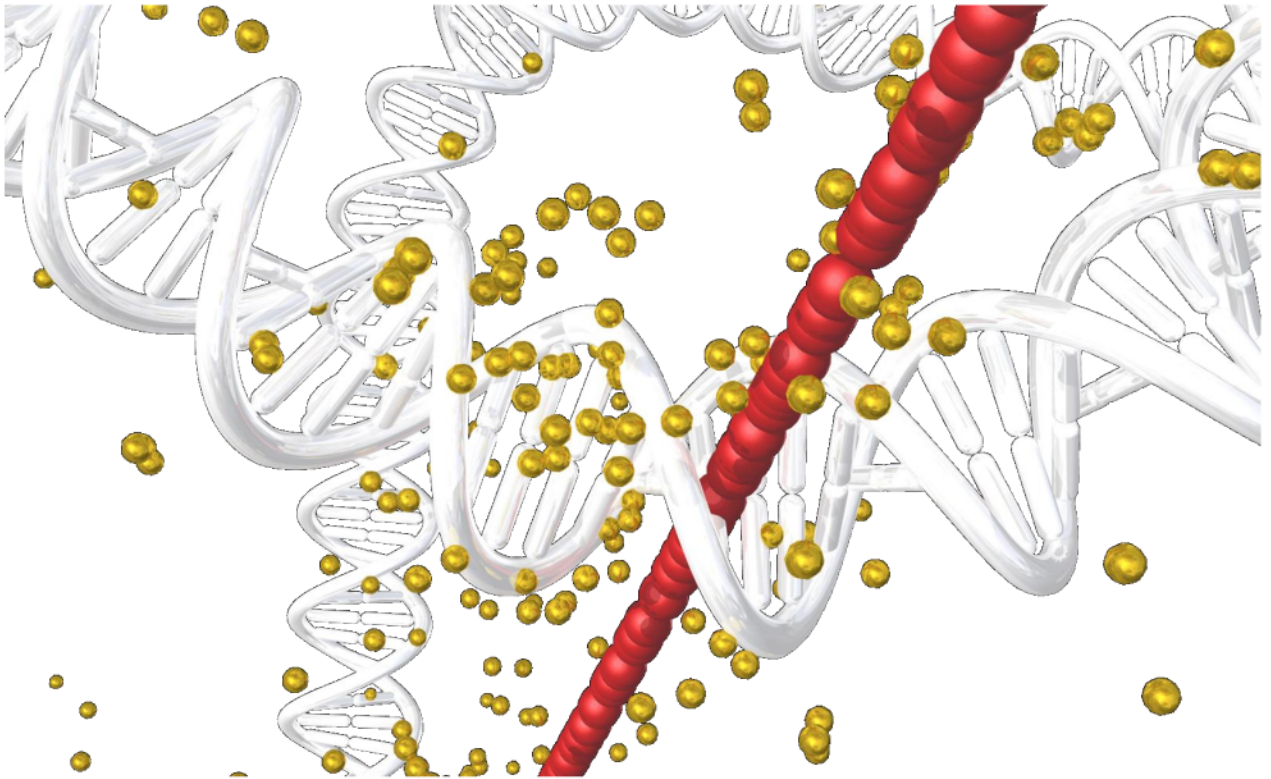
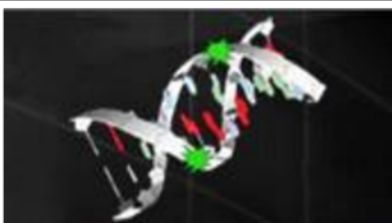


# “CHALLENGES IN MICRO- AND NANODOSIMETRY FOR ION BEAM CANCER THERAPY (MIND-IBCT)”



WIENER NEUSTADT (AUSTRIA), 07-09 MAY 2014



COST Action MP1002 Nanoscale Insights into Ion Beam Cancer Therapy (NanoIBCT)

—EURADOS—▶

European Radiation Dosimetry Group e. V.  
WG 6 Computational Dosimetry

**B<sub>o</sub>QuaRT**

EMRP Project Biologically Weighted Quantities in Radiotherapy

MiND-IBCT is the first of two workshops of the COST Action MP1002 “Nanoscale Insights into Ion Beam Cancer Therapy (NanoIBCT)”<sup>1</sup> in 2014 that explore the path between fundamental research and clinical practice in proton and heavy ion therapy<sup>2</sup>. Focussed on challenges encountered in the application of micro- and nanodosimetry for ion beam cancer therapy, MiND-IBCT is jointly organised by NanoIBCT Working Group 5 “Radiobiological scale effects” (lead: Kevin Price), Task Group 6.2 “Computational micro- and nanodosimetry” (lead: Hans Rabus) of EURADOS<sup>3</sup>, the Joint Research Project SIB06 “Biologically weighted quantities in radiotherapy”<sup>4</sup> (coordinator: Hans Rabus) of the European Metrology Research Programme (EMRP)<sup>5</sup>, and the Austrian Ion Beam Therapy Center MedAustron<sup>6</sup> which kindly provides the venue for this meeting.

To some extent, MiND-IBCT is the sequel to a discussion seminar on micro- and nanodosimetry organised in 2006 at the INFN Legnaro National Laboratory (Italy) and to an international workshop on “Challenges to the metrology of ionizing radiation in sub-micrometer dimensions” held in 2009 in Braunschweig (Germany). As with its predecessors, the main purpose of the workshop is to provide a forum not only for the presentation of progress and recent results, but also for discussion of concepts and ideas. For this purpose, dedicated discussion sessions have been planned where participants are invited to give short presentations on requirements and ideas for novel approaches in micro- and nanodosimetry with the goal of implementing the techniques provided by these fields into clinical practise.

In order to emphasize this focus on translation of the techniques into clinical practise, the sequence of sessions has been intentionally chosen such that the workshop proceeds from needs and requirements for the introduction into clinical practise via biophysical models and track structure simulation to the experimental aspects of state-to-the-art micro- and nanodosimetry. In the associated discussion sessions the following topics will be addressed:

- Approaches for introducing micro- and nanodosimetric quantities into clinical practise.
- What level of accuracy is needed, what level of accuracy can we achieve?
- Biophysical models for linking track structure and biological effects.
- What are the relevant properties of track structure that we need to measure and/or simulate in order to characterize the biological effectiveness of ion radiation?
- How to assess the uncertainty of micro- and nanodosimetric measurements and simulations?

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<sup>1</sup> Web site: <http://fias.uni-frankfurt.de/de/nano-ibct/overview/>.

<sup>2</sup> The second workshop, entitled “Translational Research in Ion Beam Cancer Therapy” or ‘TRIBCT 2014’, is organized by working group 3 of the NanoIBCT COST Action and will take place in Aarhus, Denmark from 30 September to 2 October 2014. Details will be communicated later by the organizer, David Field ([dfield@phys.au.dk](mailto:dfield@phys.au.dk)).

<sup>3</sup> EURADOS is the European Radiation Dosimetry Group, an association of more than 50 European institutions and 250 associate scientists working in the field of ionizing radiation dosimetry (<http://www.eurados.org/>).

<sup>4</sup> Project web site: <http://www.ptb.de/emrp/bioquant.html>.

<sup>5</sup> The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union. EURAMET is the European Association of National Metrology Institutes (<http://www.euramet.org/>).

<sup>6</sup> Web site: <http://www.medaustron.at/>.

