COST Action CA20129 MultIChem
Workshop
"Irradiation-driven chemistry: Multiscale approach"
CECAM Headquarters, EPFL campus, Lausanne, Switzerland
March 14-15, 2022

Scope

The Workshop "Irradiation-driven chemistry: Multiscale approach" will discuss the recent achievements and current challenges in the multiscale investigation of radiation-induced phenomena behind ion-beam cancer therapy (IBCT), ranging from nanoscale mechanisms of radiation-induced biomolecular damage to radiotherapy treatment planning.

The workshop will bring together expert theoreticians and leaders in computational modeling, experimentalists and radiotherapy practitioners studying irradiation-driven damage of biomolecular systems and exploiting this knowledge in the development of IBCT. Therefore, the workshop will provide an interdisciplinary and intersectoral forum to discuss the current state-of-the-art; theoretical, experimental and technological challenges underlying modern radiotherapies of cancer; and possible multiscale computational solutions to address these challenges.

Scientific Program

Monday, March 14

14^{30} - 16^{00}	**Workshop opening** **Andrey V. Solov'yov**, MBN Research Center, Frankfurt am Main, Germany *Multiscale approach for the physics behind ion-beam cancer therapy* **Alexey Verkhovtsev**, MBN Research Center, Frankfurt am Main, Germany *Atomistic approach for modeling irradiation-driven processes with radiosensitizing nanoparticles*
16^{00} - 16^{30}	Coffee break
16^{30} - 18^{00}	**Cécile Sicard-Roselli**, Institut de Chimie Physique, University Paris Saclay, France *What do we need to know about radiosensitization to design the most efficient nanoparticle?* **Olivier Tillement**, NH TherAguix, France *Ultrasmall Hybrid Nanoparticle as radiosensitizer: AGuIX, from bench to bedside*
19^{00} - 22^{00}	Social dinner

Tuesday, March 15

9^{00} - 10^{30}	**Nigel Mason**, University of Kent, Canterbury, United Kingdom *What fundamental data do we need to understand radiation damage and next generation radiotherapies?* **Ilia Solov'yov**, Carl von Ossietzky University Oldenburg, Oldenburg, Germany *Computational modelling of irradiation driven molecular processes in biological systems*
10^{30} - 11^{00}	Coffee break
11^{00} - 12^{30}	**Thomas Schlathölter**, Zernike Institute for Advanced Materials, University of Groningen, the Netherlands *Action spectroscopy as a tool for investigation of DNA radiation damage on the molecular level*

	Leo Sala, J. Heyrovský Institute of Physical Chemistry, Prague, Czech Republic *DNA origami nanostructures as tools to study radiation-induced damage to DNA*
12^{30} – 14^{00}	Lunch
14^{00} - 15^{30}	**Stefan Both**, University Medical Center Groningen, the Netherlands *Towards high precession proton therapy* **Kate Ricketts**, University College London, United Kingdom *Current and future perspectives of radiotherapy treatment planning and delivery: towards biologically-targeted radiotherapy*
15^{30} - 16^{00}	Coffee break
16^{00} - 18^{00}	**Brendan Dromey**, Queen's University Belfast, United Kingdom *Ultrafast Nanodosimetry: Tracking the role of nanostructure in the ultrafast response of matter to ionising radiation in real time* **Michael Hausmann**, Kirchhoff-Institute for Physics, University of Heidelberg, Germany *The nano-architecture of chromatin and DNA repair protein clusters in the cell nucleus after ionizing radiation attacks: a comparison of cancer and non-cancer cell response* **Richard Amos**, Proton and Advanced Radiotherapy Group, Department of Medical Physics and Biomedical Engineering, University College London, United Kingdom *Treatment planning for ion-beam cancer therapy: An overview*
18^{00} - 18^{15}	Workshop closing

