Materials/methods:** Three possible implementations of the 4D ML reconstruction strategies are considered and schematically represented in Fig. 1. Briefly, Method 1 (original version [2]) reconstructs the $\beta^+$ distribution in a virtual reference frame and estimates the motion fields mapping it to the Expected and to the Measured PET frames. Method 2 reconstructs it in the Expected PET frame and estimates the motion field mapping Expected PET to Measured PET. Method 3, conversely, reconstructs in the Measured PET frame and estimates the motion field taking Measured PET to Expected PET.

To initialize the reconstruction process a uniform activity distribution was considered. The three methods were validated on an analytical dataset simulating the $\beta^+$ distribution induced by two orthogonal beams on an inhomogeneous tissue on a 200x200x50 voxel grid with voxel size 2mm. Poisson statistics, 66% washout and Gaussian mismatch between Expected and Measured PET were considered.

Results were assessed after 30 iterations, by comparing: 1) the reconstructed Enhanced Measured PET with its ground truth, in terms of Normalized Mutual Information (NMI), Cross Correlation (CC) and Root Mean Square Error (RMSE); 2) the estimated motion field mapping Expected to Measured PET with its ground truth in terms of RMSE (RMSE_mot).

**Results:** Results are presented in Table.

<table>
<thead>
<tr>
<th>Method</th>
<th>NMI</th>
<th>CC</th>
<th>RMSE</th>
<th>RMSE_mot</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method 1</td>
<td>1.5</td>
<td>0.75</td>
<td>0.36</td>
<td>2.13</td>
</tr>
<tr>
<td>Method 2</td>
<td>1.5</td>
<td>0.76</td>
<td>0.12</td>
<td>1.13</td>
</tr>
<tr>
<td>Method 3</td>
<td>1.5</td>
<td>0.71</td>
<td>0.19</td>
<td>1.23</td>
</tr>
</tbody>
</table>

Method 1 performs worst than the others since the number of motion unknown variables to be estimated is double. Method 2 and method 3 perform similarly. Reconstructions were all initialized with a uniform activity distribution. The possible improvements of method 2 achievable with an initialization corresponding to Expected PET have still to be assessed.

**Conclusions:** Three possible implementations of an innovative 4D ML reconstruction strategy for PET-based treatment verification have been compared on a simulated phantom mimicking data. The two methods halving the number of motion variables showed better performances.

Method 1, b) Method 2 c) Method 3.

**Keywords:** Treatment verification, 4D ML reconstruction, ion beam radiotherapy

**References:**


169 FRED: a fast MC tool for treatment planning and dose verification in proton therapy

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**Purpose:** Particle therapy is an approach to tumor treatment which uses ion beams (in particular protons and carbon ions). The peculiar dose-depth relation of charged particles, that release most of their energy at the end of their range, enhances the dose conformity and the possibility to spare the healthy tissues. To exploit these features, the charged beam parameters need to be carefully optimized by the Treatment Planning Systems (TPS).

Commercial TPS are based on analytic representation in water (WEPL approach) of the patient and produce results in time of the order of hour(s). On the other hand Monte Carlo (MC) simulations can accurately take into account beam particle interactions, patient tissue morphology and elemental composition. Their application in the clinical routine is prevented by the huge amount of CPU needed to simulate the evolution of the beam in the patient.

We developed a software (FRED) for MC dose calculation and Treatment Planning optimization for proton therapy that runs both on CPU and on GPU (Graphics Processing Units). FRED has been tailored on the CNAO delivery system in view of applications such as an independent dosimetric verification of TPS dose distributions and a fast recalculation of the TPS taking into account daily residual positioning uncertainties.

**Materials/Methods:** FRED transports the protons in a voxelized geometry of the patient, retrieved from the DICOM information of the CT. The voxel HU of the CT is converted in elemental composition following the method by Schneider[1]. The stopping power is computed using conversion factors from the PSTAR tabulated values in water. Different models (single Gaussian, double Gaussian, Rutherford) can be used to reproduce Multiple Coulomb Scattering, while secondary protons and deuterons are produced in the beam nuclear interaction following the multiplicity, energy and angular distributions provided by ICRU63, and interpolated for other materials. Alpha and heavier fragments produced are treated as local dose deposition and (in this version) neutral particles are not produced. The RBE value of the proton is kept constant, but FRED could be easily interfaced with a library of RBE values. The FRED MC dose matrix can be processed by an optimizer based on a least-squares optimization algorithm as in [2]. All the output/input system has been adapted to the CNAO environment.

**Results:** The agreement between the CNAO clinical depth-dose database and the FRED results is within 1%.
In Figure 1, as an example of the clinical-like capabilities of FRED, a satisfactorily comparison between the DVH obtained by FRED and by MCPTPS [3] and a TPS commercial software is shown.

![Figure 5 Comparison between the DVH from Fred and ref [3]](Image)

The time needed to trace the protons and optimize the dose is 20 s on 4x GPU NVIDIA GTX 980 machine. The MC speed is 0.33 μs/primary.