## Scientific Committee

Hans Rabus (PTB, Germany)  
Hugo Palmans (NPL, UK)  
Reinhard Schulte (LLU, USA)  
Carmen Villagrasa (IRSN, France)  
Andrey Solov'yov (U Frankfurt, Germany)  
Kevin Prise (QUB, UK)  
Thorsten Schneider (PTB, Germany)  
Giulio Magrin (MedAustron, Austria)

## Venue

EBG MedAustron GmbH  
Marie Curie-Straße 5  
A-2700 Wiener Neustadt  
Austria

## Organising Committee

Thorsten Schneider (PTB, Germany)  
Hans Rabus (PTB, Germany)  
Heinke Harms (PTB, Germany)  
Sandra Prondzinski (PTB, Germany)  
Giulio Magrin (MedAustron, Austria)  
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## Accommodation

Hotels located in walking distance from MedAustron (for location refer to map on page 3):

### *Hotel Steinfeld ("A")*

Nikolaus A. Otto-Strasse 4  
2700 Wiener Neustadt  
+43-2622-26907  
[www.hotel-steinfeld.at](http://www.hotel-steinfeld.at)

### *Hotel Orange Wings ("B")*

Rudolf Diesel-Straße 32  
A-2700 Wiener Neustadt  
+43-2622 24380  
[www.orangewings.com](http://www.orangewings.com)

### *Hotel Freizeitempel ("C")*

Wiener Werkstraße 109  
2700 Wiener Neustadt  
+43-2622-20720  
[www.freizeitempel.at](http://www.freizeitempel.at)

Hotels in downtown Wiener Neustadt, about 15 minutes by bus from MedAustron:

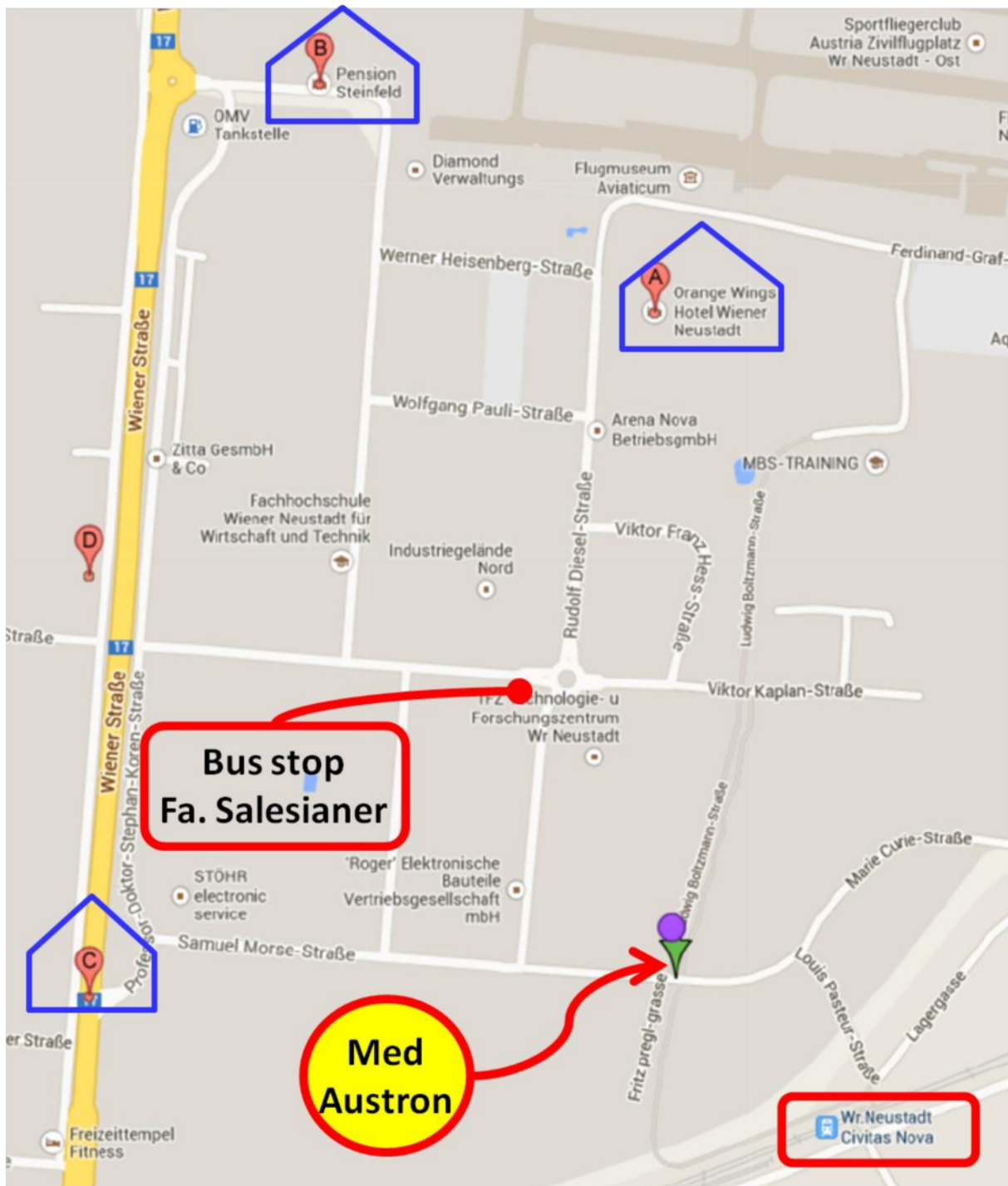
### *Hotel Corvinus*

Bahngasse 29-33  
A-2700 Wiener Neustadt  
+43-2622-24134  
[www.hotel-corvinus.at](http://www.hotel-corvinus.at)

### *Hotel Zentral*

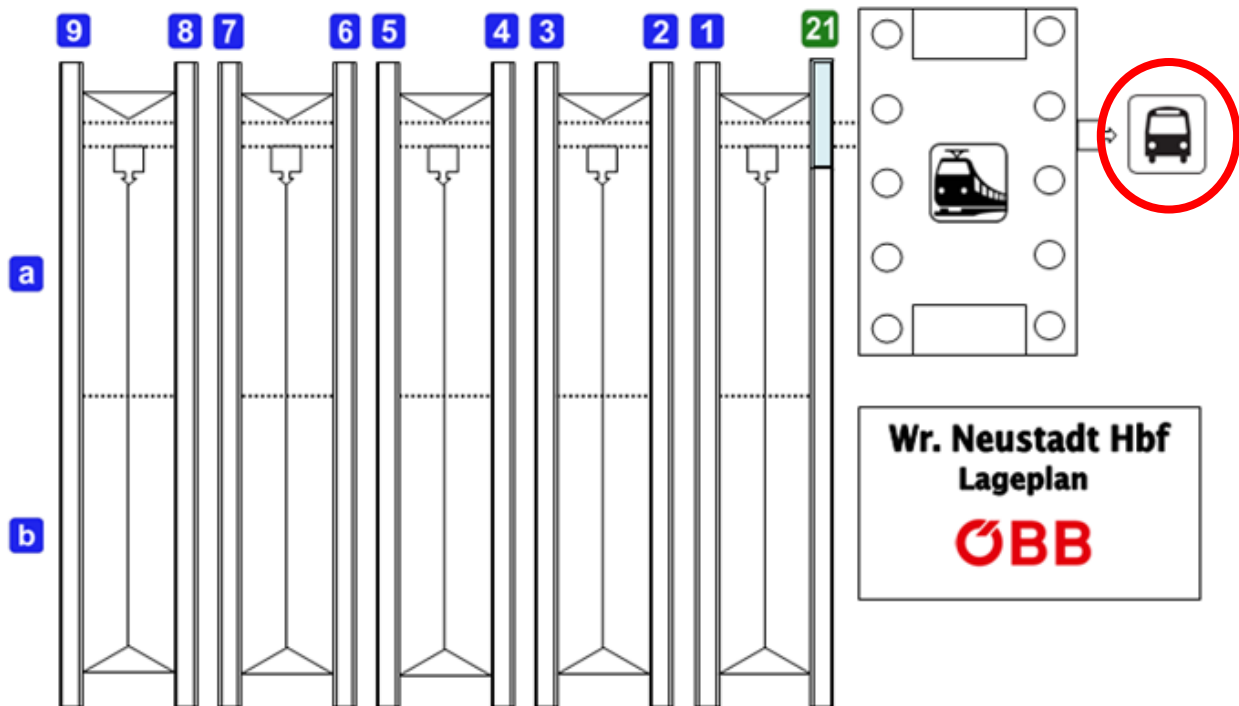
Hauptplatz 27  
A-2700 Wiener Neustadt  
+43-2622-23169  
[www.hotelzentral.at](http://www.hotelzentral.at)