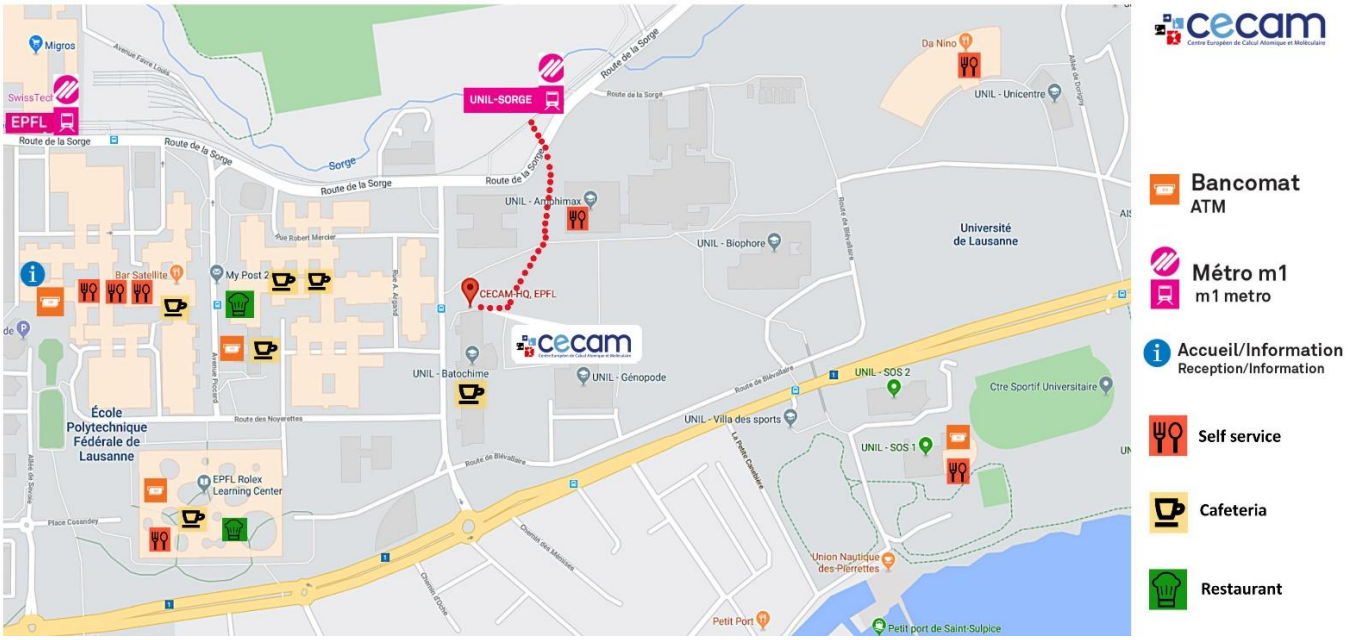
Venue and Travel Information

The workshop will be hosted by the Headquarters of the European Centre for Atomic and Molecular Computations - Centre Européen de Calcul Atomique et Moléculaire (CECAM, https://www.cecam.org/).

The address of the venue is:
EPFL campus, Batochime (BCH) building, Avenue de Forel 2, 1015 Lausanne, room BCH 2103.

The venue is located approx. 5 km away from the Lausanne main station (Lausanne-Gare) and can be easily reached by public transport.

To reach the venue from Lausanne train station take the metro M2 (entrance opposite to the train station) in direction of "Croisettes" and exit after one stop at "Lausanne-Flon". Then take the M1 metro, one floor up, direction "Renens-Gare". Exit at "UNIL-Sorge", then follow the red dots (see the map below).



The online public transport map of Lausanne is available here.

Accommodation

Participants are requested to book their own accommodation. Various accommodation options can be found (e.g. here) according to the daily allowance rate (see below).

Although we do not provide particular suggestions on accommodation, the participants may consider staying at the Tulip Inn hotel (Chemin du Cerisier 8-10, 1004 Lausanne) together with the organizers.

Reimbursement of the travel expenses

The MultIChem COST Action provides financial support to reimburse participants for their travel expenses. Detailed information about the COST reimbursement rules can be found in the Annotated Rules for COST Actions (see Section 3.1 "Travel reimbursement rules", pp. 82-88).

