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EDUCATION AND TRAINING IN MEDICAL IMAGING FOR CONVENTIONAL AND PARTICLE RADIATION THERAPY THROUGH THE EC FUNDED ENVISION AND ENTERVISION*

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Abstract. A key challenge in particle therapy today is quality assurance during treatment, which needs advanced medical imaging techniques. This issue is tackled by the EC funded project ENVISION, an R&D consortium of sixteen leading European research centres and one industrial partner, co-ordinated by CERN. ENVISION covers developments in Time Of Flight in-beam PET, in-beam single particle tomography, organ motion monitoring techniques, simulation, and treatment planning. Additionally, ENVISION serves as a training platform for the ENTERVISION project, a Marie-Curie Initial Training Network aimed at educating young researchers in online 3D digital imaging for hadron therapy. ENTERVISION brings together ten academic institutes and research centres of excellence and a leading European company in particle therapy, and is coordinated by CERN. Its multi-disciplinary training programme of ENTERVISION includes a diversified portfolio of scientific courses, complemented by specific courses aimed at developing soft skills. The ENTERVISION researchers will also benefit from the involvement in the research activity of ENVISION, and in the European Network for Light Ion Hadron Therapy (ENLIGHT). The trainees are encouraged to build a multidisciplinary network which will not only help them with their future careers but ultimately improve the transfer of knowledge and collaboration between the various disciplines of cancer treatment.

Key words: hadron therapy, education, training, radiation therapy, medical imaging, PET, in-beam, organ motion, simulation,phantom, treatment planning

1. INTRODUCTION

Hadron therapy is a fast expanding field, and its progress and implementation relies on the synergy among disciplines as diverse as physics, medicine, biology, engineering, and computing. New treatment centres are opening throughout

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Europe, and they need a new generation of experts with training and experience in these multidisciplinary domains.

A key challenge in particle therapy today is quality assurance during treatment, which needs advanced medical imaging techniques. This issue is tackled by the EC funded project ENVISION, an R&D consortium of sixteen leading European research centres and one industrial partner, co-ordinated by CERN. ENVISION covers developments in Time Of Flight in-beam PET, in-beam single particle tomography, organ motion monitoring techniques, simulation, and treatment planning.

Additionally, ENVISION serves as a training platform for the ENTERVISION project, a Marie-Curie Initial Training Network aimed at educating young researchers in online 3D digital imaging for hadron therapy. ENTERVISION brings together ten academic institutes and research centres of excellence and a leading European company in particle therapy, and is coordinated by CERN. Since the kick-off in 2011, the participating institutes have been recruiting a total of 15 researchers, coming from different academic backgrounds.

The multi-disciplinary training programme of ENTERVISION includes a diversified portfolio of scientific courses, complemented by specific courses aimed at developing soft skills that will help the researchers to build successful careers. The ENTERVISION researchers will also benefit from the involvement in the research activity of ENVISION, which will allow them to interact directly with senior scientists, and in the European Network for Light Ion Hadron Therapy (ENLIGHT)[1, 2]. Throughout the project the trainees are encouraged to build a multidisciplinary network which will not only help them with their future careers but ultimately improve the transfer of knowledge and collaboration between the various disciplines of cancer treatment.

2. THE ENVISION PROJECT

Accurate positioning is a crucial challenge for targeting moving organs, as in lung cancer, and for adapting the irradiation as the tumour shrinks with treatment. Therefore, quality assurance becomes one of the most relevant issues for an effective outcome of the cancer treatment.

In order to improve the quality assurance tools for hadron therapy, the European Commission is funding ENVISION, a 4-year project that aims at developing solutions for:

- real-time non invasive monitoring
- quantitative imaging
- precise determination of delivered dose
- fast feedback for optimal treatment planning
- real-time response to moving organs
- simulation studies.

Launched in February 2010, ENVISION [3] is a collaboration of sixteen leading European research centres and industrial partners: CERN (coordinator), Technische Universität Dresden, Medizinische Universität Wien, Université Claude Bernard Lyon 1, Oxford University, IBA, INFN, TERA, University Hospital of Heidelberg, GSI, Maastro Clinic, CNRS, CSIC, Ghent University, Politecnico di Milano, Universidad de Castilla La Mancha. Information and brochures on the project are available on its website http://cern.ch/ENVISION.

The project is organised into five research Work Packages.

2.1. WORK PACKAGE 2: TIME-OF-FLIGHT IN-BEAM PET

WP2 focuses on in-beam imaging, exploiting the positron emitting isotopes produced during therapeutic exposures to ion beams; it aims at improving image quality by limiting the region of interest with a measurement of the time difference between the photons emitted by positron annihilations in the body (Time-of-Flight Positron Emission Tomography, TOF-PET). The achievable image improvement depends on the accuracy of the TOF determination.

