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Challenges in Micro- and Nanodosimetry for Ion Beam Cancer Therapy (MIND-IBCT)

Report on an International Workshop co-organized by EURADOS

Wiener Neustadt (Austria), 07-09 May 2014

Edited by Thorsten Schneider, Heidi Nettelbeck and Hans Rabus

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on behalf of the MiND-IBCT Scientific Committee

Liability Disclaimer

Content:

Abstract

Ion beam therapy offers the possibility of excellent dose localization for treatment of malignant tumours, minimizing radiation damage in normal tissue, while maximizing cell-killing within the tumour. However, the full potential of such therapy can only be realised by better understanding of the physical, chemical and biological mechanisms.

The workshop MiND-IBCT (Micro- and Nano-Dosimetry for Ion Beam Cancer Therapy) was focussed on challenges encountered in the application of micro- and nanodosimetry for ion beam cancer therapy. MiND-IBCT was organized by Task Group 2 "Computational Micro- and Nanodosimetry" of EURADOS Working Group 6 "Computational Dosimetry" as a joint activity with Working Group 5 "Radiobiological scale effects" of the COST Action MP1002 "Nanoscale Insights into Ion Beam Cancer Therapy (NanoIBCT)"[1], and the Joint Research Project SIB06 "Biologically weighted quantities in radiotherapy (BioQuaRT)"[2] of the European Metrology Research Programme (EMRP[3]).

The sequence of sessions progressed from needs and requirements for the introduction into clinical practise via biophysical models and track structure simulation, to the experimental aspects of state-of-the-art micro- and nanodosimetry. The main purpose of the workshop was 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 were planned where participants were 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.

The meeting was held at the Austrian Ion Beam Therapy Center MedAustron, where more than 40 participants attended 20 presentations spread over four sessions.

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[1] Project website: http://fias.uni-frankfurt.de/de/nano-ibct/overview/.

[2] Project website: http://www.ptb.de/emrp/bioquart.html.

[3] 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/).

1. Programme

Wednesday 7 May		
12:00 - 13:00	Welcome Reception and Registration	
13:00 13:15	H. Rabus, R. Mayer	**Opening of the workshop**
13:15 13:40	H. Rabus	The role of microdosimetry and nanodosimetry for biologically relevant radiation quantities
	Chair: R.Schulte	**Session 1**: Introducing Micro- & Nanodosimetry in clinical practice
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	**Session 2**: Biophysical models and biological aspects
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	**Discussion**: How to introduce Micro- & Nanodosimetry in clinical practice?	

Thursday 8 May		
	Chair: H.Rabus	**Session 2**: Biophysical models and biological aspects
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	**Session 3**: Track structure calculations
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. Davídková	Carbon ion beam quality: LET spectra calculated by Geant4 at different positions along and around ion beam
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	**Discussion**: Biophysical models linking track structure and biological effects	

Friday 9 May		
	Chair: H. Palmans	**Session 4**: 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		**Discussion**: 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

2. Introduction

MiND-IBCT (Micro- and Nano-Dosimetry for Ion Beam Cancer Therapy) was the first of two workshops of the COST Action MP1002 "Nanoscale Insights into Ion Beam Cancer Therapy (NanoIBCT)"[4] in 2014 that explored the path between fundamental research and clinical practice in proton and heavy ion therapy.

Focussed on challenges encountered in the application of micro- and nanodosimetry for ion beam cancer therapy, MiND-IBCT was jointly organised by Task Group 2 "Computational Micro- and Nanodosimetry" of EURADOS Working Group 6 "Computational Dosimetry", NanoIBCT Working Group 5 "Radiobiological scale effects", the Joint Research Project SIB06 "Biologically weighted quantities in radiotherapy (BioQuaRT)"[5] of the European Metrology Research Programme (EMRP[6]), and the Austrian Ion Beam Therapy Center MedAustron, which provided the venue for this meeting.

To some extent, MiND-IBCT was 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 was 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 were planned where participants were 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 was intentionally chosen such that the workshop proceeded 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 were addressed:

- Approaches for introducing micro- and nanodosimetric quantities into clinical practise.
- What level of accuracy is needed, what level of accuracy can be achieved?
- 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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[4] Project website: http://fias.uni-frankfurt.de/de/nano-ibct/overview/.

[5] Project website: http://www.ptb.de/emrp/bioquart.html.

[6] 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/).

The sequence of sessions progressed from needs and requirements for the introduction into clinical practise via biophysical models and track structure simulation to the experimental aspects of state-of-the-art micro- and nanodosimetry. The meeting was held at the Austrian Ion Beam Therapy Center MedAustron, where more than 40 participants attended 20 presentations spread over four sessions.

3. Wednesday 7 May

Ramona Mayer, the Medical Director of MedAustron, welcomed the guests and introduced the institution. She explained that MedAustron is intended to offer numerous opportunities for clinical research, ranging from basic to translational and applied research. Almost all patients would be treated within the framework of clinical studies and new scientific and technological knowledge should be incorporated in treatment concepts immediately. The clinical research's primary goal would be to make clear medical statements about the benefits of ion beam therapy for specific indications and to compare the effectiveness of protons and carbon ions.
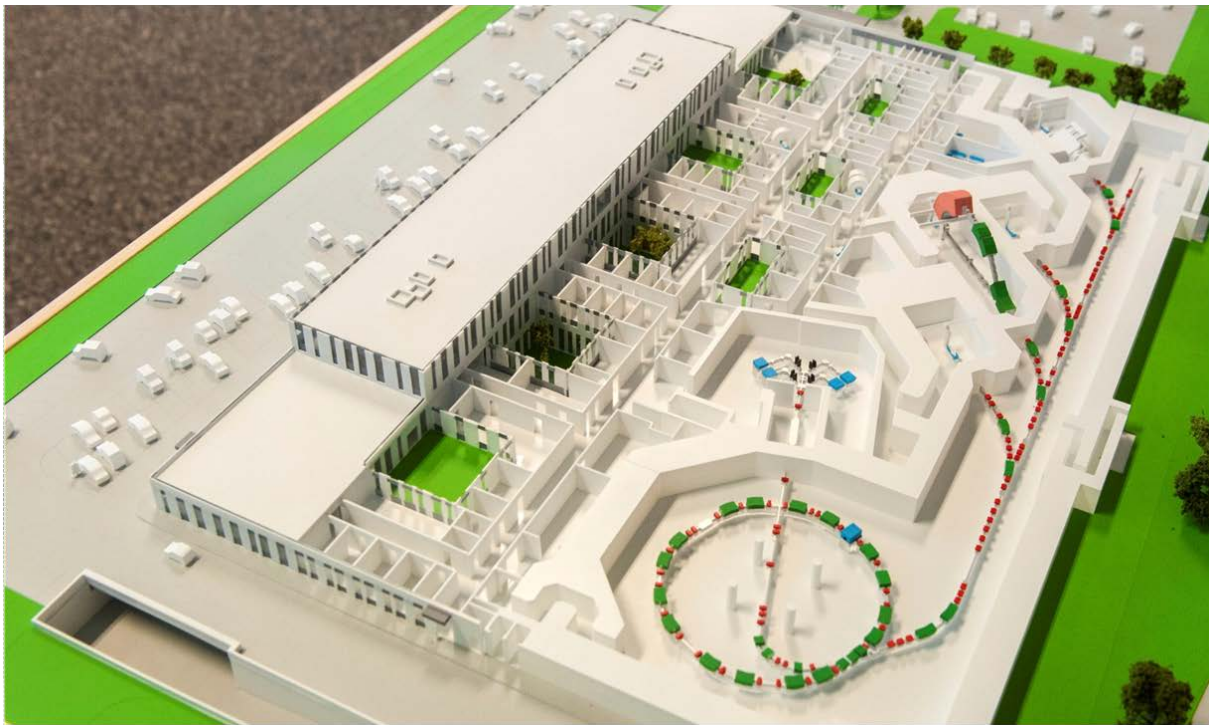
Fig 1: 3D-sketch of the MedAustron accelerator facility.

