WORKSHOP ON TRANSLATIONAL RESEARCH IN ION BEAM CANCER THERAPY

TRIBCT 2014

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Workshop on Translational
Research in Ion Beam Cancer Therapy

30th September to 2nd October 2014

Aarhus University Hospital, Skejby

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Cancer - general overview, epidemiology, overview of treatment options

10:00-10:30 **Cai Grau**, Aarhus University Hospital, Denmark:
The role of radiotherapy in cancer management

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Session 2: Radiobiology

Chair: Niels Bassler

11:00-11:45 **Jan Alsner**, Aarhus University Hospital, Denmark:
The cellular and molecular response to radiotherapy and particle therapy

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Current issues in translational particle therapy research

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Clinical evidence and need for clinical research in particle therapy

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Wednesday 1st October

Session 5: Towards the cellular level

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A novel monitoring technique for on line dose profiling in hadrontherapy treatments

10:00-10:30 **Michael Krämer**, GSI Helmholtzzentrum für Schwerionenforschung, Germany:
Biological effects in ion beam radiotherapy

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Session 6: Radiobiology in vitro

Chair: Brita Singers Sørensen

11:30-12:00 **Stephane Lucas**, University of Namur, Belgium:
In vitro radiobiology and related topics

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Mapping RBE effects at the cellular level: impact for clinical radiotherapy

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Session 7: Track Modelling

Chair: Andrey Solov'yov

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Secondary particle tracks generated by ion beam irradiation

14:00-14:30 **Andrea Mairani**, CNAO Foundation, Pavia, Italy
Application of the FLUKA Monte Carlo code in proton and heavy ion therapy

14:30-15:00 **Pavel Kundrat**, Helmholtz Zentrum München:
Track-structure based simulations with PARTRAC and modelling beyond single-cell level

15:00-15:30 **Christophe Champion**, University of Bordeaux:
The EPOTRAN project

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Session 8: Models and RBE

Chair: Annette Sorensen

16:00-16:30 **Jorge Kohanoff**, Queen's University Belfast:
Modelling radiation effects

16:30-17:00 **Brita Singers Sørensen**, Aarhus University Hospital, Denmark:
Relative biological effectiveness (RBE) variations in particle therapy

17.30 *Reception at the City Hall.* Bus will be provided.
Bus leaves from the venue to arrive at Aarhus City Hall at 17.50

19.00 *Visit and Conference Dinner at the Aros Art Gallery.*

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Session 9: Down to the Molecular Scale

Chair: Kevin Prise

09:00-09:30 **Andrey Solov'yov**, Frankfurt Institute for Advanced Studies, Frankfurt, Germany:

Nanoscale insights into ion beam cancer therapy as seen through 'a virtual microscope'

09:30-10:00 **Filipe Ferreira da Silva,** New University of Lisbon, Portugal:

Decomposition of sulphur containing moleculestriggered by low energy electron

10:00-10:30 **Annette Sorensen**, University of Stratchclyde, United Kingdom:

Enhancing the efficacy of X-ray and targeted radionuclide therapy in neuroblastoma

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Session 10: New Insights

Chair: Andrey Solov'yov

11:30-12:00 **Eugene Surdutovich**, Oakland University, USA:

Shocks and heating in ion beam tracks

12:00-12:30 **Fred Currell**, Queens University Belfast, United Kingdom:
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12:30-13:00 **Emanuele Scifoni,** GSI Helmholtzzentrum für Schwerionenforschung, Germany:

New challenges for biologically adapted treatment planning: single and multi-ion approaches

13:00-14:00 *Lunch and departure*

TUESDAY

Cancer - general overview, epidemiology, overview of treatment options

Morten Høyer[1]

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The aim of this lecture is to give a general overview of cancer therapy in Denmark. It will include a short review of cancer biology, epidemiology and treatment strategies.

With 38.000 new and almost 250.000 prevalent cases of cancer in 2014, cancer is a major health care problem in Denmark. Cancer is the elderly patients' disease and with increasing age of the Danish population, we can foresee a large increase in cancer incidence over the next 10-20 years. It is therefore of outmost importance that the health care system is prepared for this change in the population of cancer patients. It is important to emphasize that elderly patients should not be treated like young patients. They may need less toxic and less intensive therapies.

The multidisciplinary approach is important in cancer therapy. The treatment often includes surgery, radiation therapy and systemic cancer therapy. The multidisciplinary collaboration is organized in the Danish Multidisciplinary Cancer Groups (DMCGs) consisting of specialist from all relevant specialties. The DMCGs are responsible for development of national guidelines for diagnosis, therapy and follow-up of all major cancer groups, for establishment of databases for quality assessment and research and for initiation of clinical trials.

Optimal surgical techniques are important for the outcome of treatment of most cancers. The techniques have been refined over the last 10 years. It has moved from open surgical procedures over laparoscopic techniques to robotic assisted surgery. The novel methods are often more time consuming and they are more expensive than the old techniques. Most surgeons believe that the new methods are better, but there are no clinical evidence to support this belief.

Over the same time, radiotherapy has undergone a dramatic evolution. Twenty years ago, we used two-dimensional (2-D) or planar imaging for treatment planning. Nowadays we use 3-D imaging and include the motion in time as a fourth dimension in the planning of radiotherapy and imaging systems mounted on the treatment machines ensure high precision in delivery of the treatment. Unfortunately, most of these improvements were also not supported by clinical evidence.

The systemic therapy of cancer has benefited from the extreme gain of knowledge within molecular biology. Twenty years ago, chemotherapy and endocrine therapy were the most important systemic therapies. Today we have a number of new biological targeted drugs for therapy of cancers where we had no treatment options before. The novel agents are most often well tolerated and they improve to some extent the survival, but this benefit is often limited.

Treatment of cancer has improved considerably over the years. The treatments have become more efficient and less toxic and by combining local and systemic therapies, we will improve the overall therapeutic outcome.

The role of radiotherapy in cancer managment

Cai Grau

Aarhus University Hospital, Aarhus, Denmark

The cellular and molecular response to radiotherapy and particle therapy

Jan Alsner

Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark
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Radiation biology and molecular radiation oncology are rapidly evolving and exciting fields of research. Of particular interest are the signalling pathways for the cellular responses to ionizing radiation and it is becoming increasingly clear that charged particles and photons can stimulate these signalling pathways quite differently. The presentation will summarize some of the major molecular and cellular responses to ionizing radiation in general, including DNA damage signalling, DNA repair, cell cycle checkpoints, cell death, and radiation induced fibrosis. In addition, the two most recent recently described 'hallmarks of cancer', reprogramming of energy metabolism and evading immune destruction, will be discussed in relation to radiotherapy. Finally, the presentation will discuss the topic of personalized radiotherapy with focus on the biological basis for prediction of individual tumour control and risk of normal tissue toxicity.

Clinical radiobiology – morbidity, fractionation, hypoxia

Jens Overgaard

Aarhus University Hospital, Aarhus, Denmark

High precision and high conformity radiotherapy – from intensity-modulated to adaptive radiotherapy

Ludvig Muren

Aarhus University Hospital, Aarhus, Denmark

Motion management in radiotherapy

Per R Poulsen

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Radiotherapy treatments should ideally maximize the ratio between dose delivered to the tumour and to healthy tissue. This task is, however, complicated by tumour motion during the treatment delivery. The motion is most often accounted for by treating an enlarged static volume that includes both the tumour and its anticipated motion with a high probability. This approach increases healthy tissue irradiation, potentially leading to enhanced side effects, and part of the tumour may still move outside the pre-designed static target volume causing lower tumour doses than prescribed. Alternative approaches include (1) motion suppression, where different means are used to reduce or halt the tumour motion; (2) gating, where the treatment is only delivered when the tumour is in a specific location; and (3) tumour tracking, where continuous tumour position monitoring during treatment delivery is used for repeated realignment of the treatment beam to the tumour position. This presentation will give an overview of available methods to detect and compensate for tumour motion during radiotherapy delivery.