Local transportation



To go from downtown Wiener Neustadt to MedAustron take bus line G at the bus terminal “Hauptbahnhof/Busbahnhof” next to the railway station (see next figure). Departures are at 21 and 51 minutes of every hour. The destination is “Samuel Morse Str./Fa.Stöhr” (or “FH” or “TFZ”). Leave at stop “Firma Salesianer” (see map on page 4).

Site map railway station: “Wiener Neustadt”. The neighboring bus terminal is circled in red.



*Workshop Dinner:*

The workshop dinner will take place on Thursday 8<sup>th</sup> of May at 20:00 h at:

Altes Backhaus

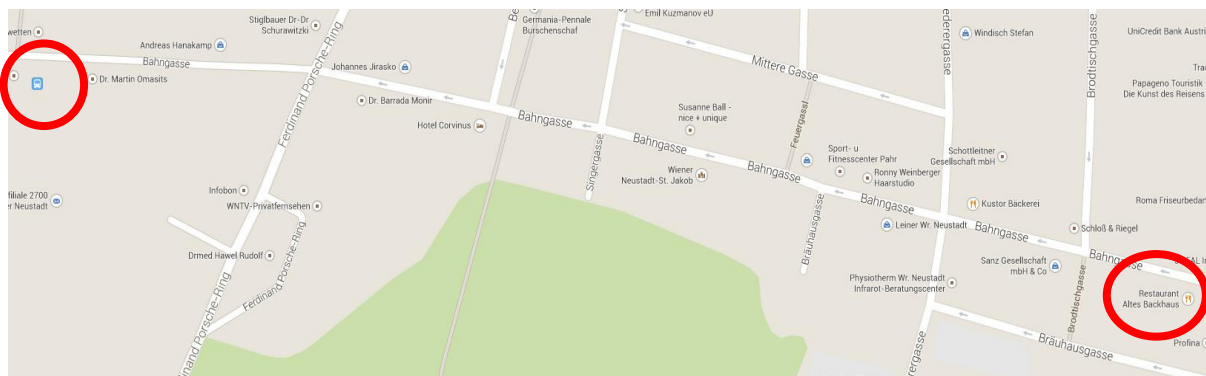
Bahngasse 1

2700 Wiener Neustadt

Tel: 02622/81089

restaurant@altes-backhaus.at

<http://www.altes-backhaus.at/>



Starting from the bus terminal you only need to go down the street ‘Bahngasse’ until you find No 1 (about 650 m).



<b>Wednesday 7 May</b>		
12:00 - 13:00	Welcome Reception and Registration	
13:00 - 13:15	H. Rabus, R. Mayer	<b>Opening of the workshop</b>
13:15 - 13:40	H. Rabus	The role of microdosimetry and nanodosimetry for biologically relevant radiation quantities
	Chair: R. Schulte	<b>Session 1: Introducing Micro- &amp; Nanodosimetry in clinical practice</b>
13:40 - 14:10	G. Magrin	Radiation quality measurements of ion beams: clinical feasibility and possible implementations.
14:10 - 14:40	E. Scifoni	Dose modifiers with particle beams from track structure to treatment planning
14:40 - 15:10	Coffee Break	
	Chair: H. Rabus	<b>Session 2: Biophysical models and biological aspects</b>
15:10 - 15:40	G. Cabal	The dependency of the alpha and beta parameters from the LQ model on LET: a bayesian model selection perspective
15:40 - 16:20	T. Friedrich	RBE for Therapy: Development of the Local Effect Model and uncertainty assessment based on the PIDE data base
16:20 - 18:00	<b>Discussion: How to introduce Micro- &amp; Nanodosimetry in clinical practice?</b>	

<b>Thursday 8 May</b>		
	Chair: H. Rabus	<b>Session 2: Biophysical models and biological aspects</b>
09:00 - 09:40	K.M. Prise	Understanding spatial and temporal track structure effects with clinically relevant ion beam studies in biological systems
09:40 - 10:20	F. Ballarini	A biophysical model linking DNA damage, chromosome aberrations and cell death
10:20 - 10:50	Coffee Break	
	Chair: G. Magrin	<b>Session 3: Track structure calculations</b>
10:50 - 11:20	W. Friedland	Track structure and initial DNA-damage simulation for ion energies around the Bragg- Peak
11:20 - 11:50	M. Davidková	Carbon ion beam quality: LET spectra calculated by Geant4 at different positions along and around ion beam

Thursday 8 May		
11:50 - 13:00	Lunch	
13:00 - 13:30	M. Bug	Simulation of electron tracks in water and DNA medium
13:30 - 14:00	C. Villagrasa	Track structure calculations with the Geant4-DNA toolkit and ongoing developments
14:00 - 14:30	Coffee Break	
14:30 - 15:00	R. Schulte	A novel approach to particle therapy radiation metrology based on nanodosimetry - concepts and first results
15:00 - 17:30	<b>Discussion:</b> Biophysical models linking track structure and biological effects	

Friday 9 May		
	Chair: H. Palmans	<b>Session 4:</b> Experimental Micro- and Nanodosimetry
09:00 - 09:30	P. Colautti	Microdosimetry of therapeutic hadron beams
09:30 - 10:00	S. Chiriotti	Critical assessment of physical data to calibrate microdosimetric spectra
10:00 - 10:30	S. Galer	Micro-calorimeters directly measuring lineal energy
10:30 - 11:00	Coffee Break	
11:00 - 11:30	S. Agosteo	Experimental microdosimetry at nanometric level
11:30 - 12:00	V. Conte	Experimental nanodosimetry of carbon ions
12:00 - 13:00	Lunch	
13:00 - 13:30	G. Hilgers	Challenges in track structure nanodosimetry
13:30 - 15:00	<b>Discussion:</b> Current problems in experimental micro- and nanodosimetry Uncertainty of micro- and nanodosimetric quantities Level of accuracy that can be achieved	
15:00 - 15:30	H. Rabus	Closing remarks





## The role of microdosimetry and nanodosimetry for biologically relevant radiation quantities

H. Rabus<sup>1</sup>, H. Palmans<sup>2,3</sup>, G. Hilgers<sup>1</sup>, P. Sharpe<sup>2</sup>, M. Pinto<sup>4</sup>, C. Villagrasa<sup>5</sup>,  
Th. Schneider<sup>1</sup>, D. Moro<sup>6</sup>, A. Pola<sup>7</sup>, S. Pszozna<sup>8</sup>, P. Teles<sup>9</sup>

