

Modeling and Verification for Ion beam Treatment planning INFN Call CSN V, 2017-2019 www.tifpa.infn.it/projects/move-it

Activity Report Summary Month 1-6

14 July 2017



Overview

Figure 0.1: MoVe IT project overview, with Workpackages and Tasks breakdown

The first 6 months of MoVe IT have been characterized by intense activity and promising initial achievements. The project has started with a high momentum in January 2017, kicked by the Kickoff Meeting and refined by the following Referee Meeting on December. Interactions with all the groups have been installed and strengthened especially by the fiirst Annual Meeting in June, while all the first prevised Milestones have been fulfilled. All the WP were actively involved, although with different relative weight. WP4 was involved in several deliverables and then a largest part of the activities was concentrated there. WP2 was scheduled to start at month 6 but the activities for the first task started in advance in order to be prepared for the analysis of the NTCP as soon as proper data will become available. Among the research highlights of this period, the implementation of PET functional imaging data in treatment planning, the characterization of O beam potentiality in hypoxic tumors comparative to other ions and a full systematic analysis of OER models for ion TPS (WP1), the first biological irradiation performed at TIFPA (WP3-4), the achievement of an approved OPBA for a challenging mouse experiment dedicated to in vivo validation of proton RBE (WP3) and many others. A summary of the status of the individual task Milestones &

Deliverables is available in Table 1, overlaid on the Gantt Chart of the project provided on submission stage. In the following we provide a summary of the actions for each WP.



Table 0.1: Status of the deliverables/milestones on the project Gantt Chart (green = completed, orange = in-progress) at the time-point of this writing (red bar).

WP0 – Organization

WP0 Leader: E. Scifoni

The organizational WP is in charge of streaming the project, facilitate exchanges between the groups, stimulate involvement of the external partners, dissemination etc.

Task 0.1 - Management:

The Management Commettee (MC), responsible of all decisions in the project, has been elected and, as suggested in the proposal and agreed by all participants, it is composed by the WP Leaders and Local responsibles: Emanuele Scifoni, Sebastian Hild (TIFPA), Pablo Cirrone, Francesco Romano, Giorgio Russo (LNS), Roberto Sacchi (TO), Gabriella Pugliese, Laura Cella (NA), Giuseppe Battistoni (MI).

The First Annual Meeting (**D0.1.2**) was organized and successfully held in Naples on 31 May/1 June, to analyse initial results obtained in month 1-5 and tune further directions. In addition to this live meeting a couple of "plenary" skype meetings open to all participants with presentations of task status update have been organized.

Every WP has scheduled meeting on an average month base. Interaction with GSI is assured by weekly skype discussions with the TIFPA group. A formal involvement in the project from new partners have been also established, in particular with NIRS (National Institute for radiological Sciences, Japan) through Dr. Shimokawa (realization of hypoxic phantoms -WP3).

A strong interaction with the partner project FOOT (CSN3) has been assured through the several common participants and the coordination of the Milano group.

2 presentations have been delivered at FOOT meetings, to enforce the mutual communication.

The MC is now preparing the **D0.1.1**, i.e. the compilation and subscription by all partners of an IP background agreement. This document, initially scheduled for June, is in progress but still pending, and it will be probably finalized, right after the August break. Contacts with the INFN IP management office have been already established, but took more time than expected.

Task 0.2 – Dissemination and TT:

Several dissemination actions have been already realized. According to the scheduled **D0.2.1**, the first action was the creation of a logo and the generation of a dedicated webpage: <u>www.tifpa.infn.it/projects/move-it</u>. Beside 5 Scientific publications in press/submitted, the MoVe IT project was presented at IBIBAM (India) and ISIT (Milan) international conferences and on an invited lecture on Particle Radiobiology at the OMA school on medical accelerators at CNAO (Pavia). A few specific report contributions were given at the SIRR (Societa' Italiana Ricerca Radiazioni) Meeting.

Several Abstract have been accepted and will be presented in Autumn meetings such as SIF, NSS, MIC. Many others have been submitted, e.g. to the MICROS conference in Venice. Also outreach activities are in preparation: TIFPA is responsible of the event "Physics 2night" during the SIF meeting in Trento on September. In this case the MoVE IT activities will be presented to general public.

The following publications related to MoVe IT activities (and explicitly acknowledging it in the text) are in press or in submitted stage at the date of this writing (in brackets corresponding WP and partner involved):

- "Oxygen beams for therapy: advanced biological treatment planning and experimental verication" - Sokol et al., subm. (min.rev.) Phys Med Biol (WP1, TIFPA, GSI)
- 2) "Modeling Oxygen Enhancement ratio for ion beams with Microdosimetric Kinetic Model" Attili et al., subm. Phys Med Biol. (WP1, INFN-TO)
- "Model-based approach for quantitative estimates of skin, heart, and lung toxicity risk for left-side photon and proton irradiation after breast-conserving surgery" -Tommasino et al. Acta Oncol. 2017 56, 730-736 (WP2, TIFPA, INFN-NA, APSS)
- 4) "Increasing the power of tumour control and normal tissue complication probability modelling in radiotherapy: recent trends and current issues." Tommasino et al., Transl Cancer Res 2017. Epub ahead on print: doi: 10.21037/tcr.2017.06.03 (WP2, TIFPA, INFN-NA)
- 5) "Proton beam characterization in the experimental room of the Trento Proton Therapy facility" - Tommasino et al., Nucl Instr Meth A in print (WP4, TIFPA, APSS)
- 6) "Design and characterization of a 64 channels ASIC front-end electronics for highflux particle beam detectors" - Fausti et al., Nucl Instr Meth A 867 (2017) 1–6 (WP4, INFN-TO)