Radiotherapy dosimetry

Claus E. Andersen[1]

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Absorbed dose to water is a physical quantity that is measured in units of gray (Gy). It serves as an important factor in the prediction of biological response to ionizing radiation both in radiotherapy and radiation protection. A comprehensive framework has therefore been established to minimize measurement uncertainty and to secure traceability to the International System of Units (SI). A driving force in this work has been to enable sharing of clinical experience, for example in clinical trials, among hospitals worldwide. This framework is, however, under constant development as new and improved treatment modalities become available.

This presentation will provide a review of the basics physics of radiotherapy dosimetry and methods of dose measurements using gas-filled detectors (ionization chambers) and solid-state detectors (e.g. alanine and organic plastic scintillators). A key element is to clearly separate the measurement problem into (i) energy absorption processes (i.e. how the detector interacts and perturb the radiation field) and (ii) signal generation processes. As the detector signal is normally generated in competition with alternative routes of energy consumption, the signal-per-dose may be strongly depend on the microdosimetric properties of the radiation (ionization density effects). Current challenges for dosimetry in MV photon beams and in particle therapy will be discussed.

Ion beam facilities for cancer therapy
Current status and challenges.

Niels Bassler

Dept. of Physics and Astronomy
Aarhus University, Denmark

Particle therapy with ion beams of protons or heavier ions show more favourable dose distributions than that of megavolt photons. Contrary to photons, ions deposit most dose at the end of their particle trajectory, which then reduces the dose in the entry channel and exit channel. This enables possibility for dose escalation in the PTV and/or reduction of side effects in the surrounding normal tissues and organs at risk.

During the last two decades particle therapy has seen a strong increase in interest in Europe, USA and Asia. Currently, about 100.000 patients were treated, and to date over 40 proton therapy centers and 6 heavy ion centers are in operation. About 20 new proton therapy facilities are under construction and are expected to be available in the next 2 years. Thus, proton therapy is entering mainstream radiotherapy as an accessible option.

The use of heavier ions for cancer therapy, however, is still considered as experimental, in part due to the complex radiobiology and the lack of availability for research due to the large scale and the associated cost of the facilities needed.

All ions face the challenge to better understand the radiobiology. Even for protons, most protocols suggest using a flat relative biological effectiveness of 1.1, which may be an oversimplification for clinical practice. Apart of carbon ions, beams of Helium-4 ions and Oxygen-16 ions will eventually become available at research facilities for patient research, which unlocks new treatment strategies such as LET-painting for overcoming radioresistance/hypoxia.

All radiobiology models applied in clinical ion therapy today rely on phenomenological descriptions, most prominently those based on amorphous track structure. In the context of the TRIBCT / Nano-IBCT forum, I intend to discuss how a simple radiation detector possibly could be used to elucidate the nature of high-LET radiation and its radiobiology.

Current issues in translational particle therapy research

Jens Overgaard

Aarhus University Hospital, Aarhus, Denmark

Clinical evidence and need for clinical research in particle therapy

Cai Grau

Aarhus University Hospital, Aarhus, Denmark

WEDNESDAY

The tumour environment

Michael Horsmann

Aarhus University Hospital, Aarhus, Denmark

A novel monitoring technique for on line dose profiling in hadrontherapy treatments

I. Mattei[1,2]

for the ARPG group

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Presenter: Paola Maria Frallicciardi, La Sapienza University, Italy

Hadrontherapy is a technique that uses accelerated charged ions for cancer treatment. The high irradiation precision and conformity achievable with heavy ions, enhance the Radio Biological Effectiveness (RBE) of such therapy while helping sparing the surrounding healthy tissues and Organs At Risk (OAR). To fully profit from the improved therapy spatial selectiveness, a novel monitoring technique, capable of providing a high precision in-treatment feedback on the dose release position, is required. Here we propose a novel approach based on the simultaneous detection of secondary protons and prompt photons that are emitted at large angles with respect to the therapeutical beam incoming direction and are correlated with the Bragg Peak (BP) position and the related dose release.

In the first part of this contribution we will review briefly the measured flux and energy spectra for secondary particles produced by ^{4}He, ^{12}C and ^{16}O ion beams of therapeutical energies impinging on thick PMMA phantoms. Such measurements afford a solid evidence that the rate of produced protons on prompt photons is large enough to supply the particle sample needed for a fast online monitor operating during a typical treatment that will be capable to provide the required O(mm) spatial resolution.

In the second part of this contribution we will present the novel dual mode hadrontherapy monitor, named "DoseProfiler" (DP), exploiting, simultaneously, the backtracking of secondary charged particles and prompt photons emitted during the irradiation of the patient. The DoseProfiler, whose final layout has been optimized using a dedicated Monte Carlo simulation based on the aforementioned experimental results, combines a tracker detector made of scintillating fibers and a calorimeter built with pixelated LYSO crystals, for gamma detection and energy measurements. Six tracker squared layers, built from two orthogonal planes of squared scintillating fibers, will provide the particle direction information, while the LYSO crystals will measure the particle energy.

A first tracker layer has already been assembled and a preliminary evaluation of the detector performances has been done using cosmic rays. The fibers system detection efficiency and the optical cross talk as well as other preliminary performances obtained with dedicated test beams will be reviewed.

Biological effects in ion beam radiotherapy

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and M. Durante[1,3]

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Radiotherapy with positively charged particles, i.e. protons and heavier ions such ascarbon, is rapidly becoming a standard method to treat cancer [1]. This is due to the favourable physical and radiobiological properties of these radiation modalities [2].
Pioneering work was performed for example at LBL or at NIRS, using passive beam delivery systems. However, most of the newly established ion beam therapy sites (HIT, CNAO, MIT, MedAustron) run an active beam delivery. This implies new possibilities but also new challenges for treatment planning systems (TPS). Charged particle beams generated by accelerators with active energy variation enable sophisticated dose distributions, which allow to treat especially radioresistant tumours in complex geometries,whilst sparing healthy tissue to a large extent. Such dose distributions can only be obtained via dedicated optimization procedures built into the TPS. Ion beams in general have a Relative Biological Effectiveness (RBE) depending nonlinearly on absorbed dose - among other quantities. Thus a versatile and reliable radiobiological model has to be an integral part of the TPS. Most - if not all - clinical sites in Europe apply the Local Effect Model (LEM), which was introduced into clinical practice in the carbon ion pilot project at GSI [3]. Likewise, the TRiP98 TPS developed in-house at GSI [4] was first used clinically within the pilot project and is now in production use as a research prototype at various sites.
In this contribution we will describe the established procedures to obtain patient treatment plans for ion beams. We will introduce the aspects of LEM important for treatment planning. Sample plans for various ion types, including protons, helium, carbon and oxygen ions will be discussed [5], emphasizing the versatility of both, the LEM and the TRiP98 TPS.