In order to be reimbursed you must receive an official invitation through e-COST indicating that you are eligible for the reimbursement. After the meeting, you will be required to fill in your online travel reimbursement request (OTRR) through the link you will find in the invitation email.

When arranging your travel and accommodation, please consider the following rules (see the Annotated Rules for COST Actions for complete and detailed information):

- Any transport you take in your country (airplane, train, bus, car…) is reimbursed based on the supporting documents provided (tickets for flights, trains and buses; proof of distance for car travel, e.g. by Google maps). Taxi, car rental, fuel and parking expenses are not eligible.

- For the flight ticket: it must be return and economy class ticket from the country of your primary affiliation (as registered in e-COST) to the country of the meeting. Seat reservation, luggage and cancellation insurance are eligible.

- Your stay in Switzerland should be covered under the Daily Allowance (DA). The DA for Switzerland is 198 €. The DA is intended to cover accommodation, meals and transport in the host country. No receipts will be required.

- The maximum DA rate that can be claimed is calculated according to the actual number of days you attend the meeting (as confirmed by your signature on the official attendance list for each day of the meeting), plus one day, permitting you to arrive on the day before the meeting and/or leave one day after.

- In the travel days, the DA is based on departure and arrival times (see p. 83 of the Annotated Rules for COST Actions).

Other useful information

Almost all Covid-19 restrictions have been recently lifted by Swiss authorities. This means that:
- There is no need to show a Covid certificate to attend the event or go to a restaurant.
- There are no catering restrictions.
- Masks are only mandatory in public transport. However, the participants may be asked to wear masks whenever they are not presenting or eating.
- Participants entering Switzerland from the Schengen States are not required to show proof of vaccination or negative tests upon entry. If your travel originates from other counties, you will have to present proof of vaccination that has been administered in full within the past 270 days. For further information, please see the webpage.

CECAM Workshop "Multiscale modelling of irradiation-driven processes for emerging technologies"

The MultIChem Workshop will be followed by a CECAM Workshop "Multiscale modelling of irradiation-driven processes for emerging technologies", which will be held in CECAM HQ during March 16-18, 2022.

The workshop will bring together expert theoreticians, experimentalists and technologists studying material properties and irradiation-driven processes relevant to selected emerging technologies (surface deposition techniques, nanofabrication, 3D nanoprinting using focused electron & ion beams, novel light sources). It will provide a forum for discussion of the current state-of-the-art, theoretical, experimental and technological challenges and possible multiscale computational solutions to address these challenges.

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Abstracts

Multiscale approach for the physics behind ion-beam cancer therapy

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The Multi-Scale Approach (MSA) to the molecular level quantitative assessment of radiation damage in biological targets consequent to their irradiation by ions and its implications to the ion-beam cancer therapy will be overviewed and its perspective will be discussed. The MSA approach was developed [1,2] to quantify the physical, chemical, and biological effects that take place when ion beams interact with biological targets.

Over the decade, the MSA has addressed a number of effects starting with ion propagation in tissue, features of the depth-dose profile with a Bragg peak, production of secondary electrons as a result of ionization of tissue, transport and energy loss by the secondary electrons along with other reactive species, the radial dose distribution around ion tracks, formation of wave fronts and consequent propagation of cylindrical shock waves around the ions' paths, etc, etc [1-5]. On the other side, the nanoscopic models of radiation damage as a result of action of secondary electrons, other reactive species, or stresses due to ion induced shock waves were explored [1,2]. Recently, it has become possible to join whole multiscale scenario within a single MSA capable calculating the cell survival probabilities [1,2]. This recipe has been tested on plasmid DNA and most recently on a number of cell lines [2,6]. A number of DNA lesions have been analysed and a criterion for lethal damage of a cell has been suggested and tested. A variety of experimental and related theoretical results such as probabilities of plasmid DNA lesions, enzyme repair foci, cell survival curves, oxygen enhancement ratios, effects of radiosensitising nanoparticles, radiation chemistry outcomes, high dose effects, etc., have become the field for either advancing the MSA or testing its predictions [2,7]. These challenges will be presented in the talk.