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<sup>3</sup> *EBG MedAustron GmbH, Wiener Neustadt, Austria*

<sup>4</sup> *Istituto Nazionale di Metrologia delle Radiazioni Ionizzanti (ENEA-IMRI), Santa Maria di Galeria, Italy*

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<sup>7</sup> *Politecnico di Milano (PoliMi), Milan, Italy*

<sup>8</sup> *National Centre for Nuclear Research (NCBJ), Otwock-Swierk, Poland*

<sup>9</sup> *Universidade Tecnica de Lisboa, Instituto Tecnológico e Nuclear (IST-ITN), Sacavém, Portugal*

Microdosimetry and nanodosimetry are areas of ionising radiation metrology in which characterisation of radiation quality in terms of measurable physical properties of charged particle track structure is aimed for. Measurement instruments for either field usually simulate microscopic target volumes in biological matter within a small range of site sizes. Within the European Metrology Research Programme (EMRP) [1], the Joint Research Project “Biologically weighted quantities in radiotherapy (BioQuaRT)” [2] is developing a multi-scale approach to track structure characterisation.

The ultimate goal of this endeavour is to achieve a clear separation of the physical and the biological contributions to the phenomenological radiation weighting factors employed so far in ion-beam radiotherapy. For this purpose, dedicated radiobiological experiments are carried out on an ion microbeam at which the radiation quality is characterised using a prototype multi-scale track structure measurement instrument consisting of an ion-counting nanodosimeter and a silicon microdosimeter. The outcomes of the biological assays will be used in conjunction with a novel simulation tool to set the free parameters of biophysical models relating track structure and biological consequences. The simulation tool under development is based on Geant4 and includes *inter alia* radiation interaction cross sections of DNA ingredients and production rates of radical species that are measured and evaluated within the project. In parallel, micro-calorimeters are being developed as microdosimeters that directly measure lineal energy in micrometric targets and will be compared with mini-TEPCS and silicon micro-telescopes to assess the magnitude of condensed phase and tissue non-equivalence effects, respectively. The three existing nanodosimeters in Europe are further developed and directly compared in the same ion beams to establish the correlation between track structure characteristics at different target sites and impact parameters.

[1] The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union. EURAMET is the European Association of National Metrology Institutes (<http://www.euramet.org/>).

[2] Project web site: <http://www.ptb.de/emrp/bioquart.html>.

## **Radiation quality measurements of ion beams: clinical feasibility and possible implementations**

**Giulio Magrin<sup>1</sup>, Ramona Mayer<sup>1</sup>**

<sup>1</sup> EBG MedAustron, Wiener Neustadt, Austria

When ion beams are used for treating cancer, a primary requirement is to have reliable forecast of the biological effectiveness of the radiation. This need is quite challenging, since, on one hand, the clinical and legal procedures in radiation therapy are quite strict allowing small uncertainties and, on the other hand, the radiation, crossing the human tissues, changes drastically its biological impact.

The clinical challenges translate to a technological demand of tools capable of mapping, possibly in three dimensions, dose and radiation quality in the irradiated volume. Although analytical computations and simulations can provide useful estimates, the direct measure of those parameters would improve ion-beam therapy since it provides an absolute reference which is the base for sharing results among different clinics.

Several facilities performing ion-beam therapy, including centers using exclusively protons, are studying detectors and procedures for measuring the radiation quality in microdosimetric as well as nanodosimetric scale. Different stages, which concern the preparation and the delivery of ion-beam therapy, are potentially affected. These are:

- the pre-clinical studies, where the radiation at which cell lines are exposed is simultaneously measured in terms of radiation quality;
- the commissioning and the treatment setup, where co-registrations of dosimetric and radiation quality parameters are performed at standard therapy conditions and in dedicated phantoms;
- the patient irradiation, where radiation quality is measured either internally, for those tumours locations which allow the insertion of detectors, or externally, for the evaluation of the impact of the secondary radiation;
- the retrospective studies, where the evaluation of the treatment outcomes, also performed with the use of three-dimensional imaging tools, is associated to the measurements of radiation quality.

The feasibility of these measurements is discussed, defining conditions, compatibilities, and limits of use. In the different cases a choice must be made either selecting standard devices, as, for instance, tissue equivalent proportional chambers, which are able to collect microdosimetric spectra at the widest range of lineal energies, or preferring miniaturization, feasibility, and simplicity in operation.

The presentation intends to initiate a discussion in which the different competences and experiences contribute to clarify the present scenario and to identify common path for the future.

## Dose modifiers with particle beams from track structure to treatment planning: Oxygen effect and nanoparticle sensitization

Emanuele Scifoni<sup>1</sup>, Cathrin Wälzlein<sup>1</sup>, Marco Durante<sup>1,2</sup> and Michael Krämer<sup>1</sup>

<sup>1</sup> GSI Biophysics, Darmstadt, Germany

<sup>2</sup> TUD Darmstadt, Germany

Ion beam induced radiobiological damage show peculiar features when considering accidental or artificial agents which modify a tissue sensitivity, which can substantially impact particle therapy [1] and open new, intriguing scenarios to related track structure analysis. Two examples of these effects are presented in this talk together with their implementation on different level of analysis.

The oxygen enhancement ratio (OER) has been known to be drastically reduced by high linear energy transfer (LET) radiation, but since typical therapeutical irradiation settings cannot achieve, at least for Carbon, a sufficiently high LET in the whole target, an accurate description of the bi-dimensional dependence of this effect on oxygen concentration and LET is needed, as well as specific treatment planning approaches, beyond the conventional concept of RBE weighted dose. This has been recently directly integrated in ion beam treatment planning [2], and also several other strategies are going developed [3]. Moreover, this concept can be in principle extended to target intratumor heterogeneities of different type, beyond hypoxia.

As for nanoparticle sensitization, while it has been shown for photon irradiation a beneficial impact on local dose deposition of their presence [4], the situation with ions is rather controversial. The track structure analysis of local dose enhancement for proton irradiation of different high atomic mass (Z) nanoparticles is presented for the first time, under several assumptions. A local radial dose enhancement of up to a factor of 2 for proton irradiation in the presence of NPs could be found for protons with several energies which is partially attributed to excess electrons from Auger cascades. The most beneficial materials in terms of local dose enhancement seems to be platinum and gold, followed by gadolinium and silver

[1] J.S. Loeffler, M. Durante, *Nat Rev Clin Oncol* 10, 411 (2013)

[2] E. Scifoni, W. Tinganelli, W.K. Weyrather, M. Durante, A. Maier and M. Krämer, *Phys. Med. Biol.* 58, 3871 (2013)

[3] N. Bassler, J. Toftegaard, A. Lühr, B.S. Sørensen, E. Scifoni, M. Krämer, O. Jäkel, L.S. Mortensen, J. Overgaard, J.B. Petersen, *Acta Oncol.* 53, 25 (2014)

[4] S. McMahon et al. *Sci. Rep.* 1, 18 (2011)

[5] C. Wälzlein, E. Scifoni, M. Krämer and M. Durante, *Phys. Med. Biol.* 59, 1441 (2014)

## The dependency of the alpha and beta parameters from the LQ model on LET: a bayesian model selection perspective

Gonzalo Cabal<sup>1</sup>, Alexander Trende<sup>1</sup>, Eleanor Blakely<sup>2</sup>, Katia Parodi<sup>1</sup>