References

]1] http://ptcog.web.psi.ch/ptcentres.html.
[2] D. Schardt, Th. Els¨asser and D. Schulz-Ertner, Rev. Mod. Phys. 82 (1), 383 (2010).
[3] Th.Els¨asser, W.K. Weyrather, T. Friedrich, M. Durante, G. Iancu, M. Kr¨amer, G. Kragl, S. Brons, M. Winter, K.J. Weber, M. Scholz, Int. J. Radiat. Oncol. Biol. Phys. 78, 1177 (2010).
[4] M. Kr¨amer, E. Scifoni, C. W¨alzlein, M. Durante, J. Phys.: Conf. Ser. 373 (1), 012017 (2012).
[5] R. Gr¨un, Th. Friedrich, M. Kr¨amer, K. Zink, M. Durante, R. Engenhart-Cabillic, and M. Scholz, Med. Phys., submitted.

IN VITRO RADIOBIOLOGY AND RELATED TOPICS

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Cancer is the leading cause of death in industrialized countries. One of the current treatment modality is radiotherapy. Even if most of the cancer cases candidates for radiotherapy are treated with sparsely ionizing radiation (like X-rays or ^{60}Co units), new modalities using protons or other heavy ions have emerged in the past decade.
Nowadays, about 100.000 patients have been treated with carbon or protontherapy systems. Although protontherapy and hadrontherapy are on the way to become treatments of choice, little data on cell survival after exposure to charged particles is available, especially at very low doses. For instance, protontherapy treatments are based on knowledge acquired with X-rays and the dose is scaled by a factor of 1.1. This approach oversimplified the effects, particularly at the end of the particle track. For hadrontherapy treatment, a very important feature is nuclear fragmentation: when heavy ions pass through an organ, even small sections for nuclear reactions produce a significant amount of lighter reaction products. This change in radiobiological efficiency between the primary ions like carbons and the lighter secondaries has to be studied in order to incorporate the effect in treatment planning.

Therefore, both for proton and higher ions based therapy the knowledge of cell survival data is a crucial issue to assess the radiosensitivity of a given cell line. Thus, fundamental studies are required to accurately determine radiosensitivity parameters for various cell lines and for various particles and energies and to examine molecular cell response pathways, which can be different when the radiation nature is modified. Such work can be performed by low energy particle accelerator that can be used to irradiate different cell lines with various particles, LET and dose rate: one can study the survival fraction and determine the RBE of a selected particle and cell line. Typical biological bioassays (cell viability, DNA damages and DNA synthesis, …) are available specially to study a set of phenomena, called the non-targeted effects, that have been discovered recently and which challenges the idea that the only critical effect of ionizing radiation in the cell is the DNA damage and that less incident energy means less death, fewer DNA breaks and fewer mutations. Those effects are: adaptive response (AR), bystander effect (BE), genomic instability (GI), inverse dose rate effect (IDRE), low dose hyper-radiosensitivity (HRS).

In this lecture we will present a general view of the various setup that are used for in-vitro radiobiology and we will discuss selected examples that are of interest for future ion based protocols.

Mapping RBE effects at the cellular level: impact for clinical radiotherapy

K.M. Prise[1], P. Chaudhary[1], T.I. Marshall[1], F.M. Perozziello[2], L. Manti[2], F.J. Currell[3], S.J. McMahon[1], J.N. Kavanagh[1], G.A.P. Cirrone[4], F. Romano[4] and G. Schettino[5]

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Rapid advances in our understanding of radiation responses, at the cellular, tissue and whole body levels have been driven by the advent of new technological approaches for radiation delivery. In radiotherapy and ion beam therapies, these have led to the application of complex treatment delivery plans aimed at maximising the conformity of dose to the tumour and minimising normal tissue dose. A major consequence is the production of dose-gradients across tumours and normal tissues as dose is "painted" into the treatment volume. At the level of individual cells within a tumour and in surrounding normal tissues, dose metering occurs both spatially and temporally as part of the overall goal of delivering a uniform dose to the tumour. Despite this, significant heterogeneity of response exists within tumours related to individual radiosensitivity, proliferation, hypoxia and intercellular communication. Our understanding of the biological consequences of radiation is based on a long history of uniform exposures in both *in vitro* and *in vivo* models which may not be applicable to current therapeutic schedules [1]. Recent experimental studies have begun to assess in simple cell culture models the consequences of modulation of dose delivery [2]. A key finding had been that alongside direct effects, intercellular bystander signaling plays an important role and new models are now being developed to determine the impact of intercellular communication on cellular response in modulated treatment fields [3].

For protons, significant differences exist between the deliveries of passively and actively scanned clinical beams, both spatially and temporally. Using clinical proton beams at we have been able to compare the biological response of cells to both passively and actively scanned beams and test for differences both within the treatment field and immediately outside. We have also mapped at high resolution the changes in Relative Biological Effectiveness along a pristine and a spread-out Bragg Peak for a range of endpoints. These studies indicate that some of the fundamental determinants of spatial dose distributions observed with clinically relevant photon energies also hold true for protons [4].

Acknowledgments: The authors are grateful to Cancer Research UK (C1513/A7047), and MRC (G1100014) for funding their work.

References

[1] K.M. Prise and J.M., O'Sullivan, *Nature Reviews Cancer,* **9,** 351 (2009)
[2] K.T., Butterworth, et al., *Int. J. Radiat. Oncol. Biol. Phys* **79,** 1516 (2011)
[3] S.J. McMahon, et al., *PLOSONE,* **8,** e54526 (2013)
[4] K.T. Butterworth, et al., *Phys Med Biol* **57,** 6671 (2012)

Secondary particle tracks generated by ion beam irradiation

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The Low Energy Particle Track Simulation (LEPTS) procedure [1] is a powerful complementary tool to include the effect of low energy electrons and positrons in medical applications of radiation. In particular, for ion-beam cancer treatments provides a detailed description of the role of the secondary electrons, abundantly generated around the Bragg peak, as well as the possibility of using transmuted positron emitters (C11, O15) as a complement for ion-beam dosimetry. In this study we present interaction probability data derived from our IAM-SCAR [3, 4] calculation method together with corrective factors for liquid environments. Using these data, single electron and positron tracks in liquid water and pyrimidine have been simulated to provide information about energy deposition as well as the number and type of interactions taking place in any selected “nanovolume” of the irradiated area. Finally, by integrating our LEPTS procedure into the GEANT4 [1] simulation tool kit, single high energy ion tracks, including secondary electron generation and its damaging effects will be presented

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References

[1] G. Garcia Gómez-Tejedor and M. C. Fuss (eds.*), Radiation Damage in Biomolecular Systems* (Springer, London, 2012).
[2] F. Blanco and G. García, Phys. Rev. A **67**, 022701 (2003).
[3] F. Blanco and G. García, Phys. Lett. A **330**, 230 (2004).

Application of the FLUKA Monte Carlo code in proton and heavy ion therapy

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Monte Carlo (MC) codes are increasingly spreading in the hadrontherapy community due to their detailed description of radiation transport and interaction with matter. MC methods are being utilized at several institutions for a wide range of activities spanning from beam characterization to quality assurance and dosimetric/radiobiological studies.
The suitability of a MC code for application to hadrontherapy demands accurate and reliable physical models for the description of the transport and the interaction of all components of the expected radiation field (ions, hadrons, electrons, positrons and photons). This becomes extremely important for correctly performing not only physical but also biologically-based dose calculations especially in cases where ions heavier than protons are involved. In addition, accurate prediction of emerging secondary radiation is of utmost importance in emerging areas of research aiming at in-vivo treatment verification.
This contribution will address the specific case of the general-purpose particle and interaction code FLUKA. Validations and applications at several experimental sites as well as proton/ion therapy facilities with active beam delivery systems will be presented:

- Generation of synchrotron accelerator libraries of proton/carbon ion beam energies and foci (i.e., lateral widths at the isocentre of the treatment unit).
- Physical database generation: laterally integrated depth-dose profiles, lateral-dose distributions at different depths, secondary fragment yields and fragment energy spectra at different depths.
- Forward MC re-calculations of physical/RBE-weighted dose distributions of proton and carbon ion treatment plans.
- MC-based treatment planning for proton and heavy ion beam therapy.