The phenomenon-based MSA is a unique method in its inclusiveness, versatility, and integrity with the high potential to *becoming practical for clinical planning of proton and ion-beam therapy* [2,8]. MBN Explorer and MBN Studio software form a solid platform for this development [9].

References:

[1] **(a)** E. Surdutovich, A.V. Solov'yov, Multiscale approach to the physics of radiation damage with ions (Colloquium paper), *Eur. Phys. J. D* **68**, 353 (2014); **(b)** E. Surdutovich, A.V. Solov'yov, Multiscale modeling for cancer radiotherapies, *Cancer Nanotechnol.* **10**, 6 (2019)

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[6] **(a)** A.V. Verkhovtsev, E. Surdutovich, A.V. Solov'yov, *Nature Sci. Rep.* **6**, 27654 (2016); **(b)** A. Verkhovtsev, E. Surdutovich, A.V. Solov'yov, Phenomenon-based evaluation of relative biological effectiveness of ion beams by means of the multiscale approach, *Cancer Nanotechnol.* **10**, 4 (2019)

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(b) A.V. Verkhovtsev, A.V. Korol, A.V. Solov'yov, *J. Phys. Chem. C* **119**, 11000 (2015);
(c) A.V. Verkhovtsev, A.V. Korol, A.V. Solov'yov, *Phys. Rev. Lett*. **114**, 063401 (2015);
(d) K. Haume, S. Rosa, S. Grellet, M.A. Śmiałek, K.T. Butterworth, A.V. Solov'yov, K.M. Prise, J. Golding, N.J. Mason, *Cancer Nanotechnol.* **7**, 8 (2016);
(e) P. de Vera, N.J. Mason, F.J. Currell, A.V. Solov'yov, *Eur. Phys. J. D* **70**, 183 (2016);
(f) K. Haume, N.J. Mason, A.V. Solov'yov, *Eur. Phys. J. D* **70**, 181 (2016);
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Atomistic approach for modeling irradiation-driven processes with radiosensitising nanoparticles

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Metal nanoparticles (NPs) made, e.g., of gold, platinum or gadolinium have been proposed as novel agents for more efficient treatment of tumors with ionizing radiation. NPs made of these metals have the capacity to enhance the biological damage induced by energetic photon and ion-beam irradiation, i.e. to act as radiosensitisers [1]. The radiosensitising effect of metal NPs is commonly attributed to strong irradiation-induced emission of secondary electrons [2,3], which induce radiolysis of the surrounding aqueous medium and thus increase the yield of hydroxyl radicals and other reactive species that may produce damage to tumor cells [4].

Radiosensitising properties of NPs may depend on many different parameters (such as size, composition and density) of the metal core, organic coatings and the molecular environment. A systematic exploration of each of these parameters on the atomistic level remains a formidable and costly experimental task but it can be addressed by means of advanced computational modeling.

This talk will present a recently developed theoretical and computational approach to analyze the formation and transport of secondary electrons and hydroxyl radicals after irradiation of coated metal NPs with ions [5]. This methodology accounts for the detailed atomistic structure of the coating material around the metal core [6], which can be characterized by means of all-atom molecular dynamics (MD) simulations using two advanced software packages, MBN Explorer [7] and MBN Studio [8]. The methodology also takes into account the important low-energy and many-body phenomena, such as collective electron excitations (the surface and volume plasmons) in the metallic core, which are the source of intense emission of low-energy electrons [3]. Results for the case study of a nanometer-sized gold NP coated with thiol-poly(ethylene glycol)-amine ($S–(CH_2)_2–PEG_n–NH_2$), one of frequently used coating materials in radiobiological experiments involving metal NPs, will be presented.