**Conclusions:** The satisfactorily dosimetric agreement between FRED predictions and TPS/dosimetric data supports its future use at CNAO as fast dose recalculation tool based on in room patient geometry and as an independent patient plans verification platform.

**Keywords:** Proton therapy, MC, GPU

**References:**

**170**
Radiolabeled Acridine Orange (AO) Derivatives as DNA-Targeted Probes for Auger Therapy

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In recent years, some Auger-emitting radionuclides clinically used for imaging/diagnostics started to be envisaged also for emitting radionuclides, 125I is of particular interest, as it emitting about 20 electrons per decay, as opposed to 4 electrons per decay emitted by 99mTc. Nevertheless, 99mTc still is the most used radionuclide in diagnostic Nuclear Medicine; therefore, the possibility of Auger therapy with 99mTc should open new avenues in cancer theranostics. Auger electrons travel a short distance within human tissues (about 1-10 nm) and, thus, the Auger-emitting radionuclide must be transported to the cell nucleus to elicit DNA damage.

Following previous encouraging results, we have designed and evaluated 99mTc(I)/Re(I) tricarbonyl complexes and 125I(127I)-heteroaromatic compounds that contain an AO group for enhanced nuclear uptake and strong DNA intercalation. To have an insight on the relevance of these radiolabeled compounds for DNA-targeted Auger therapy we have investigated: i) their ability to cause DNA chain breaks; ii) the influence of the two different radionuclides in DNA damage; iii) the effect of the distance between the AO intercalating unit and the radioactive atom (99mTc or 125I).

To address these issues several studies were carried out: i) evaluation of DNA binding and DNA damage; ii) cellular and nuclear internalization experiments; iii) H2AX assays; iv) molecular docking and nanodosimetric calculations. Both classes of compounds are able to induce DNA double strand breaks (dsb) (either in plasmids or in tumor cells) but the extent of DNA damage (e.g. dsb yield) and the role of direct effects are strongly dependent on the linker used to attach the Auger emitting radionuclide (125I or 99mTc) to the AO moiety. Experimental data were corroborated by the docking and nanodosimetric studies; furthermore, most of the tested compounds presented a moderate to high uptake in tumor cells, with a significant accumulation in the cell nucleus. Altogether, these results give impetus to pursue with the pre-clinical evaluation of these radiolabeled AO derivatives as new radioactive probes for anticancer Auger therapy.

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**References:**

**171**
The efficacy of IMRT, VMAT and IMPT to deliver highly conformal FET-PET guided boost in gliomas

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**Purpose:** Radiotherapy plays an important role in treatment of gliomas even though the clinical outcome is relatively poor, mainly due to local failure. A higher uniform tumour dose may however increase the risk of adverse effects, especially for larger target volumes. A selective boost to the 18F-fluoro-ethyl-tyrosine (FET)-PET active volume, might prolong time to progression without increasing the risk of adverse effects. The present treatment planning study investigate and compare the ability of three techniques, VMAT, IMRT and IMPT to deliver a high conformal high dose boost to the BTV in patients with gliomas.

**Material/methods:** Seven patients with a pre therapeutic PET/CT and MRI were used in the study.

For each patient a standard IMRT treatment plan giving 60 Gy in 30 fractions to the BTV and 46 Gy to the CTV(46 Gy) was calculated as a benchmark. A CTV(46 Gy) was defined as tumor and/or tumor cavity added a 2 cm margin. The BTV was defined from the PET PET and covered a tumor-to-brain cut-off ratio of PET uptake > 1.6 (pre-surgery) and > 2.1 (post-surgery). Both BTV and CTV(46 Gy) were modified to respect anatomic barriers. Planning target volumes (PTV), PTV(boost) and PTV(46 Gy) were generated by uniformly expanding the BTV and CTV(46 Gy), respectively with 3mm. The standard IMRT plans were used to define the base level of dose to the organs at risk (OAR) and PTV(46 Gy) homogeneity. To evaluate the dose to the OAR the mean dose was used. The PTV(46 Gy) homogeneity was defined as the volume of PTV(46 Gy) subtracted PTV boost which received more than 107% of the prescribed 46 Gy. The IMRT, VMAT and IMPT dose escalating treatment plans were optimized in order to get the highest achievable mean PTV boost dose, without increasing the mean dose to critical OAR and without decreasing the PTV(46 Gy) homogeneity. For all plans the dose boost was given as the integrated boost over 30 fractions. All treatment plans were carried out using the Eclipse treatment planning system (Varian Medical systems, Palo Alto, CA, USA).

**Results:** A standard IMRT plans were calculated for all patients and the base level for PTV(46 Gy) homogeneity was found to range between 65 % to 86 %, with a median value of 77%. Dose escalating, while maintaining this homogeneity, was found feasible using all three techniques. The mean doses to PTV(boost) were 77.1Gy, 79.2Gy and 85.1Gy for...