From Hadrons to Therapy: Fundamental Physics Driving New Medical Advances

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Book of Abstracts

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Aim of the workshop

The development of modern radiation-based medical imaging and treatment tools is closely interlinked with the progress in Nuclear Physics and related areas. Improving cutting-edge cancer therapies (such as radiotherapy using ion beams, targeted radionuclide therapy, or their enhancement by means of nanotechnology) and imaging techniques (e.g. positron emitting tomography) requires intensive research in Nuclear Physics along with Atomic-Molecular and Condensed-Matter Physics. Research in these fields is necessary to get a better understanding of the plethora of fundamental processes underlying their medical applications, including nuclear reactions of energetic ions in the body, radioactive decay of their fragments or of supplied radioisotopes, or the many-body processes involved in the nanoscale biomolecular radiation damage mechanisms in the condensed-phase. This workshop aims to gather theoretical, experimental and clinical experts from these diverse fields in order to foster multidisciplinary understanding and collaboration, for the advancement of radiation-based medical techniques and their fundamental physical understanding.

The aim of this workshop (the first at ECT* devoted to medical applications of Nuclear Physics) is to gather researchers from different disciplines (theoretical, experimental and clinical) working in complementary fields, so to make clinicians acquainted with the latest theoretical and experimental developments, while basic researchers can tune their work to better satisfy the actual medical needs.

Workshop organisers

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New experimental developments in hadrontherapy

Ionoacoustics for range verification in pre-clinical and clinical proton beam therapy

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The spatially and temporary localized energy deposited by pulsed protons and heavier ions beams gives rise to the emission of thermoacoustic waves [1], hereafter referred to as ionoacoustics. The initial pressure subsequent to the brief thermal heating of the irradiated volume is proportional to the dose and the medium properties, namely the mass density and the material-specific efficiency of the conversion from energy to pressure (Grüneisen parameter). Therefore, the detection of the ionoacoustic emissions at several positions on the patient's surface allows inferring information on the incident proton beam either to locate the Bragg peak in vivo or to reconstruct the underlying dose [2]. The relative simplicity, low cost, and promising feasibility of near real-time range verification that could be combined with ultrasound images of the patient's anatomy have revived interest in ionoacoustics, notably facilitated in recent years with the development of new synchrocyclotron accelerators and the emergence of ultra-high dose rate radiotherapy. Advancement in ionoacoustics is however challenged by the intrinsically low frequency of the weak pressures resulting from the energy deposition of pulsed clinical proton beams (typically a few mPa at a frequency around 50 kHz for conventional therapy) both several orders of magnitude lower than ultrasound imaging, which hampered the pre-clinical and clinical implementation of ionoacoustics. This talk will introduce ionoacoustics in the context of proton therapy, giving insights into the ongoing efforts of several groups in translating it to clinical applications. Emphasis will be placed on the critical need for dedicated sensor technology meeting the demanding sensitivity requirements as a part of a small animal system development and recent accomplishments with anthropomorphic phantoms will be discussed.

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New experimental developments in hadrontherapy

Radioactive carbon beams for simultaneous treatment and imaging

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Heavy ion particle therapy is a rapidly growing and potentially the most effective and precise radiotherapy technique. However, the sharp dose gradients and very high doses in the distal ends make it extremely sensitive to range uncertainties, which remain one of its main limitations. In clinical practice, wide margins extending in the normal tissue are commonly used to guarantee the tumor coverage, thus jeopardizing the benefits of the sharp Bragg peak. Online range verification techniques could potentially help to overcome this limitation.

One of the most established methods to verify the beam range is to exploit the β^+-emitting isotopes, produced by the ion beam in the patient's body by nuclear fragmentation processes, for positron emission tomography (PET) imaging [1]. However, PET in ^{12}C-ion therapy still does not allow to reduce the range uncertainty as desired: the long half-lives of the radionuclides in combination with the biological washout and the physical shift in the β^+ activity and dose peak do not allow a straightforward dose reconstruction.

Direct use of β^+ radioactive ion beams (RIB) for both treatment and imaging could help overcome this limitation by increasing the signal/noise ratio, mitigating the washout blur of the image and reducing the shift between measured activity and dose [2].

In this context, the BARB (Biomedical Applications of Radioactive ion Beams) project was initiated at GSI aiming to assess the technical feasibility and investigate possible advantages of RIBs in preclinical studies [3].

Besides showing the potential of RIB in a treatment planning study to estimate the magnitude of possible range margin reduction and its impact on the doses to organs at risk and on the normal tissue complication probability, the vast experimental campaign, including research ranging from basic nuclear physics and PET detectors developments to animal treatments, foreseen in this project will be presented.

In the first two years of the project ^{10,11}C and ^{15}O beams have been produced with the GSI fragment separator (FRS) and transported to the medical vault of GSI. Thanks to the upgrade of the SIS-18 in the FAIR in Darmstadt, it was possible to achieve RIB intensities sufficient to treat a small animal tumor. Beam implantation in plastic phantoms was visualized by two independent imaging setups: a dual-panel PET scanner from the UMCG (Groningen) and a subset of a high resolution small animal PET detector in development at the LMU (Munich). Range and depth dose distribution measurements have been performed with a water column setup [4]. These first experimental results will be here also presented.

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New developments in the modelling of radiation propagation and effects

On the relative role of the physical mechanisms on complex biodamage induced by carbon irradiation

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The effective use of swift ion beams in cancer treatment (known as hadrontherapy) as well as an appropriate protection in manned space missions rely on the accurate understanding of energy delivery to cells damaging their genetic information [1]. The key ingredient characterizing the response of a medium to the perturbation induced by charged particles is its electronic excitation spectrum. By using linear response time-dependent density functional theory, we obtain the energy and momentum transfer excitation spectrum (the energy-loss function, ELF) of liquid water which is the main constituent of biological tissue, in excellent agreement with experimental data [2,3]. The inelastic scattering cross sections obtained from this ELF, together with the elastic scattering cross sections derived considering the condensed phase nature of the medium, are used to perform accurate Monte Carlo simulations of the energy deposited by swift carbon ions in liquid water and carried away by the generated secondary electrons producing inelastic events (ionization, excitation, and dissociative electron attachment), strongly correlated with cellular death, which are scored in sensitive volumes having the size of two DNA convolutions [2,3,4]. The sizes of clusters of damaging events for a wide range of carbon ion energies, from those relevant to hadrontherapy up to cosmic radiation, predict with unprecedented statistical accuracy the nature and relative magnitude of the main inelastic processes contributing to radiation biodamage, confirming that ionization accounts for the vast majority of complex damage, while DEA only adds up for a minor contribution. Applications to the calculation of the ELF and REEL spectra in ceria [5] and of beta-decay will be shown in this talk [6,7]

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Need for accurate particle-impact cross sections and Monte Carlo simulations

A simple procedure to generate cross section data for Monte Carlo simulations from Quantum Chemistry calculations. Example applications to Methacrylic acid.