FLUKA's flexibility and the satisfactory agreement with several dosimetric data and nuclear fragment yields demonstrate that the code is a valuable help for supporting a large variety of applications to proton and ion beam therapy.

Track-structure based simulations with PARTRAC and modelling beyond single-cell level

Werner Friedland[1], Pavel Kundrát[1]

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The first part of this contribution focuses on simulations of biological effects of radiation on subcellular level with PARTRAC, a state-of-the-art tool for Monte Carlo simulations of radiation track structures, damage induction in cellular DNA and DSB repair via non-homologous end-joining [1]. The tool consists of dedicated modules that describe interactions of ionizing particles with the traversed medium, the production and reactions of reactive species, and score DNA damage by overlapping the track structures with multi-scale chromatin models. The DSB repair module includes the spatial mobility of the DNA ends and their enzymatic processing; it has recently been extended to simulate chromosomal aberrations [2].

The second part summarizes lessons learned from modelling two intercellular signalling systems perturbed by radiation: Radiation-induced bystander effects, which may induce non-linearities in dose-response curves and spread biological effects outside irradiated regions, and intercellular induction of apoptosis, an anti-carcinogenic mechanism selectively removing oncogenic transformed cells. Mathematical modelling enables inferring details on the mechanisms of bystander effect such as the lifetime and emission duration of bystander signals [3]. For the intercellular induction of apoptosis, modelling indicates that this phenomenon may explain the presence of dormant pre-neoplastic lesions [4]. Modelling also predicts that low-dose radiation, while enhancing this protective phenomenon *in vitro*, may reduce its anti-carcinogenic effect *in vivo*, in agreement with epidemiological data that demonstrate carcinogenic effects of low-dose radiation.

Acknowledgement: The research leading to these results has been supported by the EC through EpiRadBio and DoReMi projects, and by the German Federal Ministry of Education and Research through the projects ‘3D/4D Breakpoint Architecture’ and ‘LET-Verbund’.

References:
[1] W. Friedland, M. Dingfelder, P. Kundrát, P. Jacob, Mutat. Res. 711, 28-40 (2011).
[2] W. Friedland, P. Kundrát, Mutat. Res. 7569, 213-223 (2013).
[3] P. Kundrát, W. Friedland, Radiat. Prot. Dosimetry, submitted.
[4] P. Kundrát, G. Bauer, P. Jacob, W. Friedland, Carcinogenesis 33, 253-259 (2012).

EPOTRAN: a full-differential Monte Carlo code for electron and positron transport in liquid water

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When biological matter is irradiated by charged particles, a wide variety of interactions occurs, which leads to a deep modification of the cellular environment. To understand the fine structure of the microscopic distribution of energy deposits, the Monte Carlo event-by-event simulations are particularly suitable. However, the development of these track structure codes requires a large set of accurate multiple differential and total cross sections for describing all the collision processes including the ionization, the electronic excitation, the elastic scattering and the Positronium formation event when incident positrons are considered. In this context, we have recently developed a Monte Carlo code for electrons and positrons in water, the latter being commonly used as surrogate of the biological medium. All the processes are studied in detail via theoretical differential and total cross section calculations performed by using partial wave methods within the quantum mechanical framework. Comparisons with existing theoretical and experimental data in terms of stopping powers, mean energy transfers and ranges have shown a very good agreement. Moreover, thanks to the theoretical description of Positronium formation, we access - for the first time - to the complete kinematics of the electron capture process [1-2]. Then, the current Monte Carlo code is able to describe the detailed Positronium history, what provides useful information for medical imaging (like Positron Emission Tomography) where improvements are needed to define with the best accuracy the tumor volumes [3-4]. Besides, recent quantum mechanical models for treating the electron-induced ionization process in a realistic biological medium have been implemented into the code in order to extend its applications. Thus, an accurate description of biological volumes of interest - including the nucleobases as well as the sugar phosphate backbone - may be considered in the current version [5]. A detailed overview of the code with numerous applicative studies will be exposed during this talk

References:
[1] C. Champion and C. Le Loirec, Phys. Med. Biol. **51**, 1707 (2006).
[2] C. Champion and C. Le Loirec, Phys. Med. Biol. **52**, 6605 (2007).
[3] C. Champion, P. Zanotti-Fregonara, and E. Hindié, J. Nucl. Med. **49**, 151 (2008).
[4] P. Zanotti-Fregonara et al., J. Nucl. Med. **49**, 679 (2008).
[5] C. Champion, C. Le Loirec, and B. Stosic, Int. J. Radiat. Biol. **88**, No.1-2, 62 (2012).

Modelling radiation effects: how to cause DNA damage

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DNA damage caused by irradiation has been studied for many decades. Motivations include assessing the dangers posed by radiation, and understanding radiotherapies and how to improve their efficiency in combating cancer. A full description of the irradiation process involves multiple size and time scales. It starts from the interaction of radiation (either electromagnetic or particles) with the biological medium causing ionization and more generally electronic excitation. This is followed by the propagation of the newly created species, notably electrons and radicals, which scatter inelastically with other components of the medium, e.g. water, proteins, ions, DNA. There is then a stage of chemical diffusion of these species until they become solvated and inactivated by the medium, or they chemically react with other species by making or breaking bonds. Of particular interest is the interaction of these species with DNA, as its damage via strand breaks is generally accepted as the chemical basis of radiotherapies.

Low-energy electrons produced by ionization play an important role in this damage. This has been shown experimentally more than a decade ago using plasmid DNA samples [1], where energy-resolved cross sections for single and double strand breaks were obtained by gel electrophoresis techniques. By performing similar experiments on analogues of DNA components and water, it was proposed that electronic resonances in the region around 10 eV are responsible for fragmentation via dissociative electron attachment (DEA) processes. Since then, a significant body of work has been carried out to elucidate the role of DEA, in particular by performing experiments on increasingly large molecules also under microsolvation conditions and looking at fragmentation patterns via mass spectrometry [2].

In this presentation I will describe a programme of work that aims at understanding the behaviour of DNA components in a realistic, physiological-like environment, due to the presence of such electrons. This is done by first-principles molecular dynamics simulations of excess electrons in condensed phase models of increasingly complex DNA fragments solvated in water and in the presence of proteins [3-6]. Perhaps the most interesting conclusion is that the environment offers a large variety of mechanisms to protect DNA from strand breaks, which do not operate at the gas-phase or microsolvated levels.

References:
[1] B. Boudaiffa et al., Science **287**, 1658 (2000).
[2] S. Denifl et al., Int. J. Mass. Spectrom. **277**, 296 (2008).
[3] M. Smyth and J. Kohanoff, Phys. Rev. Lett. **106**, 238108 (2011).
[4] M. Smyth and J. Kohanoff, J. Am. Chem. Soc. **134**, 9122 (2012).
[5] M. Smyth, J. Kohanoff and I. Fabrikant, J. Chem. Phys. **140**, 184313 (2014).
[6] Bin Gu, M. Smyth and J. Kohanoff, submitted to PCCP.