On submission stage the Annual reports (D0.2.2-4) were thought to be delivered at the end of each year (M12,24,36). It will be object of discussion with the referees whether providing a

new more extended report at M12 or considering the present as the **D0.2.2**, and plan the next annual report (**D0.2.3**) for the next referee meeting (July 2018).

WP1 – Radiobiological Modeling for Treatment Planning

WP1 Leader: S.Hild

Task 1.1: RBE modeling for protons:

An important step in this task, as planned, was the realization and adaptation of the TRiP98 Beam model for the proton therapy center in Trento, in order to enable recalculation of clinical plans including an RBE.

TRiP98, in principle, has to be benchmarked against measurements, in order to produce reliable treatment simulations. However, RayStation, the treatment planning system used in the Protontherapy center in Trento have been already benchmarked. In order to reduce the needed measurements while keeping the level of accuracy TRiP98 was compared and tuned using data extracted from RayStation's base data.

In a first step a plan translator was developed to convert an actual beam plan from RayStations DICOM format into the raster format used by TRiP98. The recalculated dose distributions showed that the initial TRiP98 beam model was not able to produce sufficient compliance, most likely due to initially being developed for a synchrotron based system. In the following the depth-dose profiles which are part of TRiP98 input data have been recalculated. We used the exact same integrated depth dose profiles and absolute dose measurements, which have also been used to build the current RayStation beam model, and were kindly provided by the Protontherapy center in Trento (APSS partner). The improved TRiP98 beam model slightly overestimates the dose in the distal part of the spread out Bragg peak, and slightly underestimates the dose in the proximal part. Reasons for this behavior have been imputed to incorrect description of the lateral scattering. The beam model is currently adapted in this manner, results are pending.

Beside this important technical part of the task, the analysis of RBE impact of nuclear fragmentation of the target has been started. A contribution to the FOOT Conceptual Design Report has been delivered, on radiobiological rationale and requirements for the cross sections measurements. From an initial evaluation, for example, of intrinsic RBE distributions for different particles, – those involved as proton recoil fragments -, it emerged the need of a quite high energy resolution, on the order of 1 MeV. 2 systematic sensitivity analysis have been planned and initiated in order to provide finer requirements numbers for FOOT: a) on proton induced fragments b) on Oxygen projectile fragments (byproduct of the FOOT project, In direct kinematics, which is fundamental for accurate description of Oxygen beam model, also highly relevant for MoVe IT, see next task T2).

The initial fragment spectra for starting the sensitivity analysis have been provided by **WP4**: GEANT4 simulations (LNS) and FLUKA simulations (MI). The resulting spectra, when integrated on the full penetration depth, were matching on a qualitative level previous literature data [1].

Task 1.2: OER and ITH modeling:

M1.2.1: Translation of functional imaging data in input data

In this first period a PET reader has been added to the input interface of the GSI in-house treatment planning software TRiP98. The updated software will be referred to as TRiP98OER, since it is explicitly accounting for oxygen enhancement ratio in the optimization. In the following the now supported PET data will serve as a measure of tissue oxygenation level (in combination with data from **WP3** task **3**, see **D3.3.1**. for details). Due to the ongoing investigations concerning the relation between tissue oxygenation and PET data, the additional use of an oxygenation look-up table (OLUT) has been implemented. This OLUT is designed to realize any arbitrary data interpretation, as tissue oxygenation internally is determined by translating the loaded PET data with the provided OLUT. Post implementation the entire functional group has been tested and verified using artificial datasets of simple geometries (fig.1.1).

TRiP98OER in the latest version (April 2017) now features:

- Reading / writing of PET data (binary file and separate header)
- Reading / writing / generating OLUT data
- Treatment plan optimization accounting the OER in full 3D
- Treatment simulation accounting the OER in full 3D

The tested and verified version has been provided to the collaborators of GSI's Biophysics department where it is currently being tested with artificial as well as anonymized patient data sets and will be included in the official distribution of TRiP98.

At the same time a strict collaboration with the GSI partner (M.Kraemer and O.Sokol) lead to the exploitation of Oxygen beams for therapy, especially in hypoxic cases. Different scenarios have been explored and comparative indications about beneficial use of O beams have been critically assessed on physics and radiobiological basis [2]. The insertion of the PET importation tool extended the applicability of the method for obtaining comparative merits of different ions, one of the major aims of the full MoVe IT project, and opened the way for the introduction of a Multi-ion Treatment Planning, where different ion species are optimized at the same time [3].