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Monte Carlo Simulations of electrons in condensed matter require the knowledge of cross section data [1]. We present a simple procedure, which allows to generate a consistent set of cross sections for Monte Carlo simulations from parameters, which can be obtained from Quantum Chemistry calculations with standard software as for example the program package Gaussian.

We show how the cross sections can be converted into probabilities. We demonstrate their usage in Monte Carlo simulations of the secondary electron yield from Methacrylic acid (MAA). MAA is the main component of the gel called MAGIC (methacrylic and ascorbic acid in gelatin initiated by copper), which is a gel for radiation dosimetry [3]. In the gas-phase MAA has four different conformers. Each of them gives a different secondary electron yield.

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New developments in the modelling of radiation propagation and effects

Radiobiological model for intraoperative radiotherapy with electrons

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In radiotherapy treatments, the Radiobiological Effectiveness of Radiation (RBE) is customary assumed to be proportional to the absorbed dose. We have shown in a recent publication [1], that induced damage at the molecular level in water, in terms of induced molecular dissociations, by a 6MV X-ray beam generated by a clinical LINAC accelerator, is always proportional to the induced ionisation and therefore to the absorbed dose (typically determined with ionization chambers). Identical irradiation of living cells in water showed that biological damage, in terms of early and late apoptosis and DNA damage, resulted to be also proportional to the absorbed dose, within the irradiated area, although residual cellular damage out of this area was also observed and assigned to reactive radical diffusion (see [1] for details). This result may be expected since photon interactions with molecules do not produce significative changes in the beam energy and high energy photoelectrons are generated within the whole irradiated area so their damaging effect is homogenously distributed within the irradiated volume. However, the situation is completely different when the primary radiation beam is formed by charged particles (protons, heavier ions, electrons or positrons). These are gradually losing their energy by successive collisions with the molecular constituents of the target and therefore the interaction probabilities significantly change along the irradiation volume. In these conditions, proportionality between biological damage and absorbed dose is not expected. In this work we study the correlation between induced molecular and biological damages by a 6MeV electron beam generated by a LIAC clinical accelerator for intraoperative radiotherapy treatments in different irradiation conditions corresponding to the same absorbed dose. The molecular damage is evaluated in terms of induced molecular dissociations, via ionization, electronic and vibrational excitations and electron attachment, by using our Low Energy Particle Track Simulation (LEPTS) code [2]. The biological damage is evaluated via cell survival analysis for a constant 5 Gy dose in different beam spectral conditions.

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New experimental developments in hadrontherapy

FLASH in particle therapy

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New experimental developments in hadrontherapy

Modeling the FLASH mechanism on multiple scales

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The mysterious differential effectiveness of ultra-high dose rate (UHDR) irradiations, returning a protective effect on normal tissues for same antitumor efficacy as compared to conventional dose rates, the so-called FLASH effect, observed in numerous preclinical experiments, triggered in the last 3-4 years an exponentially growing number of biophysical modeling works attempting to investigate and explain it from the mechanistic point of view.

Since it was appearing that such a phenomenon should imply several physical, chemical and biological stages of the radiation action, different spatio-temporal scales were considered and analyzed in these modeling approaches.

An overview of these investigations will be concisely reported, with a focus on the ongoing joint efforts of GSI and TIFPA in this context, especially in the attempt of combining different scales.

In particular, radiation chemical based approaches, employing TRAXCHEM [1-2], the GSI radiation chemical track structure code and its specific extensions, allowing to go from the physical stage to the homogeneous chemical stage will be mentioned and a novel dedicated extension of the Generalized Stochastic Microdosimetric model (GSM2) [3-4] for UHDR regime, aiming at combining the DNA damage and repair kinetics with the chemical stages on several levels.

Impact of LET [3] and dose delivery features will be discussed as well.

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New experimental developments in hadrontherapy

Enhancing prompt-gamma production for real-time dose verification in proton therapy

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The main rationale for using protons in cancer treatment is based on the highly conformal dose distribution and normal tissue spearing compared to conventional radiotherapy. One of the main limits of proton therapy is the particle range uncertainty due to patient setup, dose calculation and imaging. A mispositioning potentially translates into an under-dosage of the tumor as well as an over-dosage of the normal tissue, which can significantly hinder the treatment efficacy.

We developed a novel strategy for real time range verification in proton therapy [1]. The methodology is based on the detection of prompt gammas (PG), whose production is artificially enhanced with a non-radioactive element transported selectively to the tumor with a drug carrier. Nuclear interactions of this element with protons generate a signature PG spectrum, from which the tumor position can be reconstructed exploiting existing PG Spectroscopy (PGS) methods [2].

In this study, we present the results obtained with three stable elements: 31-Phosphorous, 63-Copper and 89-Yttrium. We characterized the gammas emitted by solutions of water and the candidate elements ($CuSO_4$+H_2O, NaH_2PO_4+H_2O and $Y(NO_3)_3$+H_2O) when exposed to proton beam up to 70 MeV. We investigated the minimum element concentration in water required to detect a PG enhancement compared to a pure water solution. Using TOPAS MC, we also reproduced all experiments, as well as we studied the feasibility of the proposed methodology in a geometry closer to a clinical scenario. Both measurements and simulations indicated that ^{31}P and ^{89}Y are the most promising elements, as they produce signature PGs in the 0.8 MeV - 1.4 MeV range, with an enhancement of about 4% (^{31}P) and 1.4% (^{89}Y) at a concentration of 0.5%.

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Practical and clinical aspects of radiotherapy

A novel technology for particle beam monitoring based on thin silicon sensors

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Purpose: An innovative detector based on thin silicon UFSD detectors was developed and characterized by the medical physics group of the University and INFN-Torino for single ion discrimination and ion counting in a therapeutic particle beam.