She continued by presenting the Centre's technical infrastructure, which comprises:

> radiation rooms with horizontal beam line in combination for a robotic patient positioning system with proton energies up to 800 MeV
> a Proton Gantry
> rooms for medical radiation physics (dosimetry laboratory, software development, storage)
> radiobiological laboratory (main lab, chemistry lab, cell culture, two storage rooms, cold room)
> rooms for experimental physics (preparation room, decay room, electronics lab, vacuum laboratory, storage space)
> mechanical workshops

She concluded her presentation with some pictures taken during the construction period.

The workshop was opened by **Hans Rabus** with his talk on **"The role of microdosimetry and nanodosimetry for biologically relevant radiation quantities"**. He explained that MiND-IBCT was

jointly organised by NanoIBCT Working Group 5 "Radiobiological scale effects", EURADOS Task Group 6.2 "Computational micro- and nanodosimetry", the Joint Research Project SIB06 "Biologically weighted quantities in radiotherapy" of the European Metrology Research Programme (EMRP) and the Austrian Ion Beam Therapy Center MedAustron.
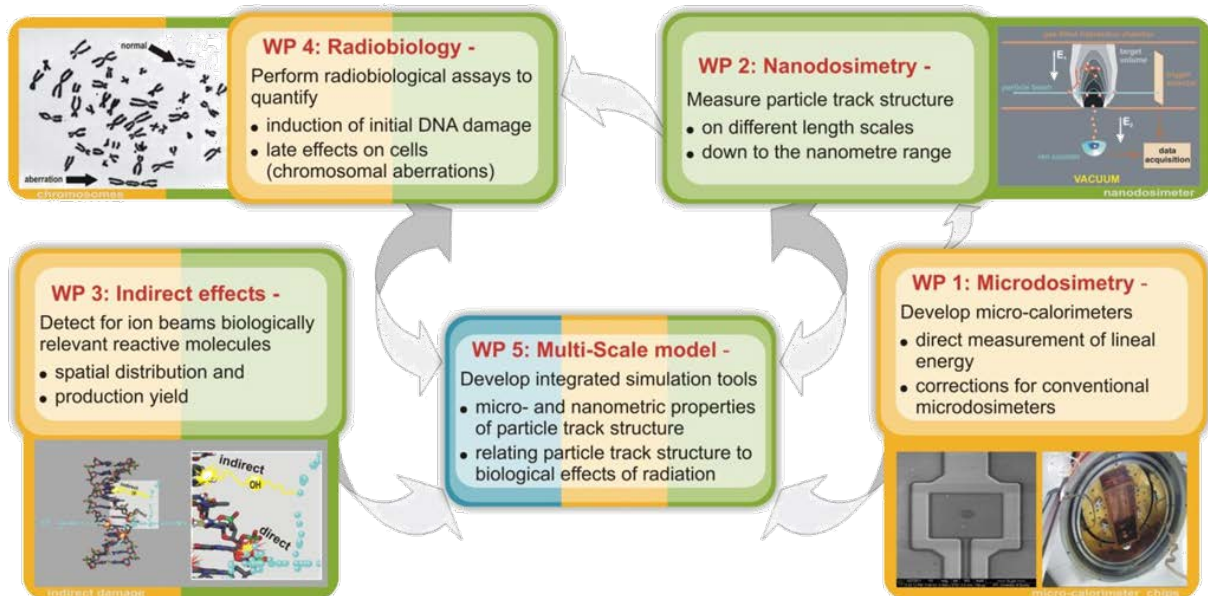

Fig 2: Outline of the Bioquart-Project

The workshop focussed on challenges encountered in the application of micro- and nanodosimetry for ion beam cancer therapy and in his opinion was to some extent the sequel to a discussion seminar on micro- and nanodosimetry held 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" at the PTB, Braunschweig (Germany), in 2009. The main purpose of the workshop, as with its predecessors, was to provide a forum not only for the presentation of progress and recent results, but also for the discussion of concepts and ideas. Thus, dedicated discussion sessions were planned where participants were invited to give short presentations on requirements and ideas for novel approaches in micro- and nanodosimetry, with the goal of implementing these into clinical practise. Rabus propounded that in order to emphasize this focus on translation of the techniques into clinical practise, the sequence of sessions had been intentionally chosen such that the workshop progresses from needs and requirements for the introduction into clinical practise, via biophysical models and track structure simulation, to the experimental aspects of state-of-the-art micro- and nanodosimetry.

Session one began with **Giulio Magrin** describing the present clinical scenario in his presentation **"Radiation quality measurements of ion beams: clinical feasibility and possible implementations."** He explained that the clinical and legal procedures in radiation therapy are quite strict, allowing only small uncertainties. The biological impact of ions crossing the human tissues, on the other hand, would change drastically. He therefore suggested that a primary requirement for ion beam treatment would be a reliable forecast of the biological effectiveness of the radiation, preferably in the form of a three dimensional map.
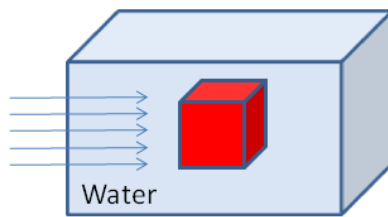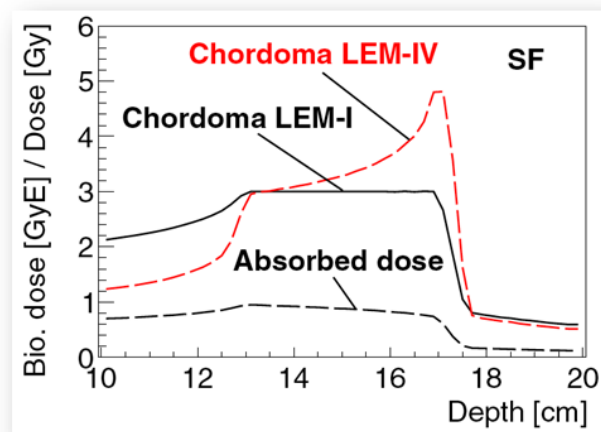
Fig 3: Variation of calculated RBE (LEM I, LEM IV) for a given dose profile

Although analytical computations and simulations would provide useful estimates, the direct measurement of those parameters would improve ion beam therapy by providing an absolute base reference for the sharing of results among different clinics. He concluded by addressing a key questions of the workshop, which was what level of accuracy is needed. Referring to a recently published article in the BJR, Magrin proposed that ideally the biological weighted dose should comply with the 2 % dose uncertainty legal requirement of photon radiation therapy and therefore the radiobiological effectiveness (RBE) should have a negligible contribution to the overall uncertainty. Consequently, biological dose discrepancies must be reduced by an order of magnitude. He closed with the question of whether a change in the reference dosimetry could provide such an improvement.