References:
[1] K. Haume, S. Rosa, S. Grellet, M.A. Śmiałek, K.T. Butterworth, A.V. Solov'yov, K.M. Prise, J. Golding, N.J. Mason, *Cancer Nanotechnol*. **7**, 8 (2016)
[2] A.V. Solov'yov (ed.), *Nanoscale Insights into Ion-Beam Cancer Therapy* (Springer International Publishing, Cham, Switzerland, 2017)
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What do we need to know about radiosensitization to design the most efficient nanoparticle?

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More than 15 years ago, Hainfeld et al. highlighted the important role gold nanoparticles (GNP) could play for therapy [1]. They demonstrated in mice that the adjunction of GNP to X-ray treatment could lead to complete tumor regression. Surprisingly, this promising effect is hardly transposed to clinical phases. One

main reason could be the absence of consensus about the benefit obtained from GNP combined with irradiation. Not only the added value of GNP can be quite different from a publication to another, but also GNP efficiency seems to highly vary from a cell type to another [2]. With this in mind, we decided to study the GNP-radiation interaction in order to get a good knowledge of the first steps of the mechanism involved, and developed a protocol to quantify the electrons and hydroxyl radicals emitted by irradiated nanoparticles [3]. Then, we compared several types of nanoparticles (gold, nanodiamonds for example) [5,6], of different sizes, and functionalized with different ligands [4]. Different radiation modalities were also studied in order to select the most efficient combination nanoparticle/radiation beam.

References:
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Ultrasmall Hybrid Nanoparticle as radiosensitizer: AGuIX, from bench to bedside

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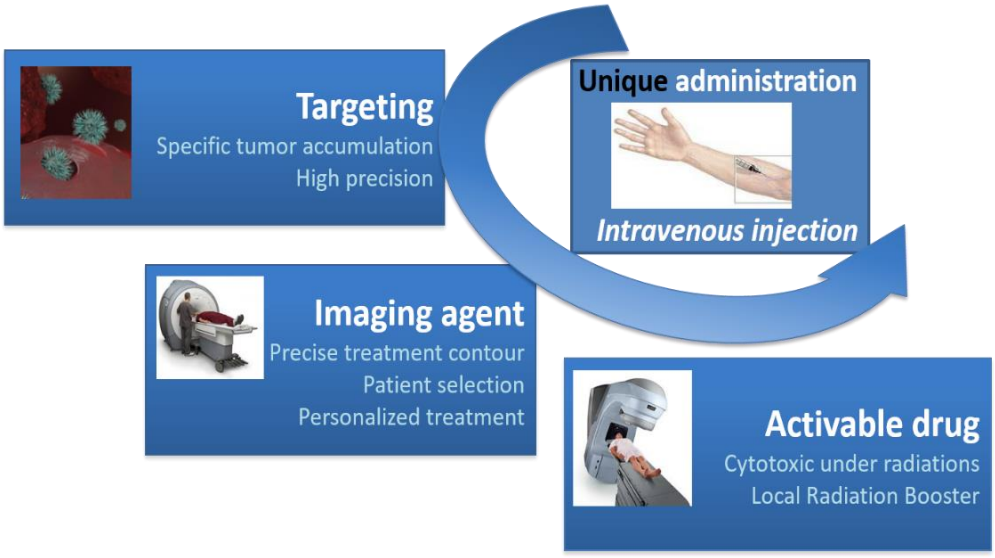
The lecture will take place in the field of nanomedicine and will describe translation to the clinic of first hybrid theranostic nanoparticle injected intravenously: AGuIX®. This nanoparticle has been designed to act as a radiosensitizer to increase locally the effect of the dose in radiotherapy and has been used in two phase Ib clinical trials: Nano-Rad (NCT02820454) for the treatment of multiple brain metastases by whole brain radiotherapy and Nano-Col (NCT03308604) for the treatment of locally advanced cervical cancer by external radiotherapy and Curie-Therapy.