Materials and Methods: Thin silicon sensors were developed, characterized and used in a prototype detector aiming at discriminating and counting single protons or carbon ions of therapeutic beams at a maximum fluence rate of 108 p/(cm2*s) with a systematic uncertainty of less than 1%. The sensor is segmented into 146 strips with a sensitive area of 2.7×2.7 cm2 to cover the beam cross-section of about 1 cm FWHM at the isocenter.

The detector is read out by six custom ASICs housed on a dedicated frontend board connected to 3 FPGAs (Xilinx Kintex7). A LabVIEW program is used to display online the counting rate of each strip and to store the data for offline analysis. An extensive characterization was performed first in the laboratory with a pulse generator and then with proton and carbon ion beams at the Italian National Center of Oncological Hadrontherapy (CNAO).

Results: Data were collected and analyzed at different beam energies at CNAO for carbon ions and protons. The beam profile was studied by measuring the number of measured particles as a function of the strip number and fitting the corresponding distribution with a Gaussian. The beam FWHM measured for different energies is compared with nominal values at the isocenter.Moreover, the counting efficiency was determined by comparing the total number of counts with the delivered number of protons for different beam fluences and energies. Finally, the uniformity over 20 identical spills was studied and was found to be better than 1% independently of the beam energy.

Conclusions: The tests performed proves the feasibility of directly measuring the particle rate during treatments. Further studies towards using this technology for beam monitoring in clinical practice require improving the radiation resistance, using finer segmentation and increasing the detector-sensitive area.

Research on targeted radionuclide therapy and associated technologies

Boron Neutron Capture Therapy, a form of hadrontherapy mediated by neutrons

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Boron Neutron Capture Therapy (BNCT) is a radiotherapy that consists in patient irradiation with low energy neutrons after the administration of a tumour-targeting borated drug [1]. The thermal neutron capture in 10B generates two high-LET, short-range charged particles that cause non-reparable damages to the cell where the reaction takes place. Provided a suitable tumour-to-normal tissue boron concentration ratio, the neutron irradiation can provide a therapeutic effect while sparing the healthy tissues. Selectivity is guaranteed by boron bio-distribution, thus BNCT is the only hadrontherapy potentially useful to control spread tumours, such as metastases, or malignancies located close to very radiosensitive targets. One of the crucial elements of a BNCT clinical facility is the availability of an intense neutron beam with precise spectral characteristics. The beam design is thus a pivotal aspect of the design of a clinical BNCT centre. Modern BNCT is based on neutron beams obtained from proton accelerators coupled to Be or Li targets. Some aspects of a facility project based on a 5 MeV, 30 microA RFQ proton accelerator, on Be target and on a Beam Shaping Assembly based on aluminum fluoride will be presented, together with the assessment of its therapeutic potential and suitability for clinical use [2]. Moreover, important advancement concerning BNCT mixed-field dosimetry will be introduced. In particular, the need of radiobiological data to feed models for the translation of BNCT dose into photon-equivalent units will be presented in light of the future work in this field [3].

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Research on targeted radionuclide therapy and associated technologies

Production of alpha emitters for cancer therapy

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Alpha emitters hold great promise to improve ligand therapy or Targeted Alpha Therapy (TAT), where an alpha emitter is attached to a biological tracer. The tracer is injected into the blood stream of a cancer patient and accumulates over time in the cells with the targeted expression, e.g. cancer cells. As alpha particles have a relative high Linear Energy Transfer (LET), it typically causes more cell kill than other options for ligand therapy, e.g. the beta emitter ^{177}Lu. Therefore, alpha emitters can be an excellent therapy choice where high LET is required as a last option due to radiation resistance and where external beam therapy with high LET particles (protons, heavy ions) is not applicable (e.g. widely-spread metastases).

First clinical treatment with the alpha emitter ^{225}Ac have caused large excitement due to successes in hard-to-treat prostate cancer [1]. ^{225}Ac does not only send out one alpha particle, but four in its decay chain. But the supply of ^{225}Ac is limited [2]. At TRIUMF, we have the appropriate accelerator (500 MeV cyclotron) to produce large quantities of ^{225}Ac by proton irradiation of ^{232}Th [3]. We successfully developed the target, the handling, and the purification to produce ^{225}Ac. As ^{227}Ac is co-produced and constitutes an unwanted contamination which could accumulate in the bones of patients, potentially causing late side effects or secondary cancer, we also developed the separation of ^{225}Ra. By utilizing the ^{225}Ra as parent isotope and incorporating it into a generator, very pure ^{225}Ac can be produced for curative intent [4, 5].

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Research on targeted radionuclide therapy and associated technologies

Cyclotron-based production of innovative radionuclides for medicine

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The cyclotron-based production of radionuclides for medicine is one of the research activities carried out in the framework of the SPES (Selective Production of Exotic Species) project at the Legnaro National Laboratories of the National Institute for Nuclear Physics (INFN-LNL). SPES aims at the construction of an advanced ISOL (Isotope Separation On-Line) facility to produce re-accelerated exotic ion beams for nuclear physics studies and to perform multidisciplinary activities, such as radionuclides production for medical applications and neutron-based research. The heart of SPES is the 70 MeV proton-cyclotron with a dual-beam extraction, installed in 2015 in a new building equipped with ancillary laboratories currently under completion. The ISOLPHARM project exploits the ISOL-technique to investigate the production of medical radionuclides, in particular ^{111}Ag [1,2]. This work will mainly present the results obtained with the interdisciplinary project LARAMED (LAboratory of RAdionuclides for MEDicine) [3,4], that in the last ten years had investigated the direct production of ^{99m}Tc, ^{67}Cu, $^{52/51}$Mn, ^{47}Sc radionuclides and in the next year will study proton-based production of ^{155}Tb. LARAMED research activities are ranging from the nuclear cross section measurements to target development and characterization, radiochemistry, radiopharmaceutical labelling, up to imaging studies and recovery of the enriched material used as target [5-16]. A consolidated network of collaborations with national and international facilities, including universities and hospitals, characterizes these research activities on medical radionuclides production at the INFN-LNL.

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Research on targeted radionuclide therapy and associated technologies

Production of unconventional radioisotopes, radiochemistry development and preclinical studies for cancer theranostics at TRIUMF

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Using unconventional radionuclides for cancer treatment has been gaining popularity in recent years thanks to the remarkable results from the clinical studies with ^{177}Lu, ^{223}Ra and ^{225}Ac [1–3]. TRIUMF launched a campaign to produce ^{225}Ac from ^{232}Th spallation [4]. Benefiting from this program, several other interesting alpha-emitters are co-produced, including ^{213}Bi, ^{227}Th, and ^{212}Pb, which we have developed processes to purify [5]. TRIUMF's ISOL facility allows the production of Tb isotopes, including ^{155}Tb which we use as an imaging companion for ^{225}Ac and ^{177}Lu [6].