The Torino group, in the meantime, in close contact with the TIFPA team, was extending tremendously the RPIanIT code for accounting for OER effect. The novelty of Torino approach was the introduction of several models, including GSI/TIFPA ones, but also developing a personal one, based on the MKM model. In the latter it was possible to introduce a particle type and dose fraction dependence which extends the accuracy of the effect description [4]. The very extensive model intercomparison performed (fig. 1.2), emphasized, among other things the importance of moving beyond a dose average LET approximation. It was also suggested to consider nonuniform spatiotemporal fractionation schemes applied to tumor heterogeneities.

Such results will allow also the onset of T2.2 which will start in September with the TCP analysis including an impact of different oxygenation.



Figure 1.1 - Test of the new tool for importing simulated PET functional information on heterogeneous irradiation, both in forward and inverse treatment planning.



Figure 1.2 - Impact of different OER models on a prostate tumor performed with RPIanIT

WP2 – NTCP/TCP

WP2 Leader: L.Cella

Task 2.1 Advanced NTCP models on proton patient data including RBE

Model-based approach for quantitative estimates of radiation induced morbidity after photon and proton irradiation

As a first step, we extended to hadrontherapy the use of NTCP models originally developed for thoracic patients receiving conventional photon RT. To this end, an in-silico dosimetric analysis was implemented for the application of treatment outcome models. The starting point was breast proton plans generated by the commercial TPS platform currently in use at the Trento Proton Therapy Center (TPTC) under the hypothesis of uniform RBE.

Ten left-side BC patients undergoing photon irradiation after breast-conserving surgery were randomly selected from a clinical database. Intensity modulated photon (IMRT) and intensity modulated proton therapy (IMPT) plans were calculated with iso-tumor-coverage criteria. Proton plans were computed with different beam configurations and with or without skin optimization. Published NTCP models were employed to estimate the risk of different toxicity endpoints for skin, lung, heart and its substructures. NTCP calculation from dose-volume and dose-surface maps was performed with in-house software developed in Matlab by IBB-CNR group. Skin NTCP evaluation suggests a lower toxicity level with IMPT compared to IMRT when the skin is included in proton optimization strategy. By NTCP model-based analysis, an overall reduction in the cardiopulmonary toxicity risk prediction can be observed for all IMPT compared to IMRT plans. Our model based analysis thus suggests that IMPT might be safely applied without increasing the risk of severe acute radiation induced skin toxicity. The quantitative risk estimates also support the potential clinical benefits of IMPT for left-side BC irradiation due to lower risk of cardiac and pulmonary morbidity [5]. The applied approach might be relevant on the long term for the setup of cost-effectiveness evaluation strategies based on NTCP predictions.

At the same time, we performed a thorough literature analysis on NTCP and TCP modeling, which lead us to collect and deliver a systematic review on the topic [6].

An additional project objective was to implement an NTCP model for radiation induced lung toxicity in patients treated for lung cancer with proton beam therapy. A research strategy relying on data-driven multivariable and innovative image-based approaches was designed for the development of robust models RP prediction.

The pipeline consists of: (1) interpatient elastic image registration (EIR) on a common coordinate system (CCS); (2) mapping of the dose of each patient into the CCS by obtained deformation fields; (3) comparison of dose map datasets associated to patients who developed toxicity and who did not by different statistical mapping schemes or by threshold-free cluster enhancement) for inference on imaging data; and (4) generation of the corresponding P < 0.05 voxel clusters. Co- registration robustness and dose mapping accuracy are evaluated by geometric and dose scores. Receiver Operating Characteristic (ROC) test will be performed on the mean doses extracted from the sub-regions.

In this framework, a central role is played by the definition of an anatomy serving as CCS. The phantom 4DXCAT, acquired at the beginning of the project, is a digital phantom containing a CT atlas complete of the definition of a very thorough set of predefined anatomic structures (several thousands). A complete interface between 4DXCAT and Matlab and

between Matlab and TP systems has been developing in order to provide full support to the development of the following subtasks.

WP3 - Biological Dosimetry

WP3 Leader: G.Russo

Task 3.1: Development of specific devices for spatially resolved proton RBE measurement

The aim of this task is to develop, test and in case patent, a new 3D biological phantoms that could be used for treatment planning verification. The first phantom that we developed is depicted in figure 3.1: an alginate 3D phantom used to verify the RBE of B16 and CHO cells along the Bragg peak after a proton beam irradiation.



Figure 3.1: a) 3D gel phantom used for the verification of the RBE along a proton beam Bragg peak. b) The 3D gel is irradiated longitudinally. This provides the possibility to move, with a confocal microscope, towards the Bragg peak and to perform a basic live/dead-assay

In a first test, CHO and B16 were seeded, embedded in the gel, one day before irradiation. After treatment with X-ray at TIFPA and proton beam at the TIFPA experimental room in the proton therapy center, a first live/dead-assay test was performed using a confocal microscope. The confocal microscope analysis provides the possibility to study the cell death progression moving towards the Bragg peak (see panel b).. Four different phantoms were irradiated at the same time

The first results were not promising; Tests showed that the phantom was not indicated for our purpose. Cells in the alginate were in a suspension state-like, not proliferating. The live/dead analysis could not reveal any differences between irradiated and not irradiate cells (control). To develop a more realistic tissue-like scaffold, where cells can grow in a more realistic manner, we then moved to a new 3D phantom. This new phantom uses a silk-net cell

scaffold as support The differences between cells growing in tissue culture flasks, alginate gel and silk-scaffold are shown in figure 3.2



Figure 3.2: Cells growing in a tissue culture flask were compared with cells growing in the silk-net and alginate based scaffold 3D gel phantom.