The objectives of this Work Package are to:

- Compare technologies for sub-ns TOF resolution
- Design, build and test a dual-head demonstrator
- Simulate a full in-beam TOF PET system
- Develop fast image reconstruction algorithms exploiting TOF for in-beam PET.

The new developments within WP2 allowed to achieve TOF resolutions approaching 200 ps, corresponding to a few cm in the body, with substantial improvements in image quality, Compton scatter rejection and artefacts reduction.

2.2. WORK PACKAGE 3: IN-BEAM SINGLE PARTICLE TOMOGRAPHY

This Work Package investigates the feasibility of applying irradiation components that promptly follow nuclear reactions between therapeutic particle beams and the atomic nuclei of the irradiated tissue for real time in-vivo dosimetry in proton and ion therapy. These radiation components comprise photons, neutrons and light charged particles. The Work Package focuses primarily on the application of prompt photons for in-vivo dosimetry with the goal to establish prompt γ-ray imaging (PGI) primarily for range measurements or even single photon emission computed tomography (in-beam SPECT - ibSPECT) for volumetric measurements to be integrated into the treatment site.

Since PGI and ibSPECT are expected to have a realistic chance to become clinically applicable, the following topics are comprehensively studied:

1. The feasibility of single photon imaging for *in-vivo* dosimetry in ion therapy;
2. Development of a system for single γ-ray imaging;
3. A fast position sensitive beam monitor;
4. Tomographic reconstruction for ibSPECT;
5. Simulation of the imaging process;
6. Investigation of the potential of secondary charged light particles for *in-vivo* dosimetry as an alternative to photon detection.

Substantial progress has been achieved in the field of developing detection systems for PGI: in total, 6 different systems are currently under investigation. These comprise two passively collimating systems (slit cameras) and four electronically collimating systems (Compton cameras). The passively collimating systems are expected to become clinically applicable in the near future, whereas electronically collimating systems (Compton cameras) have to be optimized for PGI by further systematic studies, in particular in-beam.

2.3. WORK PACKAGE 4: PARTICLE THERAPY *IN-VIVO* DOSIMETRY AND MOVING TARGET VOLUMES

For quality assurance of ion beam therapy, positron emission tomography (PET) still represents the only clinically available technique which can enable in-vivo, non-invasive monitoring of the dose delivery and beam range in the patient during or shortly after irradiation. Valuable information on the treatment delivery can be inferred from the measurement of the emerging annihilation gamma radiation following the decay of irradiation-induced positron emitters, in comparison to an expectation based on the planned treatment and actual beam delivery.

So far, the successful application of the method has only been demonstrated for stationary tumour entities in well-fixated anatomical sites not subject to organ motion. However, tumours subject to physiological motion pose even more urgent demands for in-vivo treatment verification, due to the challenges inherent to the conformal application of a moving ion beam (for state-of-the-art scanning delivery) to a moving anatomy. Therefore, this Work Package aims at assessing feasibility and enabling optimal performances of time-resolved in-vivo dosimetric imaging for validation of motion-mitigated ion beam delivery to moving targets.

The feasibility and limitations of different implementations of time-resolved, motion-correlated 4D PET imaging have been investigated in controlled phantom experiments at the GSI Helmholtzzentrum für Schwerionenforschung (GSI) and the Heidelberg Ion Beam Therapy Center (HIT), using available PET instrumentation and motion mitigated beam delivery techniques.

Moreover, proof of principle investigations have been successfully carried out to confirm the feasibility of integrating a prototype ultrasound (US) tracking system into the beam delivery and PET imaging process for monitoring internal organ motion, as a promising alternative to commonly used external motion surrogates.

The development of optimisation strategies in 4D PET-CT imaging for PET-based treatment verification of moving target is another important research activity within this work package. In particular, the focal point was the pre-reconstruction sinogram warping strategy, which aims at motion model application and count statistics optimization in the sinogram domain before image reconstruction. A full count statistics sinogram of the motion compensated 4D PET reference phase is generated by warping the sinograms corresponding to the different PET phases, according to the motion models expressed in sinogram domain. The strategy was validated on clinical-like images derived from NCAT phantom.

Research activities also focused on the application of a regional MLEM reconstruction algorithm as an innovative quantification tool in PET dosimetry, for a region-based comparison between measured and expected PET. This strategy is expected to provide improved accuracy and flexibility compared to the measurement of the mono-dimensional PET activity profiles, especially in case of inhomogeneous materials.

2.4. WORK PACKAGE 5: IN-BEAM SINGLE PARTICLE TOMOGRAPHY

PET is considered to be the state of the art technique to monitor particle therapy in-vivo. In particle therapy PET (PT-PET), the verification of treatment plans is ensured by the comparison between a measured and a simulated β^+-activity distribution, where the latter is acquired from the treatment plan (reference image). This comparison is routinely performed by well-trained observers: this is a subjective, time consuming, and expensive procedure. An automated comparison would allow a more efficient and cost saving treatment workflow.