Relative biological effectiveness (RBE) variations in particle therapy

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THURSDAY

Nanoscale insights into ion beam cancer therapy as seen through 'a virtual microscope'

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Nowadays modelling based on the solid physical principles and fundamental equations combined with advanced computational techniques and visualization methods provide a tool to observe and to investigate dynamical molecular processes in a great detail which could not be achieved by any other technology. Such a 'virtual microscope' has been utilized for the better understanding of the key molecular mechanisms responsible for the ion-beam cancer therapy.

The advance has been achieved with the use of the powerful multi-purpose software package MBN Explorer [1], designed to study structure and dynamics of molecular systems of various degrees of complexity. A broad variety of interatomic potentials implemented in the MBN Explorer allows to simulate the structure and dynamics of different molecular systems, such as atomic clusters, fullerenes, nanotubes, metallic nanomaterials, proteins and DNA, crystals composite bio-nano systems and nanofractals. A distinct feature of the package is in its universality and implemented multiscale features that make it applicable to really a broad range of problems involving complex molecular systems.

The action of 'virtual microscope' will be presented for the particular case study aiming at the understanding of Nanoscale insights into Ion-Beam Cancer Therapy (Nano-IBCT). The European Research in this research area was coordinated through the COST Action Nano-IBCT, see [2]. The emphasis in this discussion will be placed on the multiscale analysis and the molecular level assessments of radiation damage in biological targets consequent to irradiation by ions was designed in order to qualitatively and quantitatively describe the effects that take place when energetic ions interact with living tissues, e.g. the Relative Biological Effectiveness (RBE) of radiation [3]. A road towards the understanding physical aspects of ion-beam cancer therapy on the molecular level revealed that this problem has many temporal, spatial, and energy scales, while the main events leading to the cell death happen on a nanometer scale. The multiscale approach is interdisciplinary, phenomenon-based and, having started some years ago, passed several milestones making discoveries on different scales, for review see [3]. Thus, in addition to the traditional pathways of biodamage often related to secondary electrons and free radicals production in cells after irradiation [3], the multiscale approach also considers a new efficient pathway of DNA damage caused by the nanoscopic shock waves created by the strong local heating in the vicinity of the ion tracks due to the energy deposited by ions [4], the effect which can be visualised through the 'virtual microscope'.

References:
[1] I.A. Solov'yov, A.V. Yakubovich, P.V. Nikolaev, I. Volkovets, A.V. Solov'yov, J. Comp. Chem. **33**, 2412 (2012), http://www.mbnexplorer.com/ , http://www.mbnresearch.com/
[2] http://www.mbnresearch.com/project-nanoibct
[3] E. Surdutovich, A.V. Solov'yov, European Physical Journal D, Colloquium Paper, in print (2014); http://xxx.lanl.gov/ arXiv:1312.0897v1 [physics.bio-ph] 3 Dec 2013
[4] E. Surdutovich, A.V. Yakubovich, A.V. Solov'yov, Scientific Reports **3**, 1289 (2013).

Decomposition of sulphur containing molecules triggered by low energy electron

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Chemoradiation therapy is gradually becoming a dominant cancer treatment. When using chemotherapy simultaneously with radiotherapy, lower doses are required compared to radiotherapy treatments only. Such joint therapy involves a radiosensitizer that will improve DNA damage upon radiation interaction, increasing cancer cells death rate. Halouracils are an example of radiosensitizers, where such molecules are thymine analogues with the methyl group in the position C5 replaced by an halogen atom. Dissociative electron attachment [1] and electron transfer [2] studies to halouracils yield several anionic fragments that require ring breaking. Such decomposition results in its function loss, which proves its enhanced sensitivity to radiation damage.

In the last years, the scientific community has become more aware of the importance of studies addressing electron driven reactions to sulphur containing biological molecules, in order to further investigate the role of sulphur in such processes. Sulphur containing amino acids, such as cysteine and methionine, have already been subjected to DEA studies [3, 4]. Recently DEA studies to gas phase thiothymine [5] have shown the role of sulphur atom in the fragmentation process. In this communication DEA studies to sulphur containing biological prototypes as taurine, aminomethanesulphonic acid and 4-thiaproline are presented.

Acknowledgments

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References

[1] S. Denifl, S. Matejcik, S. Ptasinska, B.Gstir, M. Probst, P.Scheier, E. Illenberger, T. D. MarK, J. Chem. Phys. **120**, 704 (2004).

[2] F. Ferreira da Silva, D. Almeida, R. Antunes, G. Martins, Y. Nunes, S. Eden, G. Garcia, and P. Limão- Vieira, Physical Chemistry Chemical Physics, **13**, 621 (2011).

[3] Y.-F. Wang, S. X. Tian, and J. Yang, Physical Chemistry Chemical Physics, **13**, 597 (2011).

[4] J. Kopyra, I. Szamrej, H. Abdoul-Carime, B. Farizon, and M. Farizon, Physical Chemistry Chemical Physics, **14**, 8000 (2012).

[5] J. Kopyra, S. Freza, H. Abdoul-Carime, M. Marchaj, and P. Skurski, Physical Chemistry Chemical Physics, **16**, 5342 (2014).

Enhancing the efficacy of X-ray and targeted radionuclide therapy in neuroblastoma

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Radiotherapy (X-ray photons) is used as a curative and palliative treatment in approximately 50% of cancer patients. Despite technological advances improving the precision of radiotherapy delivery, efficacy is hampered by normal tissue toxicities and intrinsic or aquired radioresistance.

The increase in our understanding of the biological pathways underlying the response to X-irradiation over the last decade, has lead to an explosive interest in novel molecularly tumour targeted agents which when given in combination with radiation (or conventional cytotoxic chemotherapy) have the potential to radiosensitise cancer cells. Central to radioresistance mechanisms is DNA damage repair. The MRN complex (Mre11/Rad50/Nbs1) functions in both the homologous recombination and nonhomologous end joining DNA repair pathways and is involved in Double Strand Break (DSB) detection and damage signalling via the ataxia telangiectasia mutated (ATM) kinase. Mirin is a small molecule inhibitor of the Mre11-Rad50-Nbs1 complex and through disruption of Mre11 nuclease activity mirin inhibits ATM kinase activity indirectly- as a consequence Mirin has the potential to inhibit repair of DNA double stranded breaks induced by radiation.

In *in* vitro models of neuroblastoma, we have assesed the radiosensitising potential of Mirin in combination with X-irradiation and the radiopharmaceutical ^{131}I-MIBG a radiolabelled analogue of noradrenaline. ^{131}I-MIBG is a radiopharmaceutical used in the treatment of neuroblastoma. MIBG is actively taken up by neuroblastoma cells through expression of the noradrenaline transporter (NAT). Although ^{131}I-MIBG in combination with chemotherapeutics has yielded significant advances in palliative treatment cures remain elusive We have found no radiosensitising effect of Mirin when used in combination with X-irradiation however when used in combination with ^{131}I-MIBG, Mirin induced radiosensitisation. We are currently examining the mechanisms underpinning these observations to allow further development of optimum treatment schedules to allow clinical translation of MRN inhibiting drugs.