The final speaker of session one, **Emanuele Scifoni,** presented the role of oxygen concentration and the presence of nanoparticles (NP) for ion beam therapy in his talk **"Dose modifiers with particle beams from track structure to treatment planning: Oxygen effect and nanoparticle sensitization."** Results were presented to prove that intratumour heterogeneity, especially hypoxia, can be tackled using particle therapy. He also introduced a first treatment planning system (TPS) to account for oxygen enhancement ratio (OER) by optimising the quantity of survival fraction.
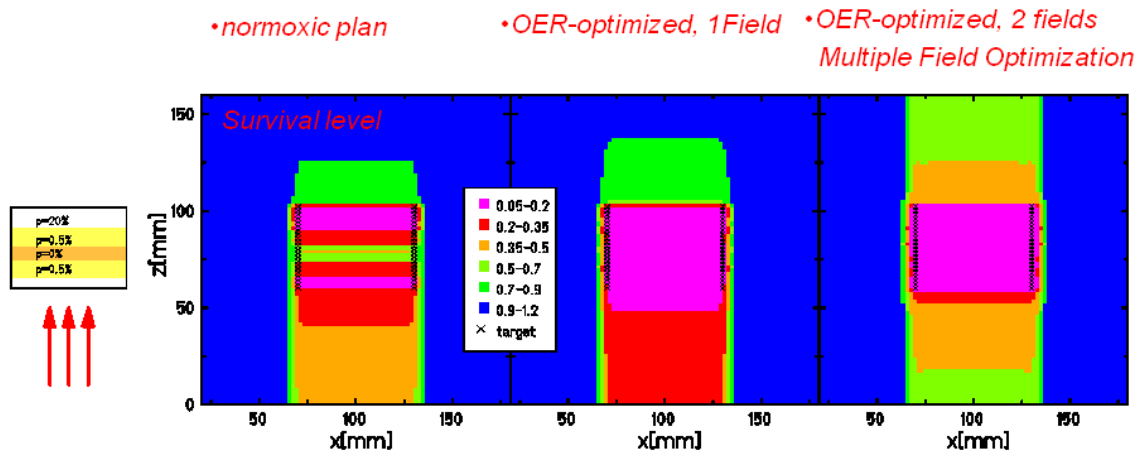
Fig 4: Treatment Plans optimized for survival level. Left: normoxic plan, middle: plan considering the oxygen enhancement ratio (OER) for one field, right: for two fields optimisation.

Scifoni explained that the treatment planning systemes (TPS) calculate iso-survival areas over different oxygenated regions and also for multiple fields. He showed that carbon ion beams can be optimised for hypoxic tumours only with moderate effect, whereas higher LET ions, such as ^{16}O, seem promising for boosted or multimodal plans. The presenter regarded the OER on the nanoscale as a "challenge for micro- and nanodosimetry" as well as the impact of the Linear Energy Transfer (LET) and particle type on radical formation and recombination.

Whilst for photon irradiation the presence of nanoparticles could be attributed to a beneficial impact on local dose deposition, the situation with ions would be ambiguous. Scifoni presented the track structure analysis of local dose enhancement for proton irradiation of different high atomic mass nanoparticles under various conditions. For proton irradiation in the presence of NPs, a local radial dose enhancement of up to a factor of two has been found for proton beams of several energies, which could be partially attributed to excess electrons from Auger cascades. He suggested that the most beneficial materials in terms of local dose enhancement would be platinum and gold, followed by gadolinium and silver.

Session two, *"Biophysical models and biological aspects"*, commenced with **Gonzalo Cabal** presenting **"The dependency of the alpha and beta parameters from the LQ model on LET: a**

Bayesian model selection perspective.” The linear-quadratic (LQ) model is concerned with two parameters, alpha and beta. While there is a common consensus on the dependency of the alpha parameter on the LET, there is no agreement on the variation of the beta parameter with LET. In the case of hypofractionated treatments, the beta parameter may have a big impact on the predicted value of the RBE of a treatment. In order to minimise the uncertainty of the alpha and beta parameter versus LET, a Bayesian model selection analysis was used. Data obtained with consistent experimental conditions for a wide range of LET values were studied using three different kinds of Bayesian model selection approach: the Akaiko Information Criteria (AIC), the Bayesian Information Criteria (BIC) and the Deviance Information Criteria (DIC).

The subsequent speaker in the session, **Thomas Friedrich**, went on to explain the concept of the Local Effect Model (LEM) in his talk **“RBE for Therapy: Development of the Local Effect Model and uncertainty assessment based on the PIDE data base.”** The original version (LEM I) is currently used for treatment planning in the European carbon ion treatment facilities. Subsequent steps towards the current improved version LEM IV, which takes into account the spatial distribution of DNA lesions on the nm-scale, as well as clustering of double strand breaks (DSB) on the µm-scale, were also described. With a number of examples, Friedrich demonstrated the applicability of this state-of-the-art model from cell survival experiments to clinical end points. He also discussed current open questions in treatment planning with carbon ions before introducing the Particle Irradiation Data Base (PIDE), which is a data base of more than 800 pairs of in-vitro cell survival experiments after ion and photon irradiation. It was suggested that this database could be used to investigate systematic effects of RBE, radiosensitivity of the cells, LET, energy and other determining factors on a purely experimental basis. The PIDE database is available online for the research community (http://www.gsi.de/bio-pide).

4. Thursday 8 May

"Understanding spatial and temporal track structure effects with clinically relevant ion beam studies in biological systems." was the topic of **Kevin M. Prise**'s talk. An overall goal of his work, he explained, would be a combined assessment of early and late cellular response and DNA damage in a range of relevant cell lines to provide systematic detailed information to help develop a rigorous theory of ion radiation action at the cellular and molecular level.

Recent experiments have been performed to assess in simple cell culture models the consequences of modulated dose delivery. Alongside direct effects, intercellular bystander signalling was also found to play an important role, resulting in the development of new models to determine the impact of intercellular communication on cellular response in modulated treatment fields. Some recent results for protons showed that significant differences exist between the effects of passively and actively scanned clinical beams, both spatially and temporally. Also differences between the response to pristine and Spread-Out Bragg Peaks (SOBP) were found, which indicated that LET alone might not be the best parameter for RBE predictions. Other findings were that the RBE variation for proton beams would not significantly extend the range of the SOBP and that a fixed RBE of 1.1 would underestimate the dose delivered to the tumour volume. There was also evidence to suggest that sub-lethal effects may also strongly vary along the Bragg curve and that they would be higher than for X-rays. And finally, that intercellular signalling would play a role when modulated photon and proton beams are used. Prise concluded that there is a need for the development of new biophysical models for advanced radiotherapies to include clinically relevant exposure scenarios.