AGuIX nanoparticles are ultrasmall (<5 nm) nanoparticles made of polysiloxane and gadolinium chelates. After intravenous administration, AGuIX nanoparticles accumulate in tumors due to Enhanced Permeability and Retention effect and are eliminated by the renal way. Their bioditribution and the accumulation in the tumor can be followed by MRI due to the presence of gadolinium. Their efficacy as a radiosensitizing agent has been shown on ten different animal models. During Nano-Rad clinical trial, 15 patients have been treated and all the doses (15, 30, 50, 75 and 100 $mg.kg^{-1}$) have been successfully validated. First evidences of the interest of the association between AGuIX and radiotherapy for the treatment of brain metastases have been observed and preliminary results are really encouraging.

References:
[1] F. Lux *et al.*, AGuIX from bench to bedside – transfer of an ultrasmall theranostic gadolinium-based nanoparticle to clincial medicine, *Br. J. Radiol.* **91**, 20180365 (2018)
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What fundamental data do we need to understand radiation damage and next generation radiotherapies?

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In order to develop the next generation of radiotherapy it is necessary to understand the fundamental radiation induced damage processes at the molecular level, in turn allowing nanoscale dosimetry analysis to replace current micro-dosimetry methodologies. This is particularly pertinent when developing ion beam therapy with its more targeted tumour irradiation.

In this presentation I will discuss both the current status of the database for atomic and molecular collisions pertinent to DNA damage and outline the challenges to expanding this database to study such collisions under cellular conditions. The RADAM database (http://radamdb.mbnresearch.com) developed under a previous COST Action MP1002 (Nano-IBCT: Nano-scale insights into Ion Beam Cancer Therapy) may be further developed within this Action.

Computational modelling of irradiation-driven molecular processes in biological systems

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Ion-induced DNA damage is an important effect underlying ion-beam cancer therapy [1-3]. This talk will introduce the methodology of modelling DNA damage induced by a shock wave caused by a projectile ion. Specifically, we will demonstrate how single- and double-strand breaks in a DNA molecule could be described by the reactive CHARMM (rCHARMM) force field [4] implemented in the program MBN Explorer [5]. The entire workflow of performing the shock wave simulations, including obtaining the crucial simulation parameters, will be discussed [6]. The presented results will demonstrate conditions at which a single ion hitting a cell nucleus at high linear energy transfer (LET) is sufficient to produce highly complex, lethal damages to a cell by the shock-wave induced thermomechanical stress. It will be revealed that accounting for the shock-wave-induced thermomechanical mechanism of DNA damage provides an explanation for the "overkill" effect observed experimentally in the dependence of cell survival probabilities on the radiation dose delivered with iron ions [7]. This vital observation provides strong experimental evidence of the ion-induced shock-wave effect and the related mechanism of radiation damage in cells.

References:
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Action spectroscopy as a tool for investigation of DNA radiation damage on the molecular level

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Gas-phase studies allow to study the radiation-induced dynamics in DNA on the molecular level and in unprecedented detail. We have recently focused on the molecular dynamics following the creation of inner-shell vacancies in DNA. In radiation therapy, such inner-shell vacancies are typically induced by high energy photons or by protons/heavy ions at Bragg-peak energies. In a series of experimental campaigns at synchrotrons, free-electron lasers, femtosecond laser facilities and heavy ion accelerators, we have employed action spectroscopy techniques to investigate for Auger decay processes [1], ultrafast intramolecular hydrogen transfer [2], charge migration [3] and energy dissipation in gas-phase DNA but also for investigation of DNA gas-phase structure [4]. The experimental data was interpreted by comparison to quantum chemical calculation.

In this talk, I will give an overview on our existing studies and an update on our current activities.