Those unconventional radionuclides require specific chelators for efficient and stable labelling, due to their larger sizes and different chemical properties compared to conventional radiometals. We have developed several novel chelators for those radionuclides [7]. The novel chelators were attached to tumour targeting peptides and were subsequently labelled with radioisotopes.

Preclinical imaging and biodistribution studies with peptides targeting melanoma or neuroendocrine tumour were performed, and the results demonstrated tumour specific uptake and low background uptake, indicating the promises of the novel radionuclides and chelators. Therapy studies with ^{225}Ac is undergoing.

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Need for accurate particle-impact cross sections and Monte Carlo simulations

Need of positron impact cross sections: Ionisation cross section calculations

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The interaction of biomolecules with positron is of special interest apropos to positron emission tomography (PET) scans [1,2]. Using positron emitters in PET scans has aided the early detection of cancer and brain disorders. Furthermore, this technique has also been considered an alternative to ion beam cancer treatments for dosimetry purposes. The cross-section resulting from the interaction of positrons with biologically relevant media is used to model single positron tracks in such media [3]. The particle-tracking codes such as PENELOPE, GEANT, and LEPTS are used to model the radiation damage at the cellular level, which require cross-sections as their basic input [4]. Positron impact cross-section calculation/measurements are in a nascent stage even though having such important applications. In the literature, the elastic and total cross sections are fairly reported; however, for the inelastic processes (ionisation, excitation, annihilation) not much data is available [5]. In the present work, we review the status of the positron impact ionisation cross-section calculation. Recently, the binary encounter bethe (BEB) method, a well-known method for electron ionisation cross section calculation has been applied for positron scattering systems showing encouraging results [6,7]. This fills the void for the total ionisation cross-section data. The input parameters required for BEB are very simple and straightforward, and hence we focus on this method. The next step will be to obtain the partial ionisation cross-section which is dependent on the accurate branching ratio determination. The progress on this problem will be presented and discussed during the events.

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Need for accurate particle-impact cross sections and Monte Carlo simulations

Relativistic quantum theory for modeling electron scattering

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In this work we present a method for calculating relativistic electron scattering with nuclei, atoms and molecules including the temperature dependence. In particular, we focus on the mean-field approximation of the Dirac equation for many-fermion systems and its self-consistent numerical solutions, which are obtained by using either radial mesh or Gaussian basis sets. The former approach is appropriate for spherical symmetric problems, such as atoms, while the second is more suitable for studying non-spherical non-periodic polycentric systems, e.g. molecules and clusters. We apply our theoretical method to electron scattering with water molecules useful for the study of ionization processes in biological systems, which are fundamental in hadrontherapy. The elastic electron scattering with liquid water, along with inelastic scattering collisions through which secondary electrons release their energy, represents a crucial event of the physico-chemical mechanism caused by the interaction of fast ion beams with a biological medium. In hadrontherapy, the energy lost by the fast ions during their way inside the bio-medium causes the emission of secondary electrons ejected through the ionization of the constituents. The calculation of scattering cross sections for collisional processes, e.g. ionization, excitation or elastic scattering, due to the passage of ion beam whitin the living tissue is key to determine the secondary electrons produced. Moreover, we will discuss and describe the extension of our relativistic computational approach to study weak nuclear decays in nuclei of medical interest.

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Advanced devices to measure energy deposition at the micro- and nanoscales

Silicon-on-insulator microdosimetry: new domain of quality assurance in particle therapy

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Charged particle radiotherapy (CPT) with helium and deuterium was first used seventy years ago by Lawrence and Tobias [1]. CPT provides a better physical dose distribution than conventional X-ray treatment with a well-defined high dose region known as the Spread-Out Bragg Peak (SOBP) which can be positioned in the tumour with much lower doses to the surrounding tissues. This higher therapeutic ratio can be further enhanced by modifying the radiobiological properties of the beam. The Linear Energy Transfer (LET) is inversely related to the beam energy and associated with a higher Radiobiological Efficiency (RBE). This relationship is complex and can be described by several models including the microdosimetric kinetic model (MKM).

Proton therapy is the most developed CPT modality and the RBE is assumed to be 1.1 compared to X-rays. However this is not correct, and the full benefit of proton therapy depends on making good use of the variable RBE by maximising higher values in the tumour and lower ones in surrounding tissue.

The denser ionisation (higher LET) produced by Carbon Ion Therapy (CIT) is particularly effective in radioresistant or hypoxic tumours. Even greater benefit can potentially be obtained by using several different ions to produce a uniform high LET distribution in the SOBP while keeping a lower dose and LET in other areas [2]. No single ion has the best dose distribution, oxygen enhancement ratio (OER), or overall hypoxic/radioresistant tumour kill. Incorporating the varying LET distributions of heavy-ions into a dose-LET optimized composite treatment plan may allow new options for the irradiation of patients with complex cancers.

The LET and RBE are highest at the end of the range as the particles are slowing down and stopping so it is important that this effect is minimised in critical normal tissues. LET optimized robust planning can help achieve this. It is also necessary to have good quality assurance of dose averaged LET (LETD) in addition to physical dose verification.

To achieve this in routine clinical practice, the Centre for Medical Radiation Physics (CMRP), University of Wollongong, has developed a portable semiconductor microdosimeter called MicroPlus which measures stochastic energy deposition by charged particles on a cellular level to calculate the dose averaged lineal energy y_D and LETD.

A treatment plan was delivered to a phantom using protons, helium, carbon, oxygen, and neon ion or combination beams. We demonstrated that measurement with MicroPlus can predict biological effects, such as cell survival fraction, RBE, and RBE-weighted dose which were in good agreement (better than 5%) with the treatment planning system [3-5].

The MicroPlus probe is already tested in clinics at several particle therapy centres and will guarantee the best treatment of cancer patients with proton and ion therapy when implemented as a tool for routine new domain of quality assurance in CPT.