In the following discussion, "How to introduce Micro- and Nanodosimetry in clinical practice", **Francesca Ballarini** presented "A biophysical model linking DNA damage, chromosome aberrations and cell death" This biophysical model focusses on DNA cluster damage and its consequences in terms of chromosome aberrations and cell survival. The model is based on the assumption 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. It is also assumed that certain aberration types (i.e. dicentrics, rings and large deletions) can lead to clonogenic inactivation. The yield of cluster lesions and the threshold distance would be the only adjustable parameters. Implementation of the model in a Monte Carlo code called BIANCA (BIophysical ANalysis of Cell death and chromosome Aberrations) resulted in simulated survival curves directly comparable with experimental data. For example, good agreement between simulations and experimental data was obtained for the survival of AG1522 and V79 cells exposed to photons, protons, alpha particles and heavy ions (including carbon and iron) with a threshold distance of 5 μm and CL yields in the range ~ 2 – 20 CLs·Gy^{-1}·cell^{-1}, depending on radiation quality (Fig. 5). This supports the hypothesis of a pivotal role of DNA cluster damage mediated by μm-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, suggest that this critical DNA damage may be identified with clusters of DSBs at the kilobasepair (kbp) scale.

Comparison with survival data - photons
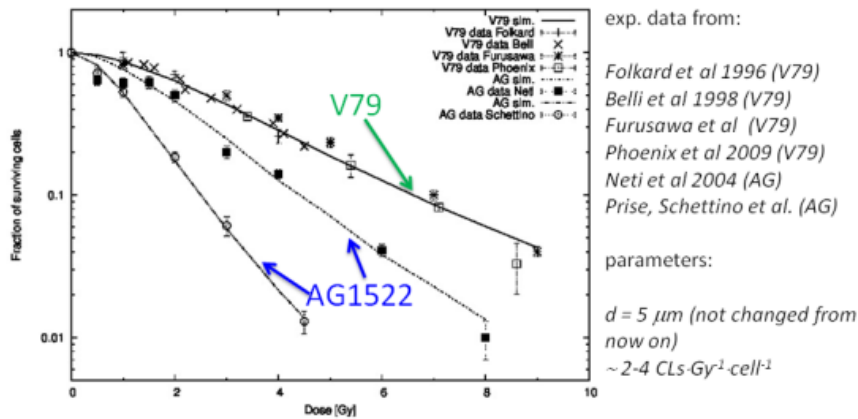
- the relationship between lethal aberrations and cell death holds not only for AG1522 cells, but also for V79 (and possibly others)
- important to take into account the specific experimental scenario

Fig 5: Simulated and experimental data for the survival of AG1522 and V79 cells exposed to photons, protons, alpha particles.

Comparison with survival data - protons
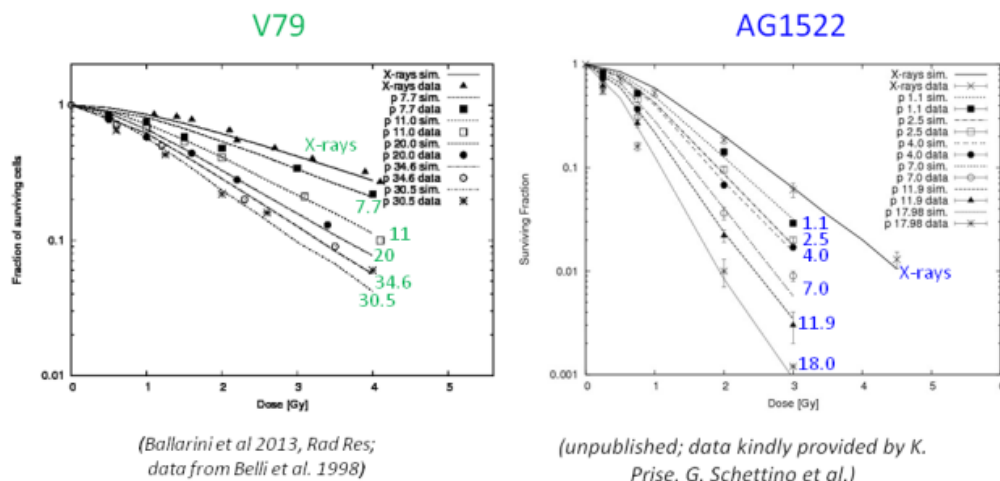
- the approach works not only for photons but also for protons
- confirmed that low-energy protons are more effective than photons ($\rightarrow$ proton therapy) (parameters: ~2-4 CLs · Gy^{-1} · cell^{-1} for V79, ~ 5-12 CLs · Gy^{-1} · cell^{-1} for AG)

Fig 6: Simulated and experimental data for the survival of AG1522 and V79 cells exposed to protons and alpha particles.

In the framework of possible applications for tumour hadron therapy, the model has been applied for the characterisation of the particle- and LET-dependence of proton and carbon cell killing. Ballarini showed that the predicted fraction of inactivated cells after 2-Gy protons was in good agreement with V79 experimental data. However, an increase of a factor of 1.6 in the LET interval corresponding to energies below a few MeV was observed in the distal region of the SOBP for proton therapy (7.7 - 30.5 keV/µm). This increase should be taken into account in clinics, especially when critical organs are located beyond the tumour position. The predicted cell killing after 2-Gy carbon irradiation was in agreement with V79 experimental data, except for an increase of a factor of 1.7 in the fraction of inactivated cells for LETs between 32.4 and 153.5 keV/µm, which was followed by a slight decrease for higher LETs. Finally, results for different depths along a carbon SOBP used for pre-clinical experiments at HIMAC in Chiba (Japan) were presented. The predicted surviving fraction along the SOBP was shown to be approximately constant, which not only agrees with measured data but also suggests that this approach may be applied to predict cell killing by therapeutic beams.

The third session of the workshop, **"Track structure calculations",** began with **Werner Friedland** presenting **"Track structure and initial DNA damage simulation for ion energies around the Bragg peak."** The "PARTRAC" Monte Carlo code and its biophysical modules for simulating track structures, DNA damage and its repair were introduced. Friedland then focussed on the implemented ion cross sections, which had been scaled from proton data by the effective charge according to Barkas formula (excluding charge transfer processes). This procedure is only applicable for specific energies above about 1 MeV/u as it overestimates the range of slow ions in water by as much as 10 µm. To solve this issue, the scaling procedure was recently modified using proton cross sections that account for charge transfer. The resulting range and linear energy transfer (LET) for C, N, O, P and Ca ions now agree with ICRU data and SRIM (Stopping and Range of Ions in Matter) calculations (Fig. 7).
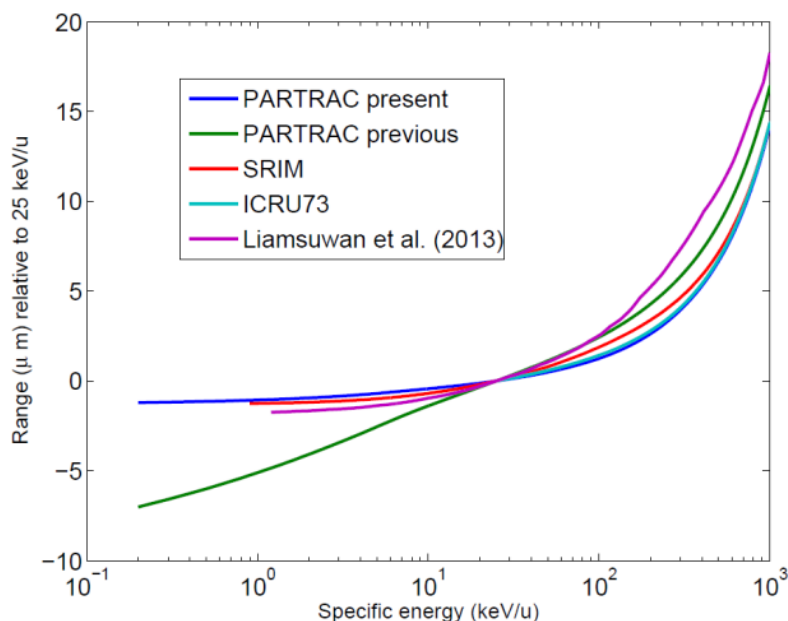

Fig. 7: Calculated ranges of carbon ions (below 1 MeV/u) in water according to PARTRAC (present, previous), SRIM, ICRU73 and KURBUC_carbon.