Another recent approach to radiosensitisation in tumours is dose enhancement by use of metallic nanoparticles. Based on their ability to increase the dose deposited in the target volume as a results of a difference in their mass energy absorption coefficient when compared to soft tissue, their highly reactive surface making modifications by conjugation of drugs or active targeting moieties relatively easy and their biocompatibility, numerous studies have reported the radiation sensitisation effect of gold. In combination with X-irradiation the radiosensitisation that can be achieved with gold nanoparticles is highly variable and depends on photon energy, particle size, and surface functionalisation amongst other factors. We have exploited the radiosensitisation potential of gold nanoparticles in combination with X-irradiation and ^{131}I-MIBG in *in vitro* models of cancer. As a single agent AuNPs were non-toxic. In combination with X-Irradiation radiosensitisation was cell line specific however this specificity was not apparent when gold nanoparticles were combined with ^{131}I-MIBG as radiosensitisation was evident in all cell lines investigated.

In tumour therapy the most likely clinically efficacious strategies are combination therapeutics utilising radiotherapy. Much work still has to be undertaken to determine optimal combinations with respect to targeting, scheduling and makeup of combinations. It is anticipated that studies such as these described have the potential to deliver real clinical applications for tumour treatment.

Towards nanoparticle enhanced radiotherapy: A research programme towards better cancer care

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Carefully designed nanoparticles containing heavy atoms have the potential to offer benefits normally only associated with heavy ion therapy but without the need for specialist ion accelerators. The vision for this kind of therapy is that is would be delivered at more traditional clinical centres such as those found in most industrial cities, using Linacs. This statement is supported by in-vivo measurements (e.g. [1]) and a nanodosimetric model [2]. However, more research is needed before the reality of such a vision can be properly assessed. In order to perform this assessment a combination of modelling and measurements are being performed.

One model successfully connects the collective atomic physics events to the biological outcome through a local probabilistic interpretation of induction of lethality [2]. However there are still puzzles concerning the biological effects even in quite simple systems [3], some of which will be discussed. Furthermore, physical chemistry measurements hint at still further enhancements yet to be realised [4]. A model able to account for the observations in general terms will be introduced. A brief 'future-look' will show how the models of the relevant processes might be incorporated into the next generation of radiotherapy planning tools [5] as nanoparticles of this type begin to enter the clinic [6].

References:
[1] S. Jain et al "Cell-Specific Radiosensitization by Gold Nanoparticles at Megavoltage Radiation Energies" Radiation Oncology Biology, 79 531-539 (2011)
[2] S. McMahon et al "Biological consequences of nanoscale energy deposition near irradiated heavy atom nanoparticles" Nature Sci. Rep. 1:18; DOI:10.1038/srep00018 (2011)
[3] S.McMahon, W.Hyland et al "Energy Dependence of Gold Nanoparticle Radiosensitization in Plasmid DNA" J.Phys.Chem.C 115: 20160–20167 DOI:10.1021/jp206854s (2012)
[4] Sicard-Roselli C et al. „A New Mechanism for Hydroxyl Radical Production in Irradiated Nanoparticle Solutions" Small **10**, 3338–3346, doi: 10.1002/smll.201400110 (2014)
[5] "Improving patient outcome by integrating the generic with the personal" on line: http://gow.epsrc.ac.uk/NGBOViewGrant.aspx?GrantRef=EP/K039342/1
[6] http://www.nanobiotix.com/news/release/nanobiotix-presents-successful-phase-i-results-for-its-lead-nanomedicine-product-nbtxr3-at-asco/

New challenges for biologically adapted treatment planning: single and multi-ion approaches

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Some of the most advanced facilities for particle therapy already running (like HIT and CNAO) or almost ready to be operational (like Med-Austron) are offering not only the great advantage of full active scanning, but also the possibility to use different type of ions.

Multimodality, i.e. the use of multiple fields of different ion species in the same treatment plan, introduces additional degrees of freedom, allowing to distribute high- and low-LET radiation arbitrarily. This is particularly attractive in order to selectively target hypoxia and potentially other types of intra-tumour biological heterogeneity.

In order to exploit these advantages, specific treatment planning tools are required.

To this end, we have extended the TRiP98 code, the first treatment planning system for particles, in several directions. The optimization engine has been modified to allow the inverse planning of different ion modalities simultaneously.

The biological effect calculation was extended beyond the RBE-weighted dose, including the oxygen enhancement ratio (OER).

Physical and radiobiological base datasets for ion beam modalities from protons to oxygen have been established, in order to account for the use of new ions, which are going to be used in the growing dedicated facilities.

TRiP98 is then the first treatment planning system optimizing several ion species as well as allowing biological effect painting across inhomogeneous targets, in the presence of hypoxic subvolumes. The OER model is validated experimentally through biological dosimetry measurements performed at NIRS and GSI. A dedicated experiment performed at GSI on a biological phantom with heterogeneous oxygenation show how TRiP98 is effective in restoring a given uniform cell killing redistributing dose, LET and different ion components accordingly (*Killing painting*).

After an overview on the recent different approaches in biologically adapted particle therapy using TRiP98 [1,2,3], we give an outlook on the possibilities of different ion beams in this respect, including the impact of different fractionation schemes for different modalities.

References:
[1] E. Scifoni, W. Tinganelli, W.K. Weyrather, M. Durante, A. Maier, M. Krämer, Phys Med Biol. **58**, 3871 (2013).
[2] N. Bassler, J. Toftegaard, A. Lühr, BS Sørensen, E. Scifoni, M. Krämer, O. Jäkel, LS Mortensen, J. Overgaard, JB Petersen , Acta Oncol. **53**, 25 (2014).
[3] M. Krämer, E. Scifoni, F. Schmitz, O. Sokol, M. Durante, Eur. Phys. J.D **68** (2014) in print

POSTERS

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Presenter:Paola Maria Fralliciardi

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***C. Popescu,** K. Bauer, S. Murphy, T.L. Pan and R.E. Palmer*

Inelastic electron interaction (ionization/attachment) with nitroimidazole

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The nitroimidazolic molecules are presently under investigation as potential radiosensitizers for so-called hypoxic tumors which are characterized by the deprival of oxygen [1]. The effect of radiosensitizers, i.e. an enhancement in the damage of tumor cells during exposure to ionizing radiation, is also ascribed partially to the action of low-energy secondary electrons which are formed in abundant amounts during the irradiation of biological tissue. The kinetic energy distribution of secondary electrons formed finds its maximum below 10 eV, where the (dissociative) electron attachment may significantly contribute to the damage cross section. In the present study we investigated a low energy electron attachment to nitroimidazole and a methylated derivative in the electron energy range between about zero eV and 8 eV. The setup used was a high resolution electron monochromator combined with a quadrupole mass spectrometer. The resulting negative ion mass spectra as well as the anion efficiency curves showed distinct differences between the two compounds. For example, while for nitroimidazole no parent anion was observable on mass spectrometric timescales, < few hundred μs, the parent anion was observed at about zero eV of electron energy for the methylated compound. In addition, the ion yield of fragment anions formed upon dissociative electron attachment (DEA) to nitroimidazole show a sharp peak structure below 2eV which is not present for the molecule in its methylated form.

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References:
[1] G. E. Adams, I. R. Flockhart, C. E. Smithen, I. J. Stratford, P. Wardman, and M. E. Watts, Rad. Res. 178, 183 (2012).

Decomposition of sulphur containing molecules triggered by low energy electron

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References

[1] S. Denifl, S. Matejcik, S. Ptasinska, B.Gstir, M. Probst, P.Scheier, E. Illenberger, T. D. MarK, J. Chem. Phys. **120**, 704 (2004).