The photon irradiation tests are planned for end July 2017 (while for proton beamtime proposal has been submitted at TIFPA PAC). After irradiation the live/dead analysis will be done but then also an immunohistochemistry analysis will be performed. The 3D gel phantom will be embedded in paraffin and then it will be cut in thin slices for studying with specific live/dead-markers the morphology and the response to the radiation.

Among the next steps:

1) To study the potential proliferation of CHO-K1 and B16 after irradiation with high dose X-rays (10 Gy or more). Cells will be seeded onto a mesh of formic acid-treated, native fibroin fibers and allowed to proliferate in order to fully colonize the scaffold. Later, fibroin meshes loaded with confluent CHO-K1 cells will be moved to custom-made irradiation chamber, moved to TIFPA labs, and irradiated with X-rays at the TIFPA labs. After irradiation, the meshes will be returned to BIOtech, cells will be detached from the fibroin mesh with Trypsin, counted, re-plated in TCP and kept in culture with medium in standard conditions.

Un-irradiated cells will be used as control.

2) Then the cells' plating efficiency, the ability to grow in this new silk phantom and studies of the survival at different doses will be performed.

3) The final experiment will be a study of the RBE along the Bragg peak using the colony forming assay and immunohistochemical analysis.

Task 3.2: Design new biological verification devices for heterogeneous (hypoxic) tumors

The aim of the second task is to develop new and advanced devices for culturing cell in hypoxic conditions. Starting from a previous device patented and used at GSI, Germany, we set up a new, smaller and easy to use hypoxic chamber.

In figure 3.3 (up) the GSI hypoxic chamber and the sample preparation scheme is shown. The chamber is cut out of one piece of polyetheretherketone (PEEK). The front wall is used

as irradiation window and has a thickness of 1 mm. A system of hose couplings allows to gas the chamber for a certain time and to keep it gas-tight afterwards for irradiation. For obtaining the required oxygen concentration, two hours with 200 ml/min of gas are necessary due to the chamber dimensions. Additionally, the chamber dimensions do not allow to use more devices together, in line, during irradiation.



Figure 3.3: Up: GSI hypoxic chamber and sample preparation scheme. Bottom: the new hypoxic chamber. The cell support (blue) is filled with cells and medium (red) and sealed with two layers of biofoil, i.e. a gas permeable foil. The cell support becomes itself the chamber support, in PEEK (green). Bottom-right, assembling phases (1 to 3), are shown in a first version for preliminary tests.

On the figure bottom, a draft of our new hypoxic chamber is represented. Our hypoxic chamber is smaller and will provide the possibility to stack up more devices in water and/or cell medium to simulate a complex tissue situation in which different oxygen concentrations and/or cell lines are plated. In this device the cell support (in blue) is filled with cells and medium (in red) and sealed with two layers of biofoil, i.e. a gas permeable foil. The cell support becomes itself the chamber support, in PEEK (green). Finally, the the assembling phases, from 1 to 3, are shown in a first version realized for preliminary tests.

Task 3.3: In vivo and molecular characterization

In vitro characterization

The *in-vitro* actvity concerns the hypoxia biomarkers characterization in *in-vitro* models. Three immortalised glioblastoma cell lines are planned to be analysed for their survival rate and molecular response to increasing doses of proton beams in normoxic and hypoxic conditions.

At the moment, the U87 glioblastoma cell line has been subjected to Proton Beam irradiation at SOBP with 4 doses (2-4-10-21 Gy) in normoxic conditions. The irradiation has been conducted positioning the plates at middle SOBP position at CATANA facility at LNS-INFN in Catania. Cell survival was analyzed 24h, 48h, 72h and 1 week after irradiation.

The graphic below shows the results of the experiment reported as a percentage of cell survival compared to the untreated sample. It is possible to observe a consistent rate of radioresistance, as the higher doses (10, 21 Gy) are not sufficient to kill completely tumor cells, which, instead, increase in cell number 1 week after the treatment (58-50% at 10 and 21 Gy).



Figure 3.4: U87 glioblastoma cells irradiated at normal conditions and scored at different time points.

In vivo: A preclinical assessment of RBE impact for proton

The *in vivo* activity concerns the assessment of variable RBE (Relative Biological Effectiveness) as function of the Linear Energy Transfer (LET) variation in generating normal tissue complication using clinical proton beams.

During the first part of 2017, the animal experimental protocol (Attached Mod_01_C) has been written and subjected to the Catania University (UniCT) O.P.B.A. (Animal welfare agency), which already has given favorable opinion on this sperimentation. The project is just submitted to the Italian Ministry of Health for the definitive approval.

Briefly, the animal sperimentation will be conducted on C57BL/6 mice.