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Advanced devices to measure energy deposition at the micro- and nanoscales

Microdosimetry with mini-TEPC in hadrotherapy

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Microdosimetry provides information about the pattern of energy deposition in biological targets that be correlated with biological effects and may be useful in planning and conducting radiation therapy. The methodology is clearly relevant to charged particle beam therapy but can provide relevant information also to BNCT, targeted internal emitters and conventional photon therapy.

In current clinical practice, the treatment planning system often includes consideration of radiation quality parameters. In proton therapy, in particular, the use of a fixed Relative Biological Effectiveness (RBE) of 1.1 to weight the physical dose is under discussion due to evidence of an increase of RBE along the depth dose profile, especially at the end of the particle range [1-2].

Considered the intrinsic uncertainty in the calculation of radiation quality parameters by analytic algorithms or Monte Carlo calculations, experimental microdosimetry is a useful tool to measure the agreement between the planned and the delivered treatment, thus reducing the uncertainties of the biological effectiveness calculated by the treatment planning system (TPS). However, at present there is no routine use of experimental microdosimetry in ion-beam therapy: while the calculated dose distributions produced by the TPS are routinely verified with ionization chambers as part of the quality assurance program, there is no commercial detector available to perform routine verification of the radiation quality.

In this talk recent development on the realization and use of miniaturized tissue equivalent proportional counters will be presented, for specific applications in particle therapy as well as in BNCT [3, 4]. Measurements performed at the 148 MeV energy-modulated proton beam at the radiobiological research line of the Trento Proton Therapy Centre will be presented and discussed.

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Nanoscale radiation damage to DNA: experimental and modelling perspectives

Applications of Nanodosimetry in Particle Therapy Planning

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In this talk, I will give an overview of the applications of nanodosimetry in particle therapy treatment planning [1]. My talk will summarize the underlying concepts of nanodosimetry and describe the development and current status of nanodosimetric detector technology. I will also give an overview of Monte Carlo track structure simulations that provide nanodosimetric parameters for proton and ion therapy treatment planning. Classical and modern radiobiological assays that can be used to demonstrate the relationship between the frequency and complexity of DNA lesion clusters and nanodosimetric parameters will be reviewed. Lastly, I will review existing approaches of treatment planning based on RBE models or dose-averaged linear energy transfer and contrast them with the RBE-independent approach based on nanodosimetric parameters.

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Nanoscale radiation damage to DNA: experimental and modelling perspectives

Nanoscale radiation damage to cellular DNA: bond-breaking mechanisms of secondary low energy electrons and their medical applications

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About 80% of the energy absorbed in cells exposed to high-energy ionizing radiation (IR), produces firstly ions and secondary electrons. These latter posse the largest portion of the deposited energy (E), with an initial energy distribution lying essentially below 30 eV and peaking around 9-10 eV. Although some low-energy ($E < 20$ eV) electrons (LEEs) can further ionize biological tissues, they mostly interact with biomolecules via the formation of a transient anions (TAs). TAs have lifetimes varying from one femtosecond to several picoseconds and can efficiently break chemical bonds by dissociative electron attachment (DEA), or by autoionization, when the target molecule is left in a dissociative excited state. In large biomolecules, such as DNA, TAs are formed on fundamental constituents (e.g., a base or phosphate group) [1].

In this talk, the results from LEE impact on plasmid DNA will be presented and the mechanisms leading to various lesions under single collision conditions will be explained. Plasmids constitute the form of DNA found in mitochondria and appear as a suitable model of genomic DNA. The plasmids were condensed on Ta substrates, and thereafter transferred to vacuum to be irradiated. The samples recuperated from vacuum were analyzed by electrophoresis and enzyme treatment to quantitate the yields of single and double strand breaks, other cluster damages, isolated base lesions, and crosslinks. From the electron-energy dependence of the damage yields, it was generally concluded that the decay of TAs into destructive channels played a major role in inducing these lesions in the 0-20 eV energy range [2].

Describing the role of LEEs in damaging the type of DNA found in living organisms has implications not only in conventional radiotherapy, but in more recent treatment modalities, such as targeted radionuclide therapy, nanoparticle-aided radiotherapy and heavy-ion radiotherapy. Examples will be provided at the conference, to illustrate the specific role of LEEs in the development of these new radiotherapeutic modalities, which produce large, localized densities of short-range LEEs, resulting in a reduction of radiation damage to healthy tissues for a given absorbed dose by cancer cells [3]. Moreover, it will be shown that chemotherapeutic drugs can amplify LEE-induced damage. Consequently, fundamental knowledge of LEE-interactions with DNA bound to such drugs should lead to improve treatments in concomitant chemoradiation therapy.

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Nanoscale radiation damage to DNA: experimental and modelling perspectives

Low-Energy Electron Damage to Plasmid DNA in Thin Films: Experimental parameters and DNA radiosensitization by terpyridine-Pt

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The interaction of low-energy electrons (LEEs) with DNA plays a significant role in the mechanisms leading to biological damage induced by ionizing radiation, particularly in radiotherapy, and its sensitization by chemotherapeutic drugs and nanoparticles [1]. Plasmids constitute the form of DNA found in mitochondria and appear as a suitable model of genomic DNA [2]. In a search for the best LEE targets, the films were deposited on oriented graphite or polycrystalline tantalum, with or without DNA auto-assembly via diaminopropane (Dap) intercalation. The damages were induced to thin plasmid films in vacuum, by 6, 10 and 100 eV electrons under single collision conditions. The yields of single and double strand breaks (SSBs and DSBs), other cluster damages (NDCD), isolated base lesions (BDs), crosslinks (CLs) and loss of supercoiled (LS) were measured by electrophoresis and enzyme treatment. Yields were correlated to the influence of vacuum, film uniformity and surface density, substrate and DNA environment. The lyophilized Dap-DNA films were found to be the most practical high-quality targets for the investigation of LEE interaction [3]. These studies pave the way to the fabrication of LEE target-films composed of plasmids intercalated with other biomolecules that could mimic the cellular environment, e.g., as a first step, by replacing Dap with an amino acid.

Terpyridine-platinum (Tpy-Pt), which bind preferentially to guanine-quadruplexes in telomeres has recently emerged as a drug having considerable potential for use in cancer chemoradiation therapy [4].Our new results indicate that the introduction of Tpy-Pt in plasmid DNA significantly enhance LEE-induced DNA damages, especially CLs, BDs and potentially lethal cluster damages. The magnitude of these enhancements suggests that LEEs play an important role in the radiosensitization mechanism of Tpy-Pt at molecular level. Some of these results will be presented at the conference with corresponding amplification factors caused by binding Tpy-Pt to plasmid DNA.