This modification was shown to improve PARTRAC's ability to simulate track structure and DNA damage by low-energy ions, and thus enabling the software to model biological effects in distal Bragg peak regions or in neutron irradiation.

Marie Davídková continued the session with her talk **"Carbon ion beam quality: LET spectra calculated by Geant 4 at different positions along and around ion beam."** Track etched detectors (TED) were used to determine LET spectra with spatial resolution less than 1 mm. LET spectra and the depth-dose distribution of the carbon ion beam had been measured with USF-4 detectors behind polymethylmethacrylate (PMMA) filters at the Heavy Ion Medical Accelerator (HIMAC) at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan. The measurements were performed along a monoenergetic carbon ion beam of energy 290 MeV/u at four different positions: at the beam extraction area, at the beginning, at the maximum, and 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 were evaluated with the aid of the Geant 4 9.6.P01 Monte Carlo toolkit (comp. Fig. 8).
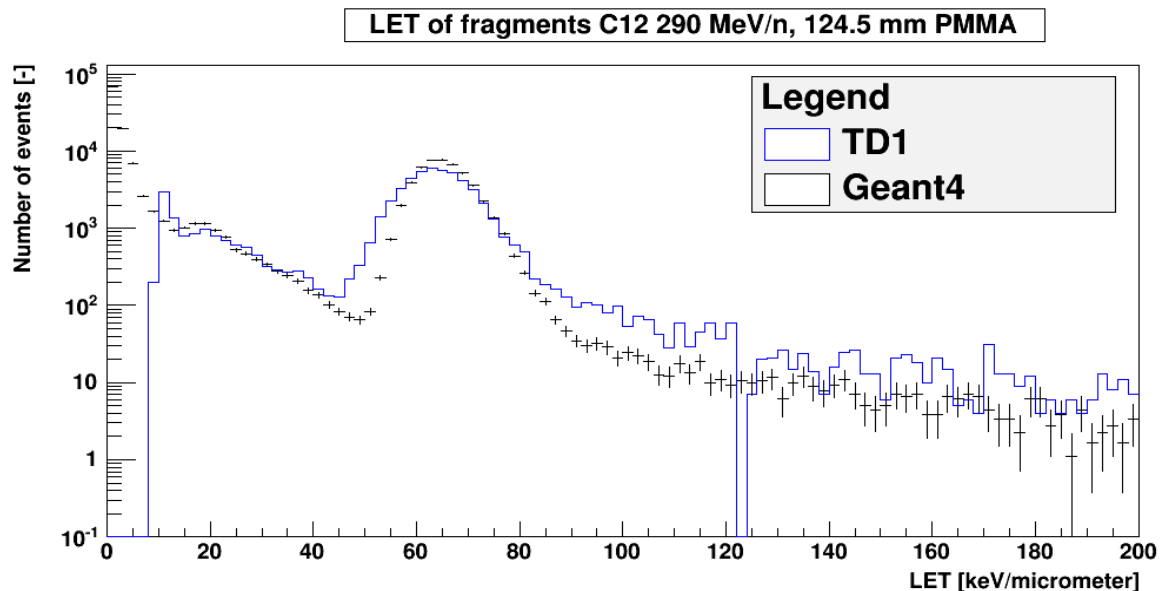
Fig. 8: Measured and calculated LET-spectra.

The subsequent speaker, **Marion Bug**, presented the **"Simulation of electron tracks in water and DNA medium."** The estimation of DNA damage caused by densely ionising radiation is based on simulated parameters of the particle track structure. Track structure simulations thus require cross section data for the interaction of incident particles (and their secondaries) with molecules of the medium. In the absence of cross section data for DNA constituents for Monte Caro simulation, biological matter has been conventionally substituted with liquid water.

Bug presented the methodology to obtain a complete data set of cross sections of DNA constituents for electrons (7°eV – 1°keV) for implementation into the Monte Carlo PTra code. The aforementioned data set is based on experimental data of total scattering cross sections, differential elastic scattering cross sections and double-differential ionisation cross sections of tetrahydrofuran, pyrimidine and trimethylphosphate. Strong variation in the energy dependence

of total cross sections (up to 70 %, Fig. 9) and the angular dependence of differential electron impact cross sections between water and DNA constituents were found.
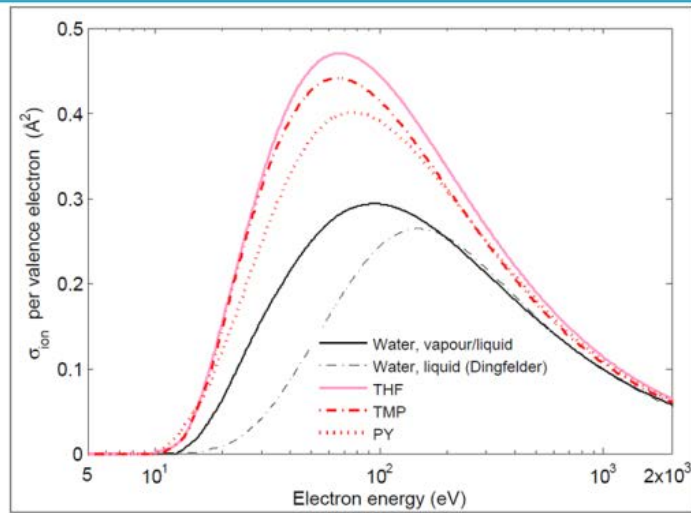

Fig. 9: Total ionisation cross sections of water (liquid, vapour), tetrahydrofuran, pyrimidine and trimethylphosphate vs. energy
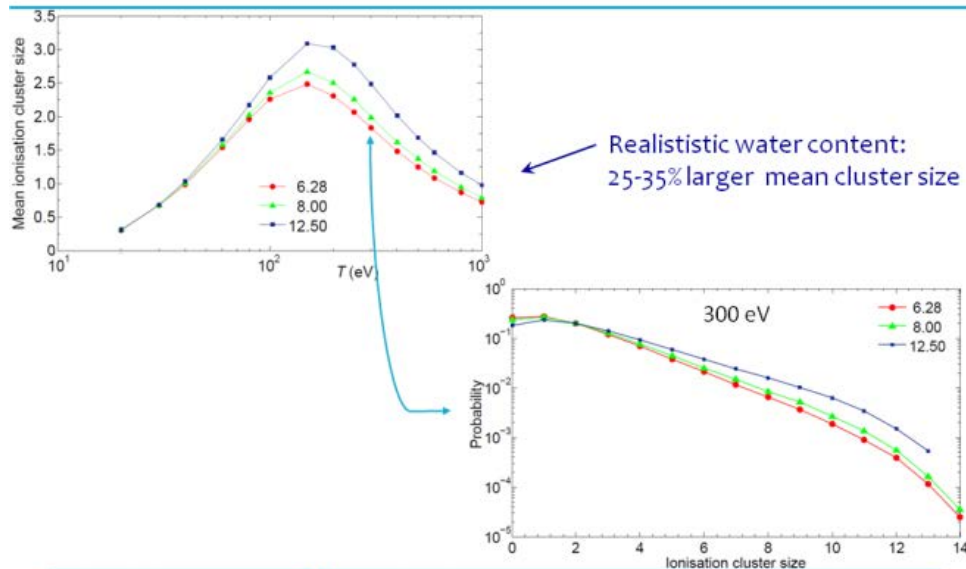

Fig. 10: (Mean)- ionisation cluster size distribution in DNA medium with varying water content

The evaluated cross section data were used to simulate the electron track structure in DNA. When the DNA medium had the same mass density as liquid water, the electron track structure (simulated with Emfietzoglou's ionisation cross sections) was similar to that in liquid water. However, the use of realistic water content of DNA medium in the simulations would lead to enhanced probabilities to produce large ionisation clusters (25 % - 35 % larger mean cluster size, Fig. 10).