[2] F. Ferreira da Silva, D. Almeida, R. Antunes, G. Martins, Y. Nunes, S. Eden, G. Garcia, and P. Limão- Vieira, Physical Chemistry Chemical Physics, **13**, 621 (2011).

[3] Y.-F. Wang, S. X. Tian, and J. Yang, Physical Chemistry Chemical Physics, **13**, 597 (2011).

[4] J. Kopyra, I. Szamrej, H. Abdoul-Carime, B. Farizon, and M. Farizon, Physical Chemistry Chemical Physics, **14**, 8000 (2012).

[5] J. Kopyra, S. Freza, H. Abdoul-Carime, M. Marchaj, and P. Skurski, Physical Chemistry Chemical Physics, **16**, 5342 (2014).

Integrative Radiobiology of X-ray vs. Protons, Helium, Carbon and Oxygen Ions

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Hadron therapy is a promising technique for cancer treatment and has received increasingly attention over the last decades. This is due to the favorable physical characteristics of charged ion beams that allow highly conformal dose distributions in the tumor region while sparing adjacent normal tissues [1]. The pioneers of hadron therapy at Lawrence Berkley Laboratory performed clinical trials with different ion species: protons, helium ions, carbon ions, neon ions, silicon ions and argon ions [2]. At the Heidelberg Ion Beam Therapy Center, in addition to the proton and carbon ion beams, used for clinical treatment, helium and oxygen beams are available for experimental investigations. Further characterization of the different ion beams' effects on biological processes in tumor and non-transformed cells is of outmost importance for current therapy improvement and future clinical applications.

In this work, we perform systematic and comparative investigation of the biological response, i.e., cell survival and DNA damage signaling of tumor cells upon the irradiation with proton, helium, carbon and oxygen beams in clinical-like scenarios. For this purpose, we investigated the effect of different irradiation qualities when the cancer cells were positioned within the high dose region of 1 cm wide Spread-out Bragg-peaks (SOBP) centered at 3.5 cm depth, and compared it to the X-rays. Moreover, we designed a setting, which allows to plan a patient-like irradiation, i.e., a 4 cm wide SOBP centered at 8 cm depth. A constant physical dose of 2 Gy has been planned for the target volume. Ten effective measurement points, i.e. the location of the flaks, have been chosen in order to cover the entrance channel, the high linear energy transfer component in the distal part of the SOBP and the fragment tail (for ions heavier than protons). Preliminary Monte Carlo calculations have been performed to evaluate dose distributions. Cell survival calculations are foreseen based on in-house biological models and the well established Local Effect Model.

These studies represent first efforts towards patient specific choice of different irradiation qualities.

[1] Schardt, D., Elsässer, T. and Schulz-Ertner, D.: 2010, Heavy-ion tumor therapy: Physical and radiobiological benefits, Rev. Mod. Phys. 82, 383-425.

[2] Castro, J.: 1995, Results of heavy ion radiotherapy, Radiation Environment Biophysics 34 , 45-48.

Interaction between co-cultured cancer and endothelial cells after proton beam irradiation

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Introduction Cancer is one of the leading causes of death in the world. At present, the available treatments are surgery, chemotherapy, radiotherapy or a combination of those. One of the major problems with the use of the conventional radiotherapy is the irradiation of healthy tissues upstream and downstream of the tumor. During the past decade, new treatment modalities have emerged: protontherapy and hadrontherapy. These therapies are less invasive and more precise. However several factors can limit the efficacy of radiotherapy, including radioresistance. It was shown that radioresistance of the tumor vasculature can decrease the radiosensibility of tumor cells.

Objective We aimed to study the molecular interactions that could lead to enhance cell survival of co-cultured cancer and endothelial cells after exposure to a broad beam of protons. To this purpose, two cell lines were used: pulmonary cancer cells (A549) and immortalized endothelial cells (EAhy926).

Results The irradiation of cancer and endothelial cells with 1.5 Gy proton beam induced a decrease in cell survival of 60% when the both cell types were cultured separately as well as in co-culture. After exposure to a dose of 1.5 Gy, a cell cycle arrest in G2/M phase was observed 8 hours or 24 hours for A549 and EAhy926 respectively. However, the co-culture of EAhy926 with A549 did not influence their cell cycle arrest. Finally, the expression of pro-angiogenic and pro-inflammatory factors was enhanced when the two types of cells were exposed to proton beam.

Conclusion These experiments reveal effects of proton beam on endothelial and cancer cells separately but, in our conditions, the effects were not modulated when these two cell types were irradiated in co-culture.

Measurement of the stopping power of water for carbon ions in the Bragg-peak energy region

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Particle radiotherapy with carbon ion beams has increasingly gained interest in recent years because of its dedicated clinical advantages compared to conventional cancer therapy with photons and electrons. The full utilization of its major advantage, a pronounced maximum in the depth-dose curve, requires the precise knowledge of the stopping power of tissue for the ion energies prevailing at the Bragg peak.

The stopping power of water has been measured for the first time for carbon ions in the energy range between 1 MeV and 6 MeV using an experimental method [1] that is based on the velocity-dependent Doppler shift of the energy of γ quanta emitted by moving excited carbon nuclei [2]. The preliminary results suggest that the stopping power of liquid water for carbon ions in the intermediate energy region is by about 25% lower than that of water vapor provided by the SRIM2013 code [3]. This difference is in the same order as predicted by the semiempirical calculation of Emfietzoglou et al. [4]. Due to the preliminary nature of the experiment, however, the present results are subject to rather high uncertainty which is about 19 %. Therefore, a new experiment with a lower experiment is in preparation.

References:

[1] W. Neuwirth, U. Hauser, E. Kühn, Z. Phys. **220**, 241 (1969)

[2] J. M. Rahm, W. Y. Baek, H. Rabus, H. Hofsäss, Phys. Med. Biol. **59**, 3683 (2014)

[3] J. F. Ziegler, M. D. Ziegler, J. P. Biersack, SRIM2013, www.srim.org, 2013

[4] D. Emfietzoglou, R. Garcia-Molina, I. Kyriakou, I. Abril, H. Nikjoo, Phys. Med. Biol. **54**, 3451 (2009)

Biological responses of normal human skin fibroblasts to proton and alpha particle beam irradiations

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Our study is aimed to compare biological efficiency of proton and alpha particle beams. Human normal neonatal skin fibroblasts were irradiated by 1.1 MeV protons and 2.5 MeV/nucleon alpha particles (He-4 nuclei) beams at Tandetron 4130MC accelerator. Cells were grown on Lumox dishes with Teflon membrane (Sarstedt, bottom membrane thickness 25 □m) at normal conditions for cell growing. Confluent cell monolayers were irradiated by doses 0.5, 1, 3 and 5 Gy of protons or alpha particles. Biological response of fibroblasts to acute irradiation was assessed using cell survival test, micronuclei formation assay and PCR gene expressions analysis of proteins responsible for DNA damage response (Gadd45a), DNA repair (Parp1, Rad51, Rad52), regulation of apoptosis and cell cycle (bax, bcl2, Birc5, p21), antioxidant functions (catalase, SOD1, SOD2, GPx-1, GPx-4), transcription regulation (p53) and fibroblast function (IL-6).
We found significantly higher frequency of micronuclei in cells irradiated by 0.5 and 1 Gy of alpha particles than in case of proton irradiation (3 fold higher). This finding is consistent with lower survival of alpha irradiated cells. In these cells, we observed also cell senescence (determined as activity of beta-galactosidase), which was not found for protons. Gene expression signature was monitored 30 min and 24 h post-irradiation. Particular gene response manifested for 1 Gy alpha radiation at 24 h post-irradiation (down-regulated DNA repair genes).
As expected, alpha radiation has higher biological efficiency than protons according our results of micronuclei and cell survival tests. The interesting new findings are related to cell senescence and gene expression in alpha irradiated fibroblasts. Alpha particles are thus another promising radiation modality, which could be used in cancer radiotherapy with higher effective doses to tumor and lower damage to normal surrounding tissues.