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<sup>2</sup> Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA

Ion beam therapy is now emerging as a very attractive therapeutic modality in the treatment of cancer. Starting from the pioneering work at the Lawrence Berkeley National Lab (LBNL) it has now reached the level of clinical deployment in several hospitals in Europe and Asia. Since most of the clinical experience in radiation therapy is based on conventional photon treatments a model is needed to understand the expected outcome of a treatment with ion beams. Several models have been proposed for that matter[1][2][3][4]. Most of them make use the so called linear-quadratic Model (LQ) as a way to link the experience gained with photon treatments with the new modalities. Under the LQ model two parameters, alpha and beta define the sensitivity of the tissue or tumour to radiation. So far, the question of modelling the outcome of a treatment has been reformulated to the question of how do the alpha and beta parameters change with different types of radiation quality. While there is a common consensus on the dependency of the alpha parameter on the Linear Energy Transfer (LET), there is no agreement on how the beta parameter varies with LET. It is known that deviations on the assessment of the value of the beta parameter might have a big impact on the predicted value of the radiobiological effectiveness (RBE) of a treatment. This is specially the case for hypofractionated treatments.

In this work we present a Bayesian model selection analysis for various types of dependencies of the alpha and beta parameter versus LET. We make use the raw data obtained from consistent experimental conditions[5] over a wide range of LET values in order to minimize the possibility of systematic errors. We use three different kinds of Bayesian model selection approaches: the Akaike Information Criteria (AIC), the Bayesian Information Criteria (BIC) and the Deviance Information Criteria (DIC).

Results will be presented and discussed. The conclusion of the analysis as well as the possibility to use of nanodosimetric data in the development of new models will be also discussed.

[1] M. Scholz M, AM. Kellerer, W. Kraft-Weyrathe, G. Kraft, *Radiat Environ Biophys.* **36**; 59-66 (1997).

[2] MC. Frese, VK. Yu, RD. Stewart, DJ. Carlson, *Int J Radiat Oncol Biol Phys.* **83**; 442-450 (2012).

[3] JJ. Wilkens, U. Oelfke, *Phys Med Biol* **49**, 2811-2825, (2004).

[4] RB. Hawkins, *Rad Res* **160**, 61-69, (2003).

[5] E. Blakely et al., *Rad Res.* **80**, 122-160 (1979).

## RBE for Therapy: Development of the Local Effect Model and uncertainty assessment based on the PIDE data base

Thomas Friedrich<sup>1</sup>, Rebecca Grün<sup>1</sup>, Marco Durante<sup>1,2</sup>, Michael Scholz<sup>1</sup>

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<sup>2</sup> Institut für Festkörperphysik, Technische Universität Darmstadt, Darmstadt, Germany

The enhanced effectiveness of carbon ions compared to photons is one of the most important rationales for carbon ion cancer therapy. Quantified as the relative biological effectiveness (RBE) its knowledge is needed for a correct optimization of appropriate treatment plans, where the goal usually is to deliver a prescribed dose homogenously across the target volume while sparing normal surrounding tissue as good as possible. However, RBE depends on various physical and biological factors, and hence the experimental / clinical determination is not trivial. Consequently biophysical models are needed which allow to predict RBE for all clinically relevant situations (i.e. for different tissues, beam energies and LET).

In the European carbon ion treatment facilities the Local Effect Model (LEM) in its original version (LEM I) [1] is used for treatment planning. In the talk the conceptual setup of this model is described. Then the following steps towards the current improved model version LEM IV [2,3], which takes into account the spatial distribution of DNA lesions on the nm scale as well as clustering of double strand breaks on the  $\mu\text{m}$  scale, are described. At hand of various examples from cell survival experiments to clinical end points the applicability of this state-of-the-art model will be demonstrated. Briefly, current open questions in treatment planning with carbon ions related to RBE are considered.

Besides RBE, uncertainties of this quantity are of interest, in particular in the context of personalized treatments. To approach this aspect a data base of more than 800 cell survival experiments after both ion and photon irradiation has been set up [4], which allows to investigate the systematics of RBE dependent on the radiosensitivity of the cells, LET, energy and some more determining factors on a purely experimental basis. Likewise, information about the fluctuation of RBE values can be gained. The so-called Particle Irradiation Data Base (PIDE) is available for the research community on the web [5]. The levels of uncertainties extracted from the data base correspond to theoretic results obtained by a sensitivity analysis of the LEM. Furthermore, such a sensitivity analysis demonstrates that the relative uncertainties in extended Bragg peaks are expected to be smaller than in monoenergetic irradiations of cells under track segment conditions and seem to be sufficiently low for reliable use of RBE modelling in treatment planning.

[1] M. Scholz et al., *Radiat. Environ. Biophys.* **36**, 59 (1997)

[2] T. Elsässer et al., *Int. J. Radiat. Oncol. Biol. Phys.* **78**, 1177 (2010)

[3] T. Friedrich et al., *Int. J. Radiat. Biol.*, **88**, 103 (2012)

[4] T. Friedrich et al., *J. Radiat. Res.* **54**, 494 (2013)

[5] <http://www.gsi.de/bio-pide>

## Understanding spatial and temporal track structure effects with clinically relevant ion beam studies in biological systems

Kevin M. Prise

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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, 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 delivery 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. 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.

[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., *PLOS ONE*, **8**, e54526 (2013)

[4] K.T. Butterworth, et al., *Phys Med Biol* **57**, 6671 (2012)

## A biophysical model linking DNA damage, chromosome aberrations and cell death

Francesca Ballarini<sup>1</sup>, Mario Carante<sup>1</sup>

<sup>1</sup> University of Pavia and INFN

We present a biophysical model linking radiation-induced DNA damage to cell death, focusing on DNA cluster damage and its consequences in terms of chromosome aberrations and cell survival. More specifically, the model assumes that DNA “cluster lesions” (CLs) initially induced within a threshold distance  $d$  can lead to mis-rejoining of chromosome fragments and thus to chromosome aberrations, and that certain aberration types (dicentric, rings and large deletions) lead to clonogenic inactivation. The yield of cluster lesions and the threshold distance  $d$  are the only adjustable parameters.

The model, implemented as a Monte Carlo code called BIANCA (Biophysical ANalysis of Cell death and chromosome Aberrations) [1-4], provides simulated survival curves directly comparable with experimental data. Recently, a systematic comparison with survival of AG1522 and V79 cells exposed to photons, protons, alpha particles and heavy ions, including carbon and iron, has been carried out. A threshold distance of 5  $\mu\text{m}$  and CL yields in the range  $\sim 2\text{-}20 \text{ CLs}\cdot\text{Gy}^{-1}\cdot\text{cell}^{-1}$ , depending on radiation quality, led to very good agreement between simulations and data. This supports the hypothesis of a pivotal role for DNA cluster damage, mediated by  $\mu\text{m}$ -scale mis-rejoining of chromosome fragments, possibly occurring within repair centres. Comparisons between the CL yields and the yields of DNA fragments of different sizes taken from the literature [5-7], suggested that this critical DNA damage may be identified with clusters of DSBs at the  $\sim\text{kbp}$  scale.