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Nanoscale radiation damage to DNA: theoretical perspectives

Excitation and ionisation cross-sections of charged particles in condensed-phase biologically-relevant materials

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The interaction of swift charged particles (either ion beams or energetic electrons) with condensed-phase materials underlies many biomedical applications of radiation. Energetic proton or carbon ion beams are used in the advanced radiotherapy technique of hadrontherapy, and their nanometric track-structure is defined by the ejection and propagation of secondary electrons [1]. Energetic electron beams are also used in radiotherapy, or are ejected by radiopharmaceuticals. Even conventional X-ray radiotherapy produces a large number of photoelectrons. Thus, an accurate modelling (needed to understand and optimise these applications) requires to accurately know the interaction probabilities of charged particles with biologically-relevant materials, particularly for very low energy (< 100 eV) electrons, which represent one of the main inductors for lethal clustered DNA damage [2].

Over the recent years, in our research group we have developed models, based on the dielectric formalism [3,4], for calculating cross sections for inelastic events (the main responsibles for biodamage), both integral and differential (in secondary electron ejection energy and angle), for arbitrary condensed-phase biomaterials (including liquid water and the DNA molecular building blocks). These models were first introduced for the impact of ion beams [5,6], to be more recently extended for electron beams by including the particularities of low energy electrons [7].

Apart from biological materials, current research also requires the knowledge of electronic interaction probabilities of charged particles with transition metals, widely used for enhancing the effects of radiotherapy by means of nanoparticles [8]. Our models are also being applied to obtain accurate energy-loss quantities for these materials [9,10].

The purpose of this contribution is to review these methods, and to show the general good agreement between theory and experiments got for both ions and electrons in a wide energy range and for a large collection of biologically-relevant materials. These models and cross sections will be very useful to advance towards a detailed modelling of nanoscale radiation biodamage.

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Nanoscale radiation damage to DNA: theoretical perspectives

Understanding solvation effects on proton irradiation of DNA from RT-TDDFT simulations

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Proton irradiation of DNA is of utmost importance for many fields, from understanding radiation damage in space and Earth to medical applications for cancer treatment. Computer simulations are highly valuable tools for understanding such process, and among these, ab initio simulations employing Real Time - Time Dependent Density Functional Theory (RT-TDDFT) allow to obtain an extremely detailed description of the process down to the electronic and atomistic scale. However, these are computationally demanding due to the required level of theory, which involves simulating in real time the non-adiabatic propagation of the electronic subsystem of the target material, which is why to date these methods have been restricted to DNA systems in absence of water [1], or at most with few solvating molecules. Here we present the results of RT-TDDFT simulations of proton irradiation of a realistic DNA system (i.e. a DNA strand in bulk water) with pre-sampled proton trajectories [2], where we have determined different important aspects of the proton irradiation process such as the stopping power of the system, the hole/excitation distribution, the spatial distribution of the holes in terms of the depopulations of the maximally localized Wannier functions and, more importantly, the influence of the surrounding water molecules. We will show that water is neither a mere spectator on the process nor a simplistic reducing or enhancing agent of the excitation process [3]. Instead, water qualitatively changes the excitation landscape of the proton-irradiated DNA, making the hole population on the different atoms and bonds qualitatively different in the solvated vs. the dry DNA case. This conclusion warns against the usual practice of extrapolating results obtained in dry DNA systems to the actual DNA system in physiological conditions, and indicates that other models for estimating radiation damage in DNA may need to be revisited.

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Nanoscale radiation damage to DNA: theoretical perspectives

Low-energy electrons and DNA: A perspective from first-principles simulations

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In this talk I will provide a general overview on the role played by low energy electrons in DNA damage. First, I will briefly discuss experimental findings and theoretical results hand in hand with the aim of describing the physics and chemistry that occurs during the process of radiation damage, from the initial stages of electronic excitation, through the inelastic propagation of electrons in the medium,the interaction of electrons with DNA, and the chemical end-point effects on DNA in a realistic, physiological environment.The role played by the aqueous solution and the amino acids from the histones in chromatin will be considered as well as thermal fluctuations. The focus of this talk will be our recent first-principles molecular dynamics simulations that address the issue of how the environment favours or prevents LEEs from causing damage to DNA [1,2]. I will finish by summarising the conclusions achieved so far, and by suggesting several possible directions for further study.

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Nanoscale radiation damage to DNA: theoretical perspectives

DNA radiation damage in the nucleosome: the molecular dynamics perspective

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Despite a vast accumulated basic knowledge in irradiating single cells and tissues, medical radiotherapy of cancer is still based on the application of simple empirical models, with little or no reference to the microscopic complexity of DNA damage and molecular repair pathways. In cell irradiation experiments, the amount of radiation-induced DNA damage is found to be systematically proportional to the dose. Conversely, clonogenic survival (at least in traditional x-ray beam external irradiation) appears to obey a linear-quadratic (L-Q) function of the dose. Empirical models fitting the L-Q behavior are derived from target theory, generally based on the following principles: (i) "hits" obey a Poisson distribution, and (ii) cell survival is due to the absence of (lethal) hits in sensitive areas of irradiated cells. However, cells survive because DNA damage is systematically repaired, not just because escaping radiation hits by chance.

Double strand breaks (DSB) are generated in much smaller proportion, and are removed with extremely fast kinetics from the damaged DNA, compared to other "simpler" lesions. Why then DSBs are so lethal for the cell? In fact, DSB repair is associated with a high error rate, much higher than for any other DNA lesion: their lethality derives by the errors in processing just a few of them. DSBs are usually associated with generating chromosome disruption. However, the ratio of translocations/DSB is of the order of 0.01 per cell/Gy. Then, do all DSBs evolve into lethal defects? Does the molecular structure of DSBs influence the repair likelihood, and the choice of repair pathway? Is there a threshold number of DSBs leading to cell arrest and subsequent death, or is it one particular type of "unrepairable" DSB that kills the cell? These are but a few key questions at the molecular scale, among many others, which can shape the actual radiation response of each cell.

In the past decade, we started a combined theoretical-experimental effort aimed at elucidating some aspects of the microscopic response of DNA to radiation, notably by focussing on the molecular dynamics of individual lesions, and statistical mechanics of damage population evolution. DSBs have been the initial focus of our work, however more recently we shifted also to including SSBs and base-damage, by connecting molecular theory with such diverse experimental techniques ranging from microsystems and microfluidics, to single-molecule force spectroscopy, to biochemical assay and cryo-microscopy. Our most recent interest is in coupling DNA molecular damage with single- and multi-nucleosome dynamics, to unravel the action of repair proteins in the early stages of their interaction with chromatin.