References:
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DNA origami nanostructures as tools to study radiation-induced damage to DNA

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Self-assembled DNA origami nanostructures folded from single-stranded DNA scaffolds contain unique addressable functionalization sites for probes, active agents, and radiosensitizers such as gold nanoparticles and halogenated nucleobases [1,2]. It has been used to study radiation damage to immobilized oligomer sequences using low-energy electrons in vacuum to extract strand break cross-sections and evaluate strand break enhancement factors [2,3]. Recent efforts from our group have led to extending these DNA-origami-based techniques in solution to complement current plasmid-based methods, specifically addressing the

complexity of the latter to accommodate radiosensitizers and evaluate sequence-specific damages. Moreover, the possibility to constrain specific DNA sequences in controlled distances from probes and sensitizers can be of interest for molecular dynamics simulations in the nanoscale. This talk will present two recent results of the use of DNA origami nanostructures to observe mechanisms of radiation-induced damage to DNA. As proof of concept, DNA origami nanotriangles under gamma (~1.2 MeV) and proton beam (30 MeV) irradiation are investigated [4] as well as nanoframe substrates (with an inner aperture to support DNA sequences of interest) in solution irradiated with high energy electrons (16 MeV). These studies open opportunities for using such nanoplatforms for fundamental studies of mechanisms of DNA radiosensitization and in investigating processes at high energy/doses of ionizing radiation.

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Towards high precession proton therapy

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In the last decade pencil beam scanning has become the treatment modality of choice for proton therapy. In the Netherlands pencil beam scanning has been adopted in the context of the Model Based Clinic. The proton Bragg peak is associated with the range uncertainty, limiting the use of proton therapy to its full potential. A better mitigation of uncertainty related to patient, physics, machine and biology is required towards development of high precession proton therapy across the body. Adaptive proton therapy is a promising solution for conventional radiotherapy, however, to make it clinically possible automatization of the radiotherapy processes and quality control procedures must be still developed and implemented in the treatment delivery workflow. Artificial Intelligence in proton therapy offers new opportunities to develop novel clinical workflows but also poses new challenges for treatment quality assurance. The newly developed Dutch Model Based Clinic has been emerged in Netherland for the past. Uncertainties are further exacerbated in the context of ultra-high dose rate proton therapy (FLASH) which requires a better understanding at fundamental level and development of new strategies towards clinical implementation. Therefore, the current state and an overview of necessary steps towards high precision proton therapy are presented.

Current and future perspectives of radiotherapy treatment planning and delivery: towards biologically-targeted radiotherapy

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Current radiotherapy technology enables high energy ionising radiation to treat disease in a highly controllable spatial and dosimetric distribution, aiming to provide tumour control by killing cancer cells while simultaneously sparing healthy surrounding tissues. Radiation cell kill depends upon many factors including characteristics of the radiation and biological properties of the cells and their environment. However, there is an extreme underuse of cellular biological information in planning radiation treatment. Each patient receives an individualised treatment optimised using physics models of radiation, but current models bear little correlation with radiation sensitivity, presenting a disconnect between physical radiation dose and biological effect. Accounting for radiation sensitivity in treatment planning would offer a powerful tool to

minimise radiation induced toxicity and maximise tumour control. This talk will present a summary of current radiotherapy planning and clinical delivery processes, and explore areas of potential future development towards biologically targeted radiotherapy. The eventual goal is a new personalised framework incorporating cancer biology (cellular and environmental factors) into physics models, bridging the current gulf between physics and biology in radiotherapy. The first step is to understand how cellular and environmental factors as well as radiation properties affect radiation induced cell death, currently not understood. An exemplar of this new bio-targeted system is nanoparticle-enhanced radiotherapy (NERT); nanoparticles have the potential to be targeted to sites of radiation resistance wherein they offer dose-boosting properties. Recent results of nanoparticle-enhancement of radiation-induced biological damage will be presented and steps forward discussed.