In the framework of possible applications for tumor hadron therapy, the model has been applied to the characterization of the particle- and LET-dependence of proton and carbon cell killing. The predicted fraction of inactivated cells after 2-Gy protons was in good agreement with V79 experimental data [8], showing an increase by a factor  $\sim 1.6$  between 7.7 and 30.5  $\text{keV}/\mu\text{m}$ . This LET interval corresponds to energies below a few MeV, which are always present in the distal region of Spread-Out Bragg Peaks (SOBP) used in proton therapy; this should be taken into account in clinics, especially when critical organs are present beyond the tumor. Also the predicted cell killing after 2-Gy carbon was in agreement with V79 experimental data [9], showing an increase in the fraction of inactivated cells by a factor  $\sim 1.7$  between 32.4 and 153.5  $\text{keV}/\mu\text{m}$ , followed by a slight decrease for higher LET values. The model has also been applied to predict cell death at different depths along a carbon SOBP used for pre-clinical experiments at HIMAC in Chiba (Japan). The predicted surviving fraction along the SOBP was basically constant (less than 10%), suggesting that this approach, which does not use RBE values that can introduce uncertainties, may be applied to predict cell killing by therapeutic beams.

[1] F. Ballarini, *J. Nucleic Acids* **2010**, article ID 350608, <http://dx.doi.org/10.4061/2010/350608> (2010)

[2] F. Ballarini et al., *Radiat. Prot. Dosim.* **143**, 523-527 (2011)

[3] F. Ballarini et al., *Radiat. Res.* **180**, 307–315 (2013)

[4] F. Ballarini et al., *Radiat. Environ. Biophys.*, in press (DOI: 10.1007/s00411-014-0537-6) (2014)

[5] B. Rydberg, *Radiat. Res.* **145**, 200-209 (1996)

[6] A. Campa et al., *Int. J. Radiat. Biol.* **81**, 841-854 (2005)

[7] D. Alloni et al., *Adv. Space Res.* **40**, 1401–1407 (2007)

[8] M. Belli et al., *Int. J. Radiat. Biol.* **74**, 501-509 (1998)

[9] W. Weyrather et al., *Int. J. Radiat. Biol.* **75**, 1357-1364 (1999)



## Track structure and initial DNA damage simulation for ion energies around the Bragg peak

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Radiation damage induced by low-energy ions significantly contributes to the high relative biological efficiency (RBE) of ion beams in distal Bragg peak regions. Further, slow light ions released through nuclear interactions of neutrons are responsible for the wide energy dependence of neutrons' RBE.

In the PARTRAC family of biophysical Monte Carlo codes for simulating track structures, DNA damage and its repair [1], ion cross sections are scaled from proton data [2] (excluding charge transfer processes) by the effective charge according to Barkas [3]. This procedure, however, is applicable only for specific energies above about 1 MeV/u; for slow ions, it overestimates their ranges in water by ~ 5 – 10  $\mu\text{m}$ .

To solve this issue, the scaling procedure has been modified by using proton cross sections that account for charge transfer, i.e. reproduce the slowing-down behaviour of protons/hydrogen atoms. The resulting range and linear energy transfer (LET) for C, N, O, P and Ca ions agree with ICRU data [4] and SRIM calculations [5]. This modification improves PARTRAC's ability to simulate track structures and DNA damage by low-energy ions, thus enabling to model biological effects in distal Bragg peak regions or in neutron irradiation. Results will be presented at the workshop.

Acknowledgement: Supported by the EC through the DoReMi/INITIUM project.

- [1] W. Friedland et al, *Mutat. Res.* **711**, 28-40 (2011)
- [2] M. Dingfelder et al, *2000 Rad. Phys. Chem.* **59**,255-275 (2000)
- [3] W. H. Barkas, *Nuclear Research Emulsions* (1963)
- [4] ICRU Report **73** (2005)
- [5] M. D. Ziegler et al, *Nucl Instrum Meth B* **268**, 1818-1823 (2010)

## Carbon ion beam quality: LET spectra calculated by Geant4 at different positions along and around ion beam

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Track etched detectors (TED) have been used as LET spectrometers in heavy ion beams for many years. Although LET and fluence working ranges of TEDs are limited, at optimal fluence range corresponding to etching conditions, TEDs can be used to determine LET spectra with spatial resolution less than 1 mm. LET spectra and the depth-dose distribution of the carbon ion beam have been measured behind polymethylmethacrylate (PMMA) filters at Heavy Ion Medical Accelerator (HIMAC) at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, using USF-4 detectors [1,2]. The measurements have been performed in the experimental exposure room HIMAC-BIO along monoenergetic carbon ion beam with energy 290 MeV/u in different positions: 1) at beam extraction area, 2) at the beginning, 3) maximum, and 4) behind the Bragg peak region (0, 117.24, 147.29 and 151.32 mm of water equivalent depth respectively). The LET spectra inside and outside of the primary ion beam have been evaluated.

The experiment was simulated using the Geant4 9.6.P01 Monte Carlo toolkit [3,4]. The calculated and experimental LET spectra were compared to verify that the TED covers correctly major part of the LET spectrum. Beamline geometry of the experimental setup at HIMAC accelerator is based on on-site measurements and personal communication with NIRS researchers. The FTF\_BIC physics list and a production threshold of 5 $\mu$ m were used for the presented simulations. The detector was represented by a 0.5 mm thick plexiglass slice ("G4\_PLEXIGLASS" NIST material) or water layer. Magnets present in the experimental setup were not taken into consideration due to a lack of description. The contribution of different particle types to absorbed dose has been calculated and compared to the experimental results.

[1] F. Spurný et al., Radiat. Prot. Dosim. **143(2-4)**, 519–522 (2011)

[2] K. Pachnerová Brabcová, I. Ambrožová, F. Spurný, Radiat. Prot. Dosim. **143(2-4)**, 440–444 (2011)

[3] S. Agostinelli, J. Allison, K. Amako, Nuclear Instr. and Meth. in Phys. Res. A **506**, 250–303 (2003)

[4] J. Allison et al. IEEE Trans. on Nucl. Sci. **53**, 270–278 (2006)

## Simulation of electron tracks in water and DNA medium

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The estimation of DNA damage caused by densely ionizing radiation is based on simulated parameters of the particle track structure. Track structure simulations require the cross section data for the interaction of the incident particles and their secondaries with molecules of the medium. Biological matter is conventionally represented by liquid water, as cross section data of DNA constituents were previously fragmentary. Hence, a possible influence of the difference in cross section data on simulated track structure parameters could not have been investigated.

We present the evaluation of interaction cross sections of DNA constituents for a simulation of the transport of electrons with energies between 7 eV and 1 keV. These new data are based on measurements of total scattering cross sections [1, 2], differential elastic scattering cross sections [1] and double-differential ionization cross sections of tetrahydrofuran, pyrimidine and trimethylphosphate. The evaluated cross section data were implemented in the Monte Carlo code PTra [3] and used to simulate the electron track structure in DNA medium. The particle track structure can be characterized by nanodosimetric quantities, such as the probability distribution of ionization cluster size [3] (i.e. number of ionizations produced per primary particle within a nanometric volume). Hence, nanodosimetric quantities were calculated in simulations of electrons with energies below 1 keV in water and DNA medium. The differences in the results obtained in the different media are discussed.

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[1] W.Y. Baek et al., Phys. Rev. A **86**, 032702 (2012).

[2] W.Y. Baek et al., Phys. Rev. A **88**, 032702 (2013).

[3] B. Grosswendt, Radiat. Prot. Dosim. **110**, 789 (2004).

## Track structure calculations with the Geant4-DNA toolkit and on-going developments

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**Presented on behalf of the Geant4-DNA collaboration**

The main purpose of the Geant4-DNA project (<http://geant4-dna.org>) is to extend the functionalities of the Geant4 Monte Carlo toolkit [1] in order to allow users to model the early radio-induced damages at the DNA level.