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Enhancing radiotherapy by means of nanotechnology

Contrast-enhanced synchrotron radiation therapy: From bench to bedside

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Radiation therapy remains a fundamental tool for cancer treatment, but selective dose deposition within a targeted-tumor, while sparing surrounding structures, remains a challenge. This objective can be achieved by loading the tumor with high-Z elements prior delivery of radiation therapy. Synchrotron sources are ideal sources since they provide high-intensity and tunable monochromatic X-rays within the optimal energy-range.

We evaluated the ability of various high-Z elements, either as molecular agents (iodine [1-4] or gadolinium [5, 6] contrast agents) or in the form of nanoparticles [gold [7] or gadolinium [5, 6], to act as radiation dose-enhancers through theoretical and experimental studies.

Clonogenic assays were first used to quantify cell survival after irradiation in the presence of the dose-enhancers using monochromatic X-rays from a synchrotron or 1.25 MeV photons from a ^{60}Co source. Preclinical studies were then performed on rats bearing F98 glioma after administration of either iodine as contrast agent or AuNPs. In parallel, Monte Carlo simulations were performed to evaluate the dose for comparisons.

Finally, a clinical study was performed using an iodinated contrast-agent as the radiation dose enhancer [8-11]. Fourteen patients with brain metastases received one fraction of the overall radiotherapy treatment at the synchrotron, the additional fractions were delivered using a conventional Linac at the Grenoble university hospital. Radiosensitization was demonstrated with all agents in combination with X-irradiation at low energies. The radiation dose-enhancements were found to be highly energy-dependent for all agents. Secondary-electron-emission generated after photoelectric events appeared to be the primary mechanism by which Iodine and Gd contrast agents or AuNPs act as dose-enhancers. Increase of the animal's survival was observed after iodine systemic injection or intracerebral infusion of AuNPs. The phase I-II clinical studies demonstrated the feasibility of this technique. Our overall experience will be summarized, pointing out the advantages and difficulties of applying this method for the treatment of brain tumors.

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Enhancing radiotherapy by means of nanotechnology

High Z-elements and low energy radiation to improve efficacy of radiotherapy: mechanistic aspects

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To improve the efficacy of radiotherapy one of the objective is to increase the dose delivered to the tumour while sparing the surrounding healthy tissues. The strategy we have used consists in loading the tumor with high-Z elements such as metallic nanoparticles in combination with low energy radiations. Indeed, for low energy radiations (keV range) the absorption coefficient of heavy elements is higher than that of normal tissues (assimilated as water) and thus the deposited energy is increased proportionally to the heavy element concentration. The photoelectric effect thus induced generates photo and Auger electrons that locally, around the heavy element significantly increase the dose delivered. Such an effect could be compared to the one produced by high Linear Energy Transfer particles, increasing locally the production of radicals.

We thus have evaluated the efficacy of several heavy atoms containing molecules or nanoparticles and efforts have been made to better understand the undergoing mechanisms responsible for the observed radiosensitization effect [1-3]. Using dosimetric gels or oxidative DNA lesions as biomarkers, we have shown that in vitro, the deposited dose increases linearly with the heavy atom concentration and experimental data were found to be in agreement with theoretical ones. More recently, experiments were conducted with nanoscintillators having the properties to emit UV light upon exposure to X-irradiation. These nanoscintillators containing heavy atoms, also induce a significant radiation dose enhancement at least in vitro [4]. However while UV-photon emission could be observed experimentally when the powder of the nanoscintillators was irradiated, we could not detect any specific UV-induced DNA lesions when aqueous DNA solutions are irradiated in presence of the nanoscintillators. Such results strongly suggest that the amount of produced UV-photon is too low to generate significant levels of DNA lesions.

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Enhancing radiotherapy by means of nanotechnology

Experimental and computational studies of nano-structured gold as a radiosensitizer for proton and carbon ion radiation

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Nanostructured materials are widely being studied as radiosensitizers to increase the efficacy of radiation therapy in the treatment of cancer. Here we present recent results for enhanced cell killing for in-vitro irradiation by protons of malignant prostate and breast epithelial cells treated with gold nanoparticles in an energy range approaching the Bragg peak. The experiments were conducted in the ion beam facility at East Carolina University using the recently upgraded cell irradiation beamline.

In addition, we are expanding current Monte Carlo track structure simulation models to include swift-ion-induced secondary electron emission from gold; please see the presentation by Michael Dingfelder at this meeting for more details on the simulations. Furthermore, to explore differences between secondary electron production and transport in the bulk from nanostructured surfaces, we have measured doubly differential electron emission yields from gold foils and from gold nanostructures, including hydrated gold surfaces, induced by fast proton and carbon ion impact. These data suggest the importance of the surface structure on low-energy electron emission, which may affect radiation damage from secondary electrons in the cellular environment and influence cell killing.

Enhancing radiotherapy by means of nanotechnology

Track structure simulations in nano sized geometries

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Monte Carlo (MC) radiation transport codes for charged particles, including electrons, protons, light and heavy ions, provide detailed information about interaction types, spatial and temporal distributions of energy depositions, as well as radical species produced in the early physical and chemical states of radiation action with matter. This information allows to investigate the biological response to radiation and to determine the initial patterns of radiation damage in biological systems. MC codes depend on reliable interaction cross sections and transport models to produce viable results. General purpose codes use available cross section data bases and can simulate radiation transport in a wide variety of materials, while track structure codes are typically limited to a few materials like (liquid) water or cell constituents like DNA bases and density scaling is used to simulate other materials.

Radiation transport models include main basic assumptions: (a) all events are independent, (b) radiation equilibrium is observed, and (c) infinite and 3-dimensional transport in bulk media. If a particle passes through an interface, for example from one area of interest to another, the transport is stopped at the border, and a new event randomly selected in the new area. These assumptions work well if the dimensions of the areas of interest are sufficiently large compared to the mean free path, the average distance between two interactions. The Penelope code for example suggests that there should be at least 10 interactions within an area of interest to achieve radiation equilibrium. However, this situation changes when considering nano geometries, like nano particles. In this case, the mean free path is comparable to the geometry size. Transport model artefacts may be observed instead of realistic simulation results.