Before treatment, a micro-CT will be performed at CAPIR SSU of UNICT. DICOM image will be acquired and used inside an homemade Geant3 Monte Carlo application to better define the treatment configuration. The anhestesia will be performed using a mixture of isofluoran and oxygen.

The proton therapy treatment will be performed using two different depth dose distribution: 1) pristine Bragg peak and 2) Spread Out Bragg peak. In the first configuration, the region to be treated will be positioned at the "pure" entrance, delivering the doses of 14, 17, 19, 21 and 24 Gy, while in the second configuration the target will be located in the distal part of the SOBP, releasing the doses of 11, 12, 14, 16 and 18 Gy to the target.

These doses have been obtained from the literature, on the base of similar experiments performed with photons, in which the response rate (ED) of 50% was determined as a deterministic damage to myelopathy, using an hypotetical RBE of 1.1 in first configuration and an RBE of 1.4 in the latter.

The prescribed dose will be released in a single session with a dose rate between 15 and 20 Gy/min.

In the "Distal" configuration, the dose will be released using a single post-front treatment field perpendicular to the spine, thus ensuring the non-irradiation of the healthy tissues underneath the column;

in the "Entrance" configuration the dose will be delivered using a single collapsed laterallateral treatment field on the spine, so to not irradiate other tissues. In addition, the dose distribution will be homogeneous on the target and the irradiation field will have a size of 2.5 cm.

Animal placement will be carried out using a system equipped with a light field and a laser to locate the area to be radiated and the beam isocentre.

Animals will be monitored weekly. Every three months after treatment, a blood sample will be harvested andurine samples will be collected in metabolic cages.

The onset of myelopathy symptoms will be monitored by clinical evaluation once a week by testing with RotaRod and Beam balance walking. The animals will be sacrificed by cervical dislocation if there is a grade of myelopathy 3 to avoid suffering. The organs of interest will be explanted post-mortem and analyzed by basic techniques of pathological anatomy. The tissues / organs of interest and a blood samples will be frozen in liquid nitrogen / -80 ° C.

In vivo molecular characterization

The animal experimental protocol for the hypoxia molecular characterization inside tumour area is under internal revision and it will be send to O.P.B.A. (Animal welfare agency) before October 2017. The treatment will be performed using human tumor cells injected in Balb/C nude mices and a ¹⁸F-FMISO PET-CT will be acquired in order to assess the hypoxia area.

D3.3.1: Imaging tools for the hypoxia identification on the PET/CT images (software)

Imaging tool for the hypoxia identification on the PET/CT preclinical DICOM images was developed using Matlab software. This software allows also the uptake quantification, the calculation of the common molecular biomarkers, like SUV (standardized uptake value), MTV (metabolic tumor volume) and TLG (total lesion glycolysis) and their fractional change, which are needed in the clinical practice for the treatment response evaluation. TLG, which combines the volumetric and metabolic information of PET lesions, is calculated as the product of the MTV with its mean SUV. To monitor tumor response PET scans should be performed on the same mice before and at the end of treatment. Variations in molecular biomarkers in sequential scans are normalized to baseline: (%) = 100 x (post-treatment – pre-treatment)/pre-treatment.

In addition, the identification of hypoxia regions is mandatory to improve the BTV (biological target volume) delineation accuracy in the RTP (radiotherapy treatment planning). Within the CT gross tumor volume (GTV), defined on anatomical images, it is possible to define target volumes based on functional area (BTV) and to apply a strategy that will deliver radiation to these regions. On the other hand, PET segmentation is a critical task due to its lack of consistency in a cancer contour, its low image resolution, its relatively high level of noise, and the hypoxia regions within a lesion. For the above reasons, the BTV has great size variability, since it depends on the algorithm used to delineate the PET images. Visual delineation is widely-used, but it is strongly operator-dependent, even if easily applicable. For this reason, the development and implementation of robust, fast, accurate, operator and scanner independent segmentation methods is mandatory. Briefly, our algorithm, implemented in the imaging tool, based on Random Walks (RW) on graphs is used to convert DICOM images into a graph where some nodes are known (nodes with target or background label) and others are unknown. PET image is then converted in a lattice where voxel SUVs are assigned to corresponding graph nodes and edge weights are computed accordingly. The segmentation problem is to assign a label to unknown nodes: the RW method partitions the voxels into target and background classes, considering the probability that a "random walker", starting at a source node, first reaches a node with a pre-assigned label visiting

every voxel. A probability map is then produced, and a threshold p is chosen to discriminate between target and background voxels so that a voxel binary mask is created: target node value = 1 if its probability \geq p %, background node value = 0 if its probability < p %. The probability threshold p is automatically inferred by the algorithm for each slice (the probability threshold changes during volume delineation) to take into account the intensity gradient and contrast changes of the lesion over the whole target volume.



Figure 3.5 - The microPET images of a tumor lesion in a mouse. The lesion is reconstructed in 3D e some uptake information can be extracted like SUV, MTV and TLG.

WP4: Facilities and beamline simulations

WP4 Leaders: G.A.P. Cirrone, F. Romano

Main aim of WP4 is the upgrade of the three beamlines involved in the measurements (TIFPA, CNAO and LNS), including the development of Monte Carlo simulations of the setup, the establishment of a common protocol of irradiation and the realization of detectors for diagnostics and dosimetry. 4 INFN sections are involved in this WP (TIFPA, LNS, TO, MI).