A novel monitoring technique for on line dose profiling in hadrontherapy treatments

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Hadrontherapy is a technique that uses accelerated charged ions for cancer treatment. The high irradiation precision and conformity achievable with heavy ions, enhance the Radio Biological Effectiveness (RBE) of such therapy while helping sparing the surrounding healthy tissues and Organs At Risk (OAR). To fully profit from the improved therapy spatial selectiveness, a novel monitoring technique, capable of providing a high precision in-treatment feedback on the dose release position, is required. Here we propose a novel approach based on the simultaneous detection of secondary protons and prompt photons that are emitted at large angles with respect to the therapeutical beam incoming direction and are correlated with the Bragg Peak (BP) position and the related dose release.

In the first part of this contribution we will review briefly the measured flux and energy spectra for secondary particles produced by ^{4}He, ^{12}C and ^{16}O ion beams of therapeutical energies impinging on thick PMMA phantoms. Such measurements afford a solid evidence that the rate of produced protons on prompt photons is large enough to supply the particle sample needed for a fast online monitor operating during a typical treatment that will be capable to provide the required O(mm) spatial resolution.

In the second part of this contribution we will present the novel dual mode hadrontherapy monitor, named "DoseProfiler" (DP), exploiting, simultaneously, the backtracking of secondary charged particles and prompt photons emitted during the irradiation of the patient. The DoseProfiler, whose final layout has been optimized using a dedicated Monte Carlo simulation based on the aforementioned experimental results, combines a tracker detector made of scintillating fibers and a calorimeter built with pixelated LYSO crystals, for gamma detection and energy measurements. Six tracker squared layers, built from two orthogonal planes of squared scintillating fibers, will provide the particle direction information, while the LYSO crystals will measure the particle energy.

A first tracker layer has already been assembled and a preliminary evaluation of the detector performances has been done using cosmic rays. The fibers system detection efficiency and the optical cross talk as well as other preliminary performances obtained with dedicated test beams will be reviewed.

Scanning Probe Energy Loss Spectroscopy

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We are developing a new tool suitable for studying low energy electron damage of biomolecules. A scanning STM tip operated at high voltage can be used to obtain localized spectroscopic information about surfaces via energy loss measurements [1]. In this technique, known as Scanning Probe Energy Loss Spectroscopy (SPELS), the STM tip is used as a localized source of field-emitted electrons, which, upon backscattering from a surface, are analyzed by an energy-dispersive detector to obtain localized energy loss spectra. Characteristic surface excitations such as plasmons and excitons (as well as secondary electrons) can be probed with a spatial resolution below 50 nm and an energy resolution approaching 0.3 eV [2].

We report the development of a new generation SPELS instrument utilizing a 400-Channel detector, allowing sufficiently fast sampling of the energy loss spectra to allow us to obtain 2D spatially-resolved maps of energy loss features in a reasonable timeframe. We demonstrate the new instrument by mapping plasmons in Ag nano-islands on the surface of graphite and illustrate the various mechanisms give rise to the contrast obtained in the energy-resolved maps.

References

[1] A. Pulisciano, S.J. Park and R. E. Palmer, Appl. Phys. Lett. 93, 213109 (2008).
[2] F. Festy and R. E. Palmer, Appl. Phys. Lett. 85, 5034 (2004).

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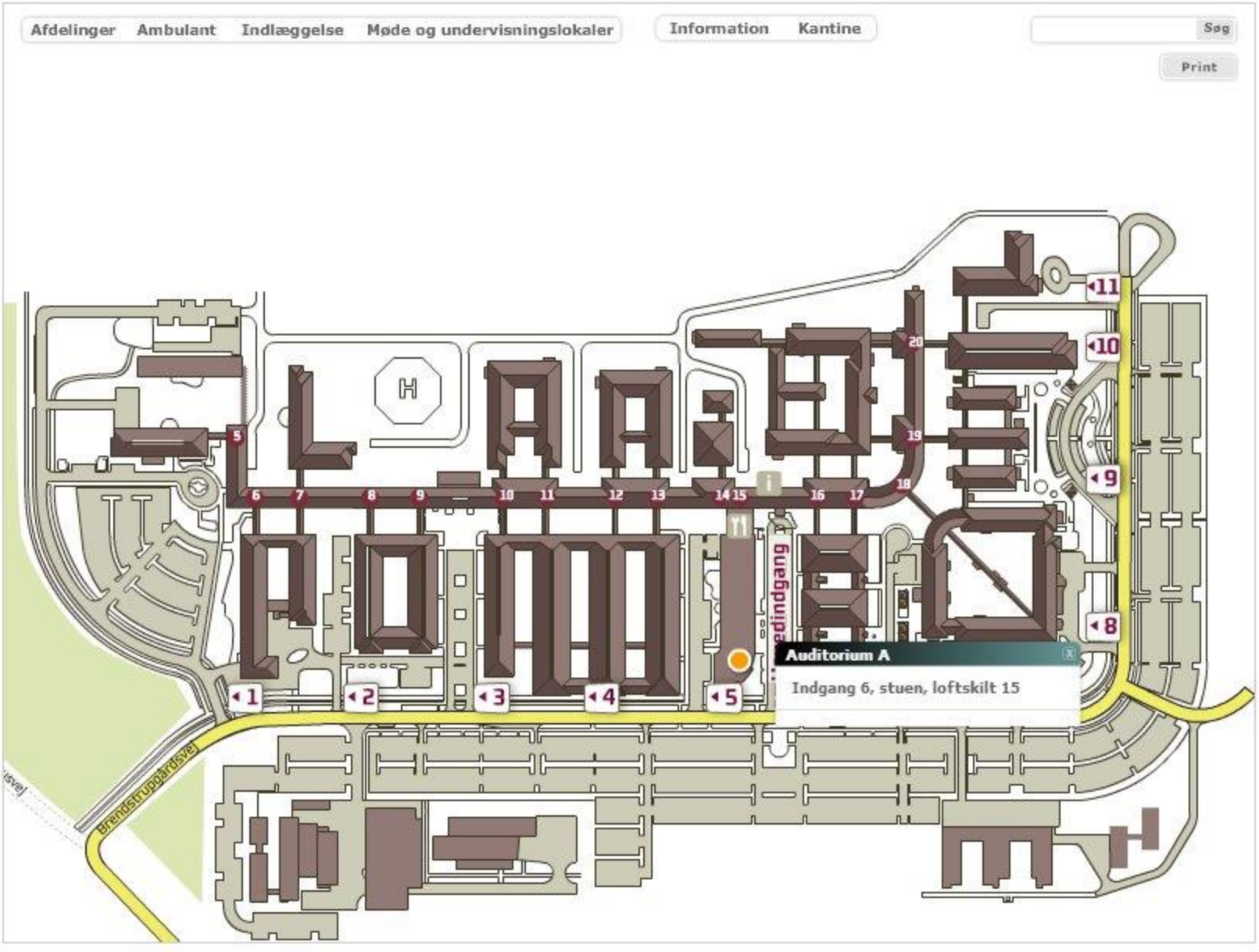
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