Indeed, radio-induced biological damages originate in the energy deposited by ionizing radiation within the cells. This energy deposition can either directly damage the biomolecules or produce reactive species (mainly radicals) in the medium (mainly water) surrounding them. A particular attention in radiobiology research is given to damages created in the DNA molecule because of its primary genetic importance and its high-sensitivity to ionizing radiation.

The occurrence probability (given by cross-sections) of the interactions leading to the initial energy deposition depends on the ionizing radiation nature, its energy and the target medium. As a consequence, the variation of these parameters leads to important differences in the resulting track structure at nanometric scale. These differences in the track structure at the biomolecular level must then be combined to the description of the induced radical transport and the target molecule in order to account for the differences in the biological effectiveness that are seen when irradiating cells with different ionizing radiations at the same absorbed dose.

In the frame of the Geant4-DNA project, physical models and tabulated data concerning the main elementary physical interactions for electrons, protons, alpha particles and light ions in liquid water have been implemented and validated [2] allowing a Monte Carlo simulation of the track structure at nanometric scale.

In this presentation, a review of these models and their validity range will be recalled. In addition, a special focus will be made in the presentation of the current status and the on-going developments concerning:

- the tools developed for the simulation of the so-called “physico-chemical and chemical” stages corresponding to the production and chemical transport of radicals in water around the DNA target,
- the geometrical descriptions of the DNA target and the associated algorithms for damage scoring

- [1] S. Agostinelli et al, “GEANT4-a simulation toolkit”, Nucl. Instrum. Methods. Phys. Res. A. **506**, 250-303 (2003).
- [2] S. Incerti, A. Ivanchenko, M. Karamitros, A. Mantero, P. Moretto, H. N. Tran, B. Mascialino, C. Champion, V. N. Ivanchenko, M. A. Bernal, Z. Francis, C. Villagrasa, G. Baldacchino, P. Guèye, R. Capra, P. Nieminen, C. Zacharatou, “Comparison of Geant4 very low energy cross section models with experimental data in water” , Med. Phys. **37**, 4692-4708 (2010)

## **A novel approach to particle therapy radiation metrology based on nanodosimetry - concepts and first results**

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## Microdosimetry of Ion Beams

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Both in proton and carbon ion therapy, therapeutic plans are based on absorbed dose measurements. The biological-effective dose is calculated by using a constant factor or an algorithm, which is based on analytical or Monte Carlo models. However, dosimeters do not measure the actual energy absorbed in biologically critical sites, as cell nuclei, chromosomes or DNA fibre, but only the average energy absorbed in the detector sensitive volume. Therefore, they are not able to monitor the biological-effective dose variations inside the SOBP, which depends mainly on single-particle interactions with critical sites.

On the contrary, microdosimetric detector measure the entire absorbed-energy spectrum in 1  $\mu\text{m}$  site, namely in a chromosome-like site. Therefore, it is suitable to monitor biological damage variations. However, the energy released in 1  $\mu\text{m}$  site by a single ionizing particle increases continuously with the particle charge increase and its velocity decrease, while the biological effect saturates. Therefore, in order to mimic the relative biological effect, the microdosimetric spectrum has to be “weighted” with an empirical function, which is extracted from biological experiments.

The microdosimetric approach has been tested with therapeutic proton beams showing a pretty good consistency with radiobiological data. Measurements with therapeutic carbon ions are beginning. Comparison and consistency with radiobiological data will point out whether the proton-used weighting function has to be changed or not.

## Critical assessment of physical data to calibrate microdosimetric spectra

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Tissue-equivalent proportional counters (TEPCs) measure distributions of ionizations produced in the gas cavity by the radiation field which are afterwards converted into distributions of energy imparted by applying a calibration factor. To calibrate the pulse height spectra, first a certain characteristic feature, a marker point, must be identified in the measured spectrum, then a precise value of lineal energy must be assigned to this marker. To calibrate the pulse height spectra, first a marker point must be identified in the measured distributions. Then, an accurate value of lineal energy must be assigned to this marker. A common marker that is often used for calibration is the so-called proton-edge (p-edge). It is a distinctive feature of a proton or neutron spectrum which corresponds to the maximum amount of energy that a proton can deposit in the active volume of the detector. In other radiation fields, i.e. hadron therapy, alpha and carbon edges can be also used for calibration.

A precise method to identify the marker point was applied to identify the p-edge with an uncertainty below 2%. To evaluate the final uncertainty of the calibration, the uncertainty of the energy value assigned to the p-edge must also be considered. The energy value to assign to the proton-edge is also not uniquely defined and can be calculated using different stopping power tables and approximations. This value can be evaluated using different approximations; the continuous slowing down approximation (CSDA) or by Monte Carlo simulations.

This study investigates how the choice of different input databases for calibration purposes influences the calibration. Three different data sets for the stopping powers and ranges have been used: from ICRU 49, from SRIM-code and from FLUKA. Despite the fact that the uncertainties in the stopping powers and ranges data are often neglected, they contribute significantly, for instance, to the final uncertainties of microdosimetric quantities. The effect of three different frequently used sets of input data was analysed for pure propane gas and for propane-TE gas mixture.

A standardization of the input data used for TEPC calibration is recommended, especially for applications in hadron therapy where an accuracy better than 5% is required.

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## Micro-calorimeters directly measuring lineal energy

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The need to better understand the biological effectiveness of different radiation modalities is well known and microdosimetry, the study of single-event energy deposition spectra, has been cited as a means of improving our understanding through a better knowledge of the energy deposition and distribution on a microscopic scale.

Of the several different methods currently available for measuring lineal energy transfer the two most commonly used types of detectors are Tissue Equivalent Proportional Counters (TEPC) and solid-state detectors (such as the silicon telescope detector). The main disadvantage to both of these types of detector is that the measurements are indirect and require correction factors in order to achieve a lineal energy measurement in tissue.

A novel detector for measuring the energy deposited at the microscopic scale is currently under development at the National Physical Laboratory. This device consists of a loop of superconductor interrupted by two weak-links, known as a DC Superconducting Quantum Interference Device or SQUID. Our device is based on the Inductive Superconductive Transition Edge Sensor (ISTED) which includes a superconducting region within the loop so that energy deposited in this absorbing region results in a change in the area of the superconducting region, due to the breaking of the Cooper pairs, which can be measured by a change in the voltage across the junctions of the SQUID [1].

The device has been modified from the original ISTED design to make it relevant to dosimetry by including a tissue equivalent layer on top of the superconducting layer [2]. The main advantage of this type of detector is that it provides a method for direct measurement of lineal energy transfer in tissue equivalent material. Other advantages include energy resolution down to ~0.2 eV, geometry similar to a cell and has a theoretical response time of less than a microsecond. The main drawback to this type of device is the complex nature of operation including the fact that the devices are operated at temperatures below 7K. Another point of importance is that the response needs to be corrected for the fraction of energy that is absorbed by the superconducting layer and for heat transfer between the various layers and the environment. This presentation will provide an overview of the device as well as the current status of the detector and its ability to measure lineal energy spectra. A discussion will also be presented on Monte Carlo simulations and numerical heat transfer simulations for the determination of correction factors.