Task 4.1: CNAO/TIFPA/LNS lines development for beam delivering and shaping and setup of common protocols

D4.1.1: For each facility: specifications of beam transport elements and of diagnostic and dosimetry devices.

The main goal of this task is to establish a common protocol for the design, update and setup of the transport beamlines involved in the project. Specifications for the beam transport elements, the beam diagnostic and dosimetry must be defined and shared between the irradiation facilities at TIFPA, LNS and CNAO.

A common protocol for relative and absolute dosimetry with proton beams with energies in the range from 60 MeV to 250 MeV has been discussed with responsibles of the facilities, on the basis of the recommendations of the IAEA Report 398 [7]. Generally the proton dosimetry to date has been based on different types of dosimeters, such as calorimeters, ionization chambers, Faraday cups, track detectors, activation systems and diodes. In this framework, for measurements of the absolute depth dose distributions, the use of plane-parallel chambers is recommended.

Another important goal is to obtain a relatively uniform dose delivered in the position where biological samples are positioned. At the treatment position, or isocenter, the minimum beam

radius have to be 1 mm. The largest expected proton beam will be 10x10 mm. The required homogeneity should not be less than 10%.

A measurement of beam spot size, uniformity and symmetry can be performed by using a system based on a scintillator detector or a scanning diode.

Within this task, the Milano unit took care of coordinating on the INFN side the work for the construction of the eXPerimental Rooom (XPR) at CNAO.

Two general meetings for the involved people were organized in Pavia this year to review the status of operations. A time schedule (GANTT chart) has been prepared at the beginning of 2017. At present they are still working for tendering to purchase some essential components. Steel chambers and beam choppers being the most important elements. Administrative delays are forcing a delay of the completion, which is now expected for the spring of 2018. The first basic implementation of the TIFPA beamline were collected in a dedicated publication [8].

D4.1.2: System for the on-line ion beam profile monitoring for the LNS zero-degree beam line

Relative dosimetry in terms of measurement of beam profile is a fundamental step in the quality procedures for radiotherapy. In particular for proton/ion beams, characterised by sharp dose gradients, detectors with an high spatial resolution result necessary for a correct beam characterisation.

The MoVe IT project aims at allowing accurate description and testing of radiobiological particle beam effects, hence a precise characterization of the physical beam properties is essential. Among the possible choices, systems based on the use of scintillating screen coupled with CCD cameras can guarantee a sufficient spatial resolution and a relatively easy simplicity of use.

The functioning principle of the system is based on the detection of the light emitted when a scintillator is hitted by the proton beam. The system, in fact, consists of a scintillating screen mounted perpendicularly to the beam axis at a fixed distance and observed by a highly sensitive charge-coupled device camera. The basic idea is the possibility to obtain real time information about the relative spatial dose distribution delivered to tissue through the measurement of the light emission in the scintillating screen.

Figure 4.1 shows the schematic layout of such kind of system.

The main advantages of such a device are the relative simplicity of assembly and the extreme velocity into the profile acquisition.

These kind of devices have been already extensively tested under passive 60 MeV proton and Carbon beams [9,10] at the INFN-LNS facility [11,12] and under 230 MeV active proton beams at the CNAO facility. Never this approach has been applied for large (up to 10 x 10 cm²) passively transported high-energy (up to 230 MeV) therapeutic beams, like those available at the TIFPA facility. In case of large beams one limitation that must be investigated and, eventually, corrected is related to the possible image distortion at the image edges.



Figure 4.1. Schematic layout of the scintillator device and sketch of the preliminary version of the analysis software

.A first preliminary experimental test of this device has been already done at LNS with a proton beam of 62 MeV. A beam time request has been already submitted at TIFPA with the aim to perform a full characterization of the developed imaging system. Specifically, the main purpose of the experimental campaign is the dosimetric characterization of the scintillator system with a set of preliminary tests in terms of energy, linearity with the number of particles and particle flux. In addition, has been already fixed at October 2017 another test at LNS in order to complete the detector characterization.

D4.1.4: <u>Development of the passive beam modulation, scattering system and on-line profile</u> <u>monitoring for the TIFPA</u>

Extensive work has been dedicated during 2017 to the development of the TIFPA passive scattering line for radiation biology experiments. After the initial definition of basic requirements (e.g. field size, dose homogeneity, D4.1.1), we started a Monte Carlo simulation study, based on the Geant4 code Hadrontherapy. Aim of this work is the design and fine-tuning of a passive scattering line to be implemented at the TIFPA facility. According to the current status, a single scattering line was implemented, which consists in a tantalum foil for beam spreading, a ridge filter for passive energy modulation and in a collimation system. Work is currently on-going to optimize the geometry of the different elements, according to the initial requirements.

In parallel to the simulation work, a test beam is scheduled for September 2017 dedicated to the test of the beam profiler developed at LNS. In parallel, we started the procedure to purchase a Monitor Chamber to be installed on the TIFPA beam line, which once calibrated will allow online monitoring of the delivered dose. After construction and characterization of the single scattering line, further upgrades will be considered, as for instance the installation of a double-scattering system that will allow increasing the transport efficiency (and thus the dose rate on target).