This communication investigates these basic assumptions and analyzes track structure simulations performed with the PARTRAC code for different geometries, from micrometer down to nanometer sizes. It is also known that cross section models change when going from infinite 3-dimensional transport (bulk) to 2-dimensional transport, i.e., through surfaces (see for example [1] and references therein). We also see differences in the experimentally obtained secondary electron emission spectra originating from bulk gold and gold nano particles; see for example contribution from Jeff Shinpaugh at this meeting.

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Practical and clinical aspects of radiotherapy

Proton imaging for hadrontherapy: status and prospects

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The currently established imaging modality used for treatment planning in ion therapy is x-ray computed tomography (CT). Due to the non-bijective relation between the photon attenuation coefficient, reconstructed with x-ray CT, and the relative stopping power (RSP) required for ion therapy treatment planning, RSP errors of about 3% may occur [1]. The use of ion CT promises to yield improved RSP estimation as input to particle therapy treatment planning [2], at a low imaging dose. Recently, proton CT (pCT) has been shown to yield RSP accuracy on par with state-of-the-art x-ray dual energy CT [3]. Several pCT prototype systems have been built or are currently in the design face [4-7].

In this talk, the current status of pCT will be first reviewed. A large number of studies has been published by different groups presenting different approaches for building a pCT scanner. For many of these systems, the RSP accuracy and the spatial resolution achievable with different pCT scanners has been quantified and compared to the theoretical limits of pCT [3, 6, 7, 8]. In addition, work has been done in investigating how the performance of these systems translates to particle therapy treatment planning/dose calculation [9,10]. As pCT systems have not yet matured to commercial products, a lot of effort is still invested into optimizing their image quality. A few of the artifact reduction methods applied to pCT will be also presented [11,12]. Finally, motivated by the envisaged use of pCT beyond simply treatment planning, to its application to image guidance, the concept of fluence modulation as a means for extremely low dose clinical imaging modality will be outlined [13].

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Practical and clinical aspects of radiotherapy

Proton therapy x-ray CT calibration by proton tomography

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Purpose: The dose computation in the proton treatment planning system (TPS) is based on the proton relative stopping power normalized to liquid water (RSP) distribution in the target volume. Presently, the RSP maps are extracted from x-ray computed tomographies (xCT) of the patient. Namely, the photon attenuation coefficients (CT Hounsfield Units – HU), are translated into RSP values using empirical methods based on conversion tables. These methods introduce an uncertainty on the actual position of the Bragg peak inside the patient [1], which has to be mitigated by means of the use of safety margins around the target and organs at risk. To avoid this two-step process and to reduce the intrinsic errors, we propose a different approach based on the direct use of 3D RSP maps obtained with a proton computed tomography (pCT) system. Recently, a pCT system has been developed in the framework of *INFN*-funded research projects [2].

Methods: The pCT system has been tested at the *Trento Proton Therapy Center*. At first, we implemented a custom-built phantom made of five different synthetic cylindrical inserts, to probe the performance parameters, i.e. spatial resolution, accuracy and noise spectrum. A filtered backprojection algorithm, taking into account the protons' most likely path, allowed reconstructing the phantoms' RSP 3D maps [3]. Then, pCT and xCT were acquired on a biological phantom (bovine specimen) stabilized with a formalin solution and embedded agar-agar gel. The direct, voxel-by-voxel comparison of HU and RSP maps of the biological phantom provides a cross-calibrated xCT calibration curve, i.e. a SPR-HUs look-up table, improving the description provided by the existing calibration methods.

Results: According to preliminary analysis, a resolution of about 0.65 lp/mm was estimated. Direct measurements of RSP values of the cylindrical inserts showed a mean absolute percentage error of 0.7% and a minimum obtainable noise magnitude of about 0.005 for RSP. Finally, we obtained a preliminary cross-calibration curve through the biological phantom tomographies.

Conclusions: After the performance characterization of our pCT apparatus, we constructed a preliminary HU-RSP calibration curve through the direct comparison of xCT and pCT images of a stabilized biological phantom. Then, the cross-calibration procedure will be verified on TPS in comparison with the standard CT calibration, aiming at reducing the impact of range-related uncertainties, thus improving the dose computation accuracy in proton therapy.

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Practical and clinical aspects of radiotherapy

Organ motion in proton therapy: clinical mitigation techniques of the interplay effect

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Pencil beam scanning (PBS) is the most common delivery technique in proton therapy nowadays because of its high potential to reach good dose homogeneity to the target and organs at risk (OAR) sparing. It is possible to modulate each beam in terms of position, intensity and energy to reach the best plan quality. In case of static lesions, the quality of the dose distribution can be more easily ensured as long as position and range uncertainty are taken into account. For moving targets the intra-fraction anatomy changes can have a great impact on the dose distribution [1]. This is true for any type of external beam radiotherapy because the anatomy being treated is not the same as the one used during the planning [2–3].

In PBS proton therapy treatments the active delivery system adds another source of uncertainty to the final dose distribution: the active delivery and the movement of the target can lead to an interplay effect[4-5]. This effect is more evident when the delivery time structure is on the same scale as the organ motion. The interplay effect is more severe for pencil beam scanning treatments because of the high gradient dose distributions achievable with ions respect with modulated photon radiotherapy and the resulting dose distortion can be clinically unacceptable.

There are different methods to reduce the interplay effect [5]. These methods can be distinguished into two classes: motion mitigation techniques (like abdominal compression and breath hold) and dose distortion mitigation (like beam gating, rescanning, beam tracking, spot size variations) techniques.

A combination of these methods can be used to mitigate the interplay effect [17]. Both of these classes bring with them some negative effects. For example, motion mitigation techniques can be uncomfortable for the patient and it must be verified if the patient can comply with these procedures before starting the treatment workflow. Dose distortion mitigation techniques have an impact on the treatment duration and this could conflict with the scheduling of the treatments(especially in a multi-gantry facility) or with the patient compliance. Typically, the formers are the first used in a proton therapy facility to mitigate the interplay effect because the commissioning time and the definition of the procedures are faster and easier to implement.

In clinical practice the best combination of these techniques has to be used in order to ensure the most robust treatment possible. In this presentation clinical examples like liver, lung, mediastinal and heart tumours will be presented to show practical applications of these methodologies.

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Practical and clinical aspects of radiotherapy

Protontherapy: state of the art and challenges

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