On behalf of the Geant 4-DNA collaboration, **Carmen Villagrasa** presented **"Track structure calculations with the Geant 4-DNA toolkit and on-going developments."** The main purpose of the Geant 4-DNA project (http://geant4-dna.org) is to extend the functionalities of the Geant 4 Monte Carlo toolkit so as to allow users to model the early radio-induced damages at the DNA level. A review of this toolkit and its validity range was given with particular focus on the current status and ongoing developments, such as tools for the "physico-chemical" and "chemical" stages, geometrical descriptions of the DNA target and the associated algorithms for damage scoring.
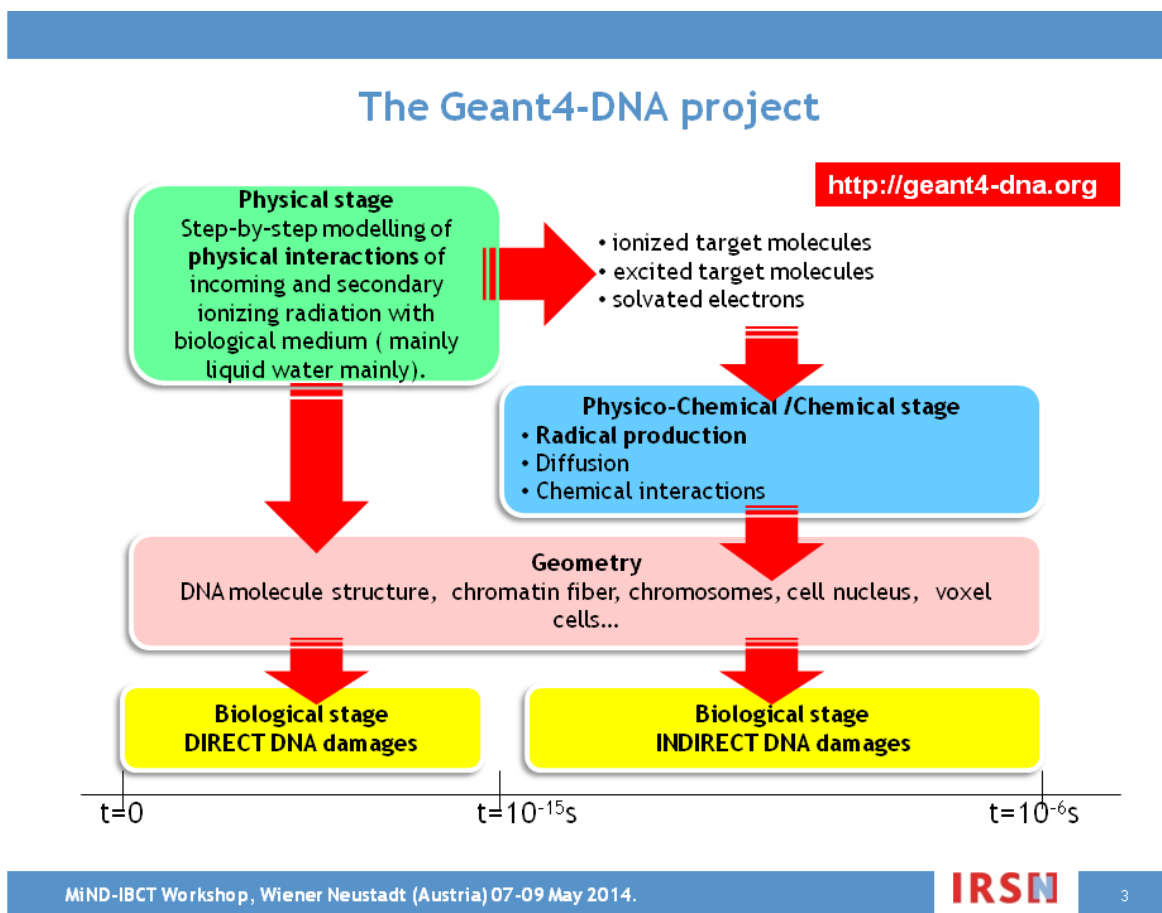
Fig. 11: Sketch of the Geant 4-DNA project

The final speaker in the session, **Reinhard Schulte**, presented **"A Novel Approach to Particle Therapy Radiation Metrology Based on Nanodosimetry – Concepts and First Results."**

The author opened the talk with his statement that the concept of the biologically effective dose D_{RBE} as a multiplication of the Relative Biological Effectiveness (RBE) and the clinical dose D ($D_{RBE} =$

RBE × D) is a flawed concept. Protons and ions have a depth-dependent biological effect profile with, for instance, a higher biologically effective dose in the distal third of the SOBP. Furthermore the RBE of protons and ions depends not only on depth but also on dose and tissue or endpoint.

In proton therapy, a constant RBE of 1.1 is assumed, recently endorsed by ICRU report 78, but all would know that it is not correct. Schulte proposed that nanodosimetry-based treatment planning may be able to address some of these issues.

The remainder of the talk was divided into three sections: Nanodosimetry: concepts and devices, radiobiological rationale and treatment plan optimisation for protons. The first section dealt with a brief overview of the history and present status of nanodosimetry and a description of a 2-D ion detector developed in the LLU Radiation Research Labs for track structure study of protons and heavier ions.

Fig. 12: 2-D Ion detector for track structure study of protons and heavier ions developed in the LLU Radiation Research Labs.

The next section addressed the radiological rationale behind nanodosimetry, leading to the question of which quantity should be optimised in a treatment plan. Schulte proposed that perhaps it should be to optimise the yield of large ionisation clusters in the tumour whilst minimising their yield in critical normal tissue. In order to create uniform cell killing, the yield of small (2 - 3) and large (4 - 10) ionisation clusters in the target should be made uniform as well.