Task 4.2: Monte Carlo Simulations for beamlines characterization and Target Stations for in vitro – in vivo experiments

D4.2.1: Implementation, inside the Hadrontherapy Geant4 application, of the LNS zero degree beam line for ion-beams irradiation

The Hadrontherapy official Geant4 advanced example has the aim to study issues related to hadrontherapy with protons and light ion beams as well as to provide users with the tool for general-purpose investigations in this field [13]. Hadrontherapy permits the simulation, via simple macro commands, of a beam line for proton/ion therapy including all the necessary transport elements: diffusion and modulation systems for spatial and energy distribution of particles, collimators, transmission detectors, as well as detectors for dose distribution measurements [14.15]. Accordingly to the deliverable number 4.2.1 has been inserted the complete geometry of the zero degree experimental room at Laboratori Nazionali del Sud of Istituto di Fisica Nucleare (LNS-INFN). This beam line is devoted to ion beam measurements and radiobiological experiments.

Each elements of the beam line has been simulated and realistically represented in order to have an open source application able to provide the corrected dose and LET distribution in a typical radiobiological experiment.

The beam exits in air through a 50 μ m kapton window. Just before the exit window in vacuum, a scattering foil made of 15 μ m tantalum is placed, with the tasks of spreading the beam and on-line monitoring the beam current. Along the beam line the particles pass through a plastic collimator that eliminate the beam components with a larger spread in angle. After this element, the beam cross a transmission ionization chamber that provide a full control of ions beam doses during irradiations. In the end, a brass tube final collimator provides a beam with a circular spot size and flat fluence distribution.

An important upgrade of the beam line simulation has been the ripple filter inserting along the beam line to reach an acceptable homogeneity of the Spread Out Bragg Peak (SOBP) for the carbon ions beam with 62 MeV/n.



Figure 4.2: Experimental data and simulation results of depth dose distribution obtained with 62 MeV/n Carbon ion beams.

The ripple filter is made of a thin plate of Plexiglass (PMMA, 120x120x1.4 mm) with a periodic structure very fine. Its geometrical design consist on a set of pyramidal structure with an angle of 60.09 degree and spaced of 1.4mm. The comparison of the simulation with the experimental depth dose distributions are shown a good accordance (entirely 3% of difference). These data were acquired by the air ionization Markus chamber with the spatial distribution ranging between 10 and 100 µm and are shown in Figure 4.2.

In conclusion in accordance with the deliverable fixed at June 2017 the beam line has been completely simulated and the geometry has been validated with the experimental results. In Figure 4.3 is shown the final layout of the beam line complete of the following elements:

- a scattering foil;
- two ripple filters placed at the distance of 7 cm from each other;
- a PMMA collimator;
- a monitor chamber;
- a brass collimator tube;
- a water phantom with a detector.



Figure 4.3: A sketch of the beam line geometry implemented inside Hadrontherapy advanced example.

D4.2.2: Redefinition classes for the LET/RBE calculation and for the specific beam energy distributions (LNS and TIFPA beamline) and specific cell lines that will be used in the experiment.

Monte Carlo approach for LET calculation

The Relative Biological Effectiveness (RBE) is a complex variable strictly related to several parameters such as the dose, Linear Energy Transfer (LET), tissue and cell type. For monoenergetic beams, LET values are easily obtained from tables, but in the case of clinical beams, calculations of averaged LET distributions are necessary in order to obtain realistic predictions.

Several studies have been carried out in this field and analytical algorithms were developed for this purpose [16-18]. Most of the Monte Carlo simulations use a very similar method to calculate LET but in most of cases they don't take into account impact of changes of transport parameters involved in these calculations. The main aim of deliverable number 4.2.2 is developed a tool based on a Monte Carlo code able to calculate the LET dose distribution and RBE map in a biological sample.

A critical analysis based on using three different LET calculation methods has been carried out. It has been individuated the best method to calculate the averaged LET dose for primary particle and has been implemented a method to calculate the total let dose that is completely independent to transport parameters such as secondary electron production threshold and voxel size. In Figure 4.4 is reported the LET-primary dose as a function of the depth for differents cut values.



Figure 4.4: Dose average LET calculated with different cut value with a 62 MeV proton beam. The information are scored in voxelized water phantom divided in slabs with 100 um of thickness

Since LET depends on particle species, as well as on its energy, heavier particles have higher energy loss per unit length. Recent progress in hadrontherapy field has made to exploit the peculiarities of different ion species. For instance, helium and lithium ions have been proposed in light of their improved lateral dose distributions compared with protons; at the same time they have a relative biological effectiveness lower than that of carbon, and thus, they are easier to adopt for clinical use. Oxygen is also considered a good candidate, especially due to its high LET distribution, which makes it particularly attractive for the irradiation of hypoxic tumors (see **WP1**).

One of the major critical parameter that influence the choice of a specific ion beam with a particular dose distribution is the Linear Energy Transfer that gives a quantitative description of the radiation quality of the beam. In this context a set of simulation with different ions beam have been carried out. In Figure 4.5 is shown the LET value as a function of the depth obtained for carbon and oxygen with 62 MeV/n.