Ultrafast Nanodosimetry: Tracking the role of nanostructure in the ultrafast response of matter to ionising radiation in real time

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Ionisation dynamics on the nanoscale seed the processes that govern relaxation to macroscopic equilibrium in irradiated matter. Therefore, understanding the conditions that underpin this transition is critical in a wide range of applications from healthcare to radiation science. Recently we have demonstrated that laser driven ion accelerators can provide an ultrafast tool for studying this inherently multiscale regime with temporal resolution < 0.5 ps [1,2]. Here we demonstrate that it is possible to interrogate these ultrafast processes in real-time by contrasting how recovery scales with interaction dimensionality for different ionising species. We employ single-shot optical streaking to track the decay time constant, τ_c, of free carriers in matter irradiated by picosecond-scale (ps, 10^{-12} s) pulses of X-rays and protons from a single laser-driven accelerator. First by exploiting the nanoscopically heterogeneous density of SiO_2 aerogels, our results reveal a sharp discontinuity in the scaling of τ_c with average density (ρ_{av}) for proton and X-rays interactions. Cross referencing these observations with novel numerical simulations exposes the delicate interplay between the nanoscale conditions and emergent mechanisms, namely electron-phonon interaction, that drive ultrafast recovery in irradiated bulk SiO_2. Next we demonstrate how this technique can be exploited to reveal delays in the onset of solvation of electrons ionised by the passage of protons in pristine H_2O i.e. no scavenging agents [3]. Modelling again reveals how this delay can be linked to nanocavitation associated with the generation of proton tracks in H_2O. This is made possible only by the ps-scale absolute timing resolution provided by the multispecies (i.e. X-ray and proton) capability of laser-driven accelerators. Finally, we present preliminary results that show how this platform can open a new route to the real-time study of the relative growth and decay of multiple radiolytic species due to protons interacting in aqueous solutions and biologically relevant samples.

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The nano-architecure of chromatin and DNA repair protein clusters in the cell nucleus after ionizing radiation attacks: a comparison of cancer and non-cancer cell response

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Application of ionizing radiation has an increasing impact on bio-medical research, cancer diagnosis and tumour treatment. Nevertheless, there are a lot of open questions concerning the understanding of radiation DNA damaging mechanisms and repair processes within the light of radio-sensitivity or radio-resistance and, thus, individualized medical applications. The three-dimensional architecture of genomes on the micro-, meso- and nano-scale acts in combination with epigenetic modifications as an important player of gene regulation and, consequently, fundamental biological processes such as DNA damage response and repair. So far only little is known about the impact of chromatin architecture on DNA double strand break (DSB) repair pathway selection and progression at individual damage sites. How does **a cell nucleus as system as a whole**, process DSBs and re-organize the chromatin towards functionally intact repair units? We present investigations of spatial and topological parameters of chromatin and DNA repair foci during a time period of repair to glimpse key aspects related to this question. Nano-probing of radiation-induced chromatin damage sites and the recruited DNA repair proteins in combination with super-resolution Single Molecule Localization Microscopy (SMLM) are powerful methods for geometric and topological analyses of nano-structures in single cells and at single DSB sites and, thus, to study mechanisms of their formation and repair pathway regulation. We used variable tools for such investigations based on image-free high- precision SMLM, nano-scaled molecule distribution analyses, appropriate metrics following Ripley´s distance frequencies and cluster formation analyses, as well as topological quantifications employing persistence homology. Comparing the topology of repair foci by persistence homology suggests general similarities in repair cluster formation, indicating a well-defined non-random, molecule topology at given time points during repair. However, at the same time, the data reveal a specific nano-architecture of DNA damage foci for a given chromatin domain and cell type. Characteristics of chromatin architecture around complex damage sites, repair focus nano-architecture or (similar) spatial arrangements of repair proteins may contribute to control repair process. Our studies contribute to the understanding of whole system cellular radiation response in cancer and non- cancer cells.

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Treatment planning for ion-beam cancer therapy: An overview

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Compared to conventional radiotherapy techniques, ion-beam cancer therapy (IBCT) promises an improved therapeutic ratio due to favourable dose deposition characteristics. Treatment planning and delivery techniques for IBCT have evolved rapidly in recent years, however there remain questions to be answered before the full potential of ion-beams can be exploited. This presentation will provide an overview of contemporary IBCT treatment planning techniques, highlighting physical and biological uncertainties to be addressed.