Furthermore, in case of hypoxic regions, the number of small ionisation clusters should be enhanced by the low-LET OER (i.e. ~2.7) to achieve a uniform cell killing.
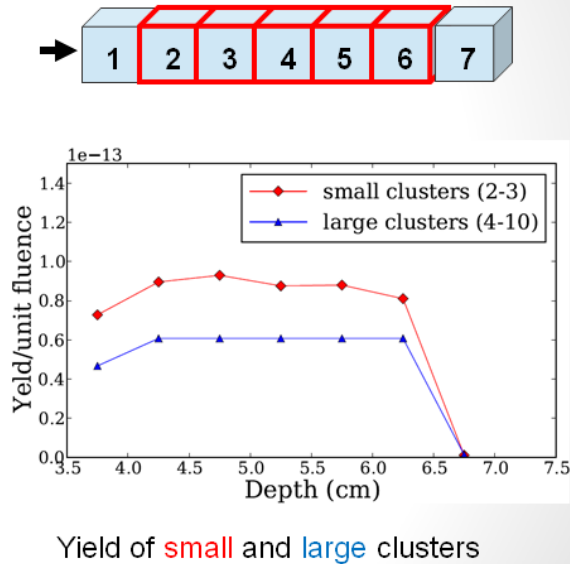
In the final section of the talk, a method was presented to optimise a simplified proton treatment plan with the goal to obtain a uniform distribution of small and large ionization clusters. The optimisation was performed by simulation of ionisation cluster size (ICS) distributions and was undertaken on three separate levels. The first was the macroscopic level, where the patient was represented by a 15 x 15 x 15 cm^3 water cube enclosing a planning target volume (PTV) comprising a stack of five cubic water voxels, each with 5 mm long sides, aligned in the beam direction. The energy spectrum and number of protons per unit entrance fluence were scored at the entrance of each voxel from simulations performed with Geant 4 using the Hadronic and Standard EM-physics classes (two additional voxels proximal and distal to the PTV were also scored).

On the next level, the nanoscopic level, the Livermore EM models (down to 250 eV) were activated within the voxels, and the DNA physics model was used for radiation transport within a 2 μm-thick slab at the centre of each voxel. Tracks for nanodosimetric sampling were collected in 108 cylinders of 500 nm diameter and 500 nm height placed in a plane at the centre of the (2 μm-thick) slab. The output of the simulation comprised the coordinates of all ionisation events produced in the nanometric sensitive volume (SV) per proton entering the macroscopic phantom.

At the third level, nanodosimetric sampling was performed. Geant 4 simulated tracks were sampled with 105 cylindrical volumes of 2 nm diameter and 16 nm length, randomly distributed throughout the larger SV. The numbers of ionisations were scored in each sampling cylinder together with the corresponding ionisation cluster size distributions (absolute and conditional), which were calculated for unit and weighted pencil beam fluences. The optimised fluence for each pencil beam was then determined numerically (Fig. 13).

Fig. 13: Yields of small and large clusters after optimisation

Schulte concluded his talk with a few open questions regarding this method:
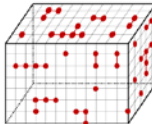
- What would be the most relevant sampling (sensitive) volume to score nanodosimetric ionisation cluster size distributions for bio-effectiveness?
- What would be the upper limit of cluster size that should be considered?
- What would be the tolerance limits of large clusters (> 3 ionisations per SV) for normal tissues?
- How important would be the influence of regional spacing of ionisation clusters for bio-effectiveness?

In the discussion following session three, **Bernd Heide** presented **"A Percolation Model for Calculating SSB- and DSB-yield"**, which is essentially a new statistical model to calculate the yield of single strand breaks (SSB) and double strand breaks (DSB) for analysing the geometry dependence of the cluster distribution. Percolation models would be simple statistical models such as those known in solid state and polymer physics. A representative problem, from which the name "percolation" was derived, is assuming that a liquid is poured on top of a porous material, would the liquid be able to make its way from hole to hole and reach the bottom? This question would be modelled mathematically as a three-dimensional network of $n \times n \times n$ sites, in which the bonds between any two neighbours may be open (allowing the liquid through), with probability p, or closed with the independent probability q.

Fig. 14: Outline of the percolation model

Heide described his model scenario of a homogeneous, monoenergetic electron beam irradiating a water cylinder of 2 nm in both diameter and height. Further assumptions were a triangular lattice structure, where it is assumed that a SSB takes place if one molecule is ionised 1 to 3 times and that a DSB occurs if two or more neighbouring molecules had been hit ($q = 1$).

A key assumption for his model would be a connection of p with the ionisation probability $W = \omega * \sigma_{ion}$ in the sense that ω represents the number of atoms (sites) per area and thus p is equal to σ_{ion}. The presentation concluded with preliminary yet promising results.

5. Friday 9 May

Paolo Colautti opened the final session of the workshop **"Experimental Micro- and Nanodosimetry"** **with his talk on "Microdosimetry of Ion Beams".** Conventional dosimetry was critiqued in that it is not concerned with physical occurrences at the sub-cellular level. Dosimeters cannot measure the actual energy absorbed in biologically critical sites, such as cell nuclei, chromosomes or DNA fibre, but only the average energy absorbed in the detector's sensitive volume. They are therefore unable to monitor the biological-effective dose variations inside the SOBP, which depends mainly on single-particle interactions with critical sites. Microdosimetric detectors, on the other hand, can measure the entire absorbed-energy spectrum in a 1 μm site, which corresponds to the size of chromosomes. These detectors should therefore be suitable for monitoring biological damage variations.

An additional problem is that the biological effect saturates with increasing linear energy transfer but not the energy released in a 1 μm site by a single ionising particle. In order to compensate for this, the microdosimetric spectrum is "weighted" with an empirical function (extracted from biological experiments) so as to mimic the relative biological effect. Colautti showed results obtained with the microdosimetric approach for therapeutic proton beams, which were consistent with radiobiological data. Further investigations with this approach for therapeutic carbon ion beams and subsequent comparison with relevant radiobiological data would point out whether the aforementioned weighting function would require modification.
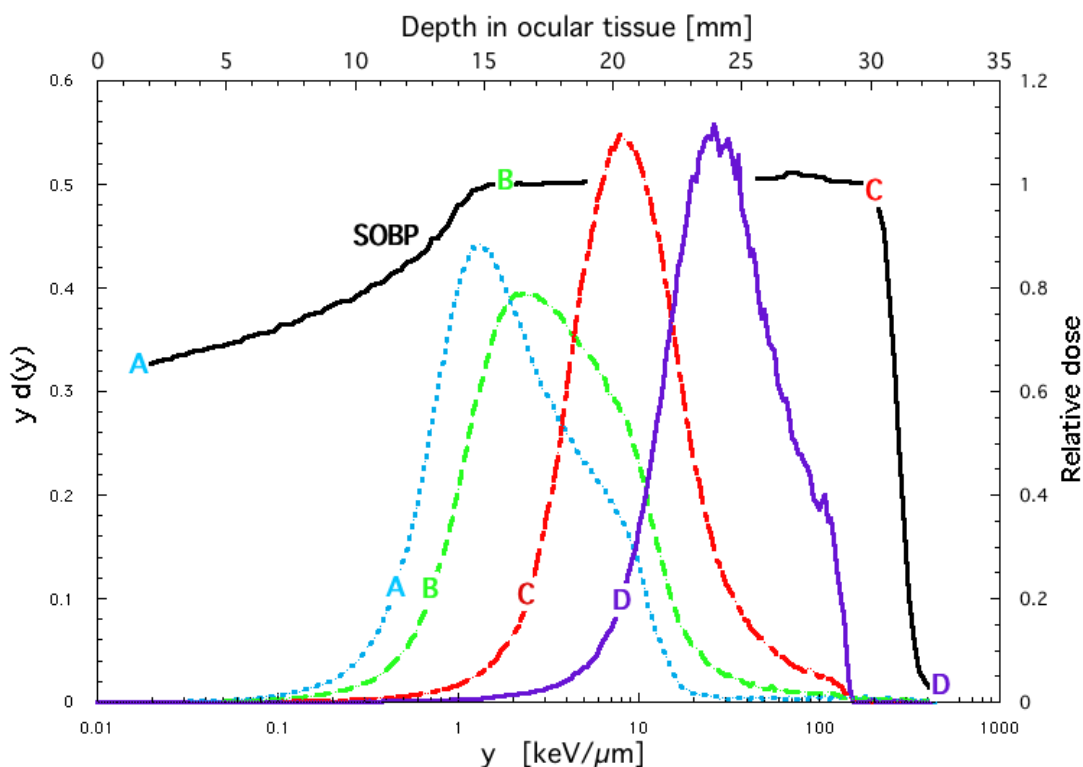
Fig. 15: Microdosimetric spectra and dose profile of the therapeutic 62 MeV-proton beam of Lacassagne (Nice) medical centre