Figure 4.5: Dose average LET calculated for an oxygen (on the left) and carbon ion beams (on the right) of 62 MeV/n.

In accordance to the deliverable 4.2.2, entirely December 2017, it will be implemented the averaged LET total and primary track calculation and will be completely validated the LET class with experimental data acquired with microdosimetric devices.

At the same time, Milano unit, as a link to the FOOT experiment, has started a new Montecarlo simulation, based on the FLUKA code, in view

of producing more detailed predictions about target fragmentation in proton therapy. First results have been presented at the MoVE-IT collaboration meeting, and are now tuned in order to be passed to WP1, for radiobiological impact assessment.

Monte Carlo approach for RBE calculation

A module, dedicated to coupling Geant4 with radiobiological models (like LEM and MKM), has been developing and final results will be validated against experimental data. Previously obtained tables of alpha and beta values for LEM are used run-time to obtain cell survival and RBE, with a Monte Carlo approach based on the information scored inside a voxelized water phantom. In particular, have been considered the following parameters acquired event-by-event: the deposited energy, track length and particles type.

A preliminary verification of the output has been carried out in a simple configuration using CHO cells, in order to simply verify the correct implementation of the code (Figure 4.6). Further studies in realistic configurations (i.e. mixed fields) are in progress.



Figure 4.6:: Comparison between LEM model results and LEM implementation in Geant4 for monoenergetic beams: protons at 8, 50 and 200 MeV; carbon ions at 8, 50 and 400 MeV/n.

In agreement to the deliverable number 4.2.2, no later than December 2017 the data related to prostate cancer cells, melanoma and glioblastoma will be inserted.

Task 4.3: Detectors for beam flux and beam energy measurement

M4.3.1: Beam tests of different UFSD test structures, including radiation damage (August 2017)

Three beam tests have been performed at CNAO with the therapeutic proton beam, to evaluate the counting and timing properties of UFSDs. During the last test in April 2017, we acquired 32 runs (2*1010 p each run, FWHM 1 cm), with the proton beam energy ranging from 62 to 227 MeV and different fluxes (Degrader 20-100). Two sensors pads of 50 um

thickness (1,2 x 1,2 mm2; 1 mm Ø) have been mounted at a distance of 1 cm from each other in a metallic box to keep them aligned among themselves and to the beam. The two outputs were fed into a broadband amplifier, visualized through an oscilloscope (40 GS/s), and acquired through a digitizer, 5 GHz sampling rate, providing snapshot of 200 ns duration. This allowed to study the shape and duration of the signal produced by the proton tracks, typically 2 ns duration with an amplitude well described by the Landau formula. The signal-tonoise was determined and it was shown that it increases with the detector bias voltage, as expected by the presence of the gain layer. It was proven that a good separation of the signal from the noise can be achieved even at the largest beam energy, where the minimum ionization is induced in the sensors. The signals from the two sensors were found to be well correlated, and the distribution of the difference in time between two corresponding signals was used to determine the time resolution of the sensors, resulting in approximately 35 ps. However, a highly non-uniform time structure of the CNAO beam at the ns scale was observed leading to a pileup effect larger than expected for a uniform proton rate. The pileup inefficiency was measured by using the charge integrated by a pinpoint dosimeter positioned behind the detectors as the reference. Several online pileup correction strategies are currently under development.

M4.3.2: Design ready of the VLSI chips for the silicon counter, production of UFSD prototypes (January 2018)

Prototypes of strip detectors were designed and are being produced by FBK in Trento. Samples with two geometries, (30 mm length x 5.6 mm width, 146 um pitch and 15 mm length x 5.6 mm width, 216 um pitch) will be available with different doping modalities for the gain layer to try to improve the radiation resistance of the device. The first samples, doped with Boron, are just arrived and first characterization on a probe station were made. A 12 channels readout board from the PPS detector of CMS is available for the first tests of the sensors.

The design of a new readout chip TERA10 for the sensors, featuring a preamplifier followed by a comparator with a programmable threshold, is in an advanced stage. The digital signals from each channel will be read by an FPGA implementing the particle counting and the algorithms for pileup correction. The design goals of the new chip are rather tight. Signals out of the preamplifier should very short, few ns at most, to reduce the signal pileup probability. Moreover, a large input dynamic range is required considering that the charge input ranges between 3 and 130 fC. Two alternative designs, a charge sensitive preamplifier based on the TOFFEE design and a differential transimpedance amplifier, both providing a LVDS output digital pulse are under investigation. Prototypes of the two chips are designed in UMC 110 nm technology and will be submitted through Europractice before the end of the year.

Summary

In conclusion, we can say that this first 6 month period of the project was successful, with several important steps achieved, No particular problems for the evolvement of the project have been detected to now. All the Milestones have been fulfilled and several milestones and deliverables scheduled for future times have been already initiated, some of them even completed. The only deliverable with some delay is the organizational **D0.1.1**, I.e. the delivering of a IP background agreement signed by all partners. However, the slight delay in this single action will not induce any hinder to the overall project.

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