This work package aims at developing a software tool to automatically detect differences between the reference and the measured image. Two separate techniques were investigated, and the final software tool will combine both for a future clinical use. As of 2012, the activities focused on the automated detection of patient setup errors with PT-PET, as well as in phantom experiments to thoroughly test the algorithms.

To achieve these aims, two purpose-built phantoms have been designed and constructed to accurately determine 3D dose distributions, and investigate the influence of internal patient movement. Experiments at the particle therapy facility CNAO or HIT will be performed on 3D dosimetry measurements with protons and carbon ions in the two phantoms with different detector systems.

The analysis of the results for clinical relevance just started, with the assessment of treatment delivery mitigated by inter-fraction displacements. The current focus is on prostate indications.

2.5. WORK PACKAGE 6: MONTE CARLO SIMULATION OF *IN-VIVO* DOSIMETRY

This Work Package aims to develop dedicated simulation tools appropriate for use in hadron therapy applications, in order to reliably predict and understand all possible signals useful for treatment monitoring. This WP benefits from the participations of groups working with three different codes (GEANT4/GATE, FLUKA, MCNP), and who already have experience in the field.

The first task is to define the physics models appropriate to characterise the interactions of interest in hadron therapy, in order to develop complete simulations of ibPET and ibSPECT experiments, from the treatment beam to the imaging data acquisition. The simulation work has been summarized into a report including:

1) the description of the physical models available to describe the interactions of interest in hadron therapy;
2) the results of the comparison between the available experimentally measured observables and the corresponding simulated ones;
3) the identification of the shortcomings of available physical models for hadron therapy, and recommendations regarding the reliability and uncertainties of the physics models available in the different simulation codes.

This report represents a unique compilation of results obtained using Fluka, GEANT4, and MCNP codes for the modeling of the physics involved in hadron therapy experiments, providing a reference document for all those involved in Monte Carlo simulations of hadron therapy experiments

Subsequent studies focused on the accurate description of the detection of emitted secondary particles and the production of beta+ emitters, understanding the differences between different codes and optimizing the selection of physical variables necessary to improve the agreement between simulated and experimental data. Finally, the collaboration started to put together all the tools and procedures to manage realistic patient treatments, thanks to the collaboration of some hadron therapy centres that provided actual treatment planning results. This allowed to produce a set of examples, available to the community, where all the steps, from treatment to secondary detection, are accounted for.

3. THE ENTERVISION PROJECT

The European training network in digital medical imaging for radiotherapy (ENTERVISION) was established in February 2011 in response to the critical need for reinforcing research in online 3D digital imaging and the training of skilled professionals. ENTERVISION brings together 11 beneficiaries – ten academic institutes and research centres of excellence and the leading European company in particle therapy.

The ENTERVISION project offers research and training opportunities to 16 young scientists (13 Early Stage Researchers and 2 Experienced Researchers) from all over the world. They come from different fields: physics, medicine, electronics, informatics, radiobiology, engineering but together are forming a collaborative network with a common goal: improved cancer treatment with early detection and more precise treatment of tumours. The institutes involved in the project are the leaders in their field and are already involved together in the ENVISION project; by training the Marie Curie researchers, they are forming the specialists of the future.

The research activities within ENTERVISION are organised in four distinct work packages:

1. Hardware and software solutions for signal handling, data acquisition and processing for image based in-vivo dosimetry Physics, detectors, electronics, informatics, engineering
2. Modeling of in-beam PET and SPECT imaging devices Physics, informatics
3. Nuclear fragmentation studies Physics, informatics
4. Integration of treatment related imaging and dosimetry data.

Intercalated into the training programme, the researchers have the opportunity to perform hands-on work in the following fields:

– Development of in-beam Positron Emission Tomography monitoring techniques
– Development of Single Particle Tomography techniques
– Adaptive treatment planning, and organ motion
– Optical imaging, cell irradiation, and biological phantom design
– Monte Carlo simulation of in-vivo dosimetry.

The actual technology development of this next-generation image based in-vivo dosimetry is being carried out in the EC funded project ENVISION: this project has not been designed to incorporate a platform for knowledge development for future generations of researchers and ENTERVISION bridges this gap between R&D and training.

The researchers have made good progress in their individual research projects and have had the opportunity to attend several training courses. These are multidisciplinary and build their scientific knowledge as well as communication and leadership skills greatly enhancing their career development and employment prospects.

The researchers have attended other ENLIGHT and EU project meetings (*e.g.* PARTNER ITN training courses enhancing cross-fertilization) where they have presented their work and listened to and interacted with the leading experts in the hadron therapy field with unique learning and networking opportunities.

Further information can be found at www.cern.ch/entervision.

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