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[1] L. Hao, *et al.*, *Supercond Sci Technol*, 16, 1479–82 (2003)

[2] S. Galer, *et al.*, *Radiat. Prot. Dos.* 143(2-4) 427-431 (2011)

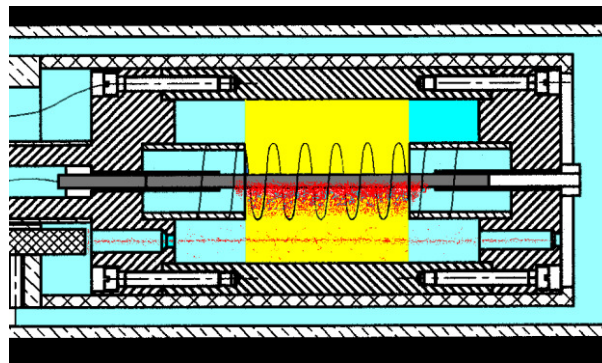
## Experimental Microdosimetry at Nanometre Level

Stefano Agosteo<sup>1</sup>, Paolo Colautti<sup>2</sup>, Valeria Conte<sup>2</sup>, Roberto Delbono<sup>1</sup>, Davide Bortot<sup>1</sup>, Elena Sagia<sup>1</sup>, Andrea Pola<sup>1</sup>

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By definition, the microdosimetric spectrum and the associated weighting function depend on the site size. Since different radiobiological end-points can be related to critical sites of different size, special avalanche-confinement TEPCs have been constructed that operate down to few tens of nanometres, that means the chromatin fibre size (Cesari et al. 2002). The detector is a gas proportional counter where the electronic avalanche is forced to occupy a limited volume around the anode wire by a co-axial helix. The detector is sketched in the figure.



*Cross sectional view of the avalanche confinement TEPC. The yellow region is the detector sensitive volume. Red dots represent ionisation events. The red-dots line at the bottom represent the ionisation events due to one alpha particle emitted by the <sup>244</sup>Cm calibration source. The primary electrons of the alpha source drift towards the helix, beyond which they are multiplied by the intense electric field (the red dot cloud).*

The track structure of the interacting particle, which is disregarded in the microdosimetric approach, plays a significant role at nanometre level, where the site size is smaller than the ion track structure.

A new avalanche confinement TEPC is being constructed. Measurements will be performed in ion beams and results will be analysed on the basis of track structure properties assessed with the LNL track nanodosimeter.

## Experimental nanodosimetry of carbon ions

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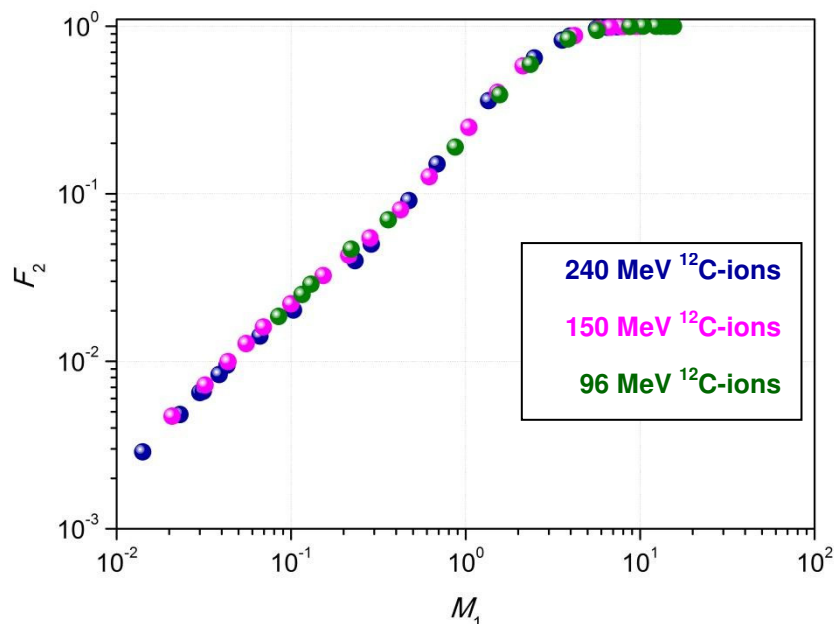
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The biological efficiency of ionizing particles is clearly related to their track-structure properties on a nanometric scale. Nowadays these properties can be measured directly, and not only modelled by Monte Carlo simulations. Three experimental setups exist, which allow the direct measurement of ionizations produced inside small gas volumes by ionizing particles directly crossing them, or passing nearby at given impact parameter. Two devices are based on single-ion counting [1, 2], the other device is the so called track-nanodosimeter, installed at the TANDEM-ALPI accelerator complex of LNL, which is based on single-electron counting [3]. In the LNL track-nanodosimeter the target volume, 3.7 mm in diameter and height, is filled with gaseous propane at a density of  $\rho = 5.47 \mu\text{g}/\text{cm}^3$  and the diameter has a mass per area of about  $2 \mu\text{g}/\text{cm}^2$ . Hence, at a density of  $1 \text{ g}/\text{cm}^3$  the target volume is comparable in size to a segment of the chromatin fibre, 20 nm in diameter and height. The impact parameter  $d$  is changed by moving the target volume perpendicularly to the centre line of a circular pencil beam of primary particles (beam radius  $r_{\text{beam}} = 0.4 \text{ mm}$ ).

Considering the emerging interest for carbon ions in radiotherapy, during the last year the study of particle track structure properties was concentrated on carbon-ions at energies close to the Bragg peak. Ionization-cluster-size distributions produced by 96 MeV, 150 MeV and 240 MeV  $^{12}\text{C}$ -ions were measured experimentally. The shape of the distributions in the track-core region results to be mainly determined by the mean free ionization path length of the primary particles, whereas in the penumbra region the shape is almost independent of the impact parameter, and also of the particle velocity.

Some descriptors of the track structure can be derived from the measured ionization cluster-size distributions. Here, the attention is focused on the mean ionization-cluster size  $M_1$  and on the cumulative probability  $F_k$  of measuring cluster sizes  $\nu \geq k$ . The track-structure related quantity  $F_k$  is interesting from a radiobiological point of view, because an increasing  $k$  corresponds to a damage of higher complexity, and  $F_k$  saturates for increasing radiation quality (expressed here by the mean number of primary ionizations produced along a given path length) in a similar way as the radiobiological cross sections do for increasing Linear Energy Transfer (LET). The figure shows the cumulative probability  $F_2$  as a function of the mean ionization cluster size  $M_1$ , for carbon-ions at different velocities.



[1] V. Bashkurov et al., IEEE Trans. Nucl. Sci. **56**, 2859-2863 (2009)

[2] G. Hilgers et al., this issue

[3] V. Conte et al., New J. Phys. **14**, 093010 (2012)

## Challenges in track structure nanodosimetry

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The primary challenge in the experimental nanodosimetry is to experimentally access the track structure parameters of a primary particle track in a volume element of nanometer dimension. As direct measurements of individual interactions in liquids and solids in a sufficiently small target volume at present are not possible, measurements of track structure parameters are restricted to measurements in targets consisting of rarefied gases.

At present, three different types of nanodosimeters capable of carrying out this kind of measurements do exist. Although these devices are all different in design, they are all restricted to the measurements of ionization interactions, and they all face the same kind of experimental problems. Therefore the nanodosimeter operated at PTB will be presented as a representative. The presentation covers various experimental aspects as for instance the collection of the secondary ions which were created along the primary particle track, the determination of the parameters of the primary particle's track and the determination of the size of the sensitive volume element. Exemplarily, recent measurement data from carbon ion beams are presented.

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