The session continued with **Sabina Chiriotti** presenting a **"Critical assessment of physical data to calibrate microdosimetric spectra."**
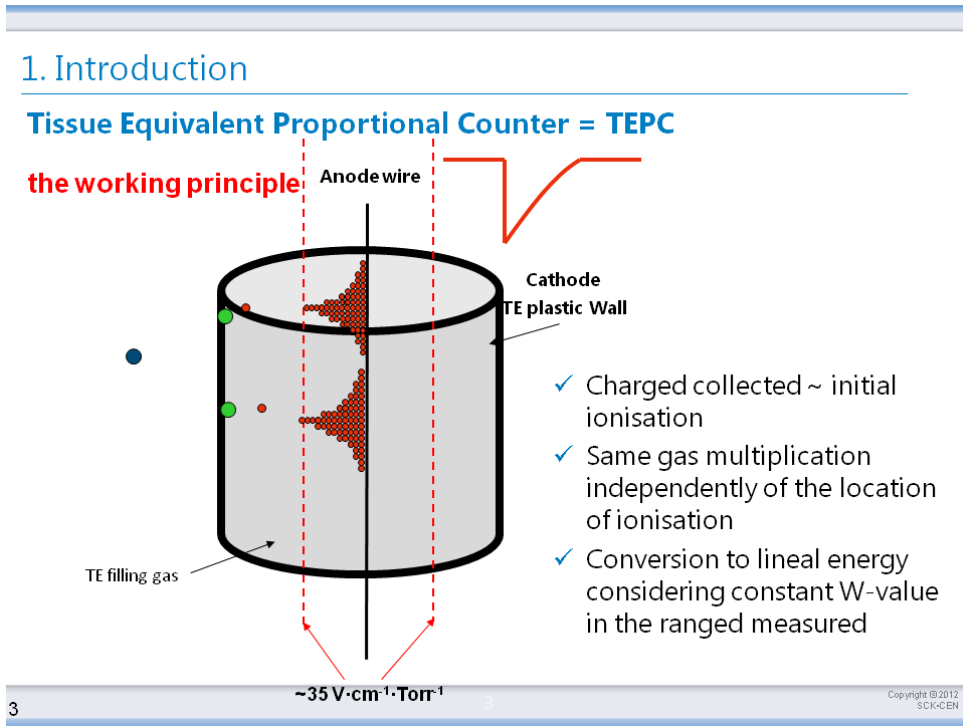

Fig. 16: Working principle of the Tissue Equivalent Proportional Counter (TEPC).
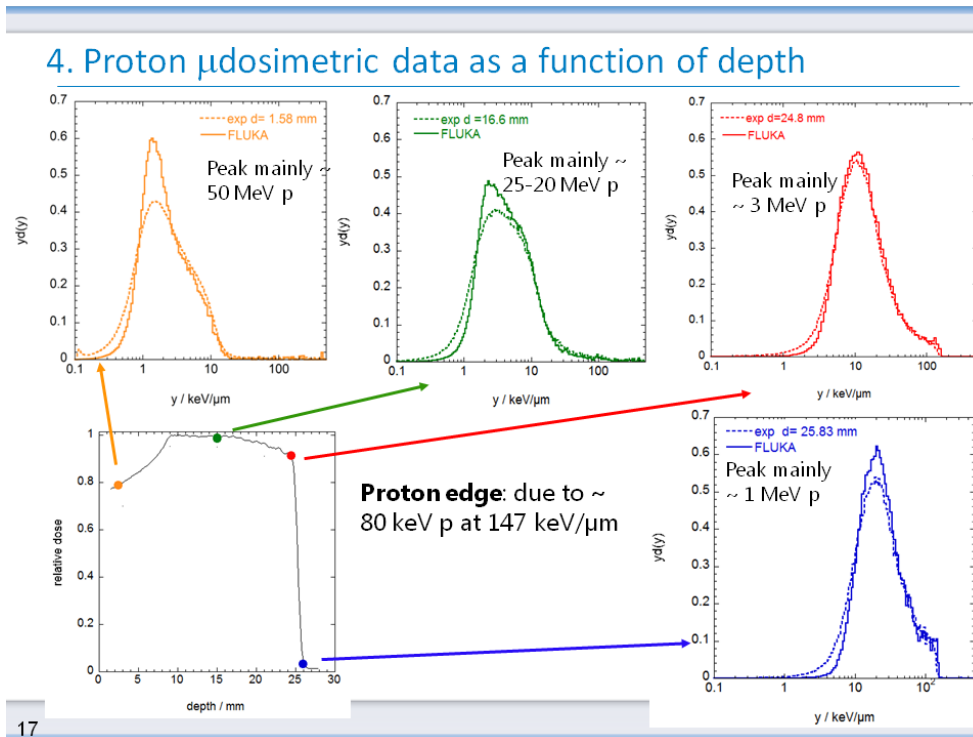

Fig. 17: Measured and calculated microdosimetric spectra for proton beams at specific energies.

Tissue-equivalent proportional counters (TEPCs) are used to measure the distribution of ionisations produced in the gas cavity by the radiation field, which can then be converted by application of a calibration factor into a distribution of energy imparted. The present work investigated how the choice of three different input databases (ICRU 49, SRIM-code and FLUKA) can influence calibration.

Despite the fact that the variation in stopping power data is often neglected, the choice of input database does have a significant impact. The input data for TEPC calibration should therefore be standardised, especially for applications in hadron therapy where uncertainties of less than 5 % are required.

In the third talk of the session **"Micro-calorimeters directly measuring lineal energy"**, **Seb Galer** presented a novel detector based on the principle of a Superconducting Quantum Interference Device for measuring the energy deposited at the microscopic scale which is currently under development at the National Physical Laboratory (UK). The main advantage of this type of detector is that it would provide 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 a theoretical response time of less than a microsecond. The main drawback of this device is the complex nature of operation which is carried out at temperatures below 7 K. The detector response also needs to be corrected for the fraction of energy absorbed by the superconducting layer as well as the heat transfer between the various layers and the environment. Results from Monte Carlo and numerical heat transfer simulations were presented for the determination of such correction factors.

Stefano Agosteo addressed the possibility of using TEPCs at the nanometre scale in his talk **"Experimental Microdosimetry at Nanometre Level."** Performing measurements at the nanometre scale would allow the TEPC's data processing to take advantage of all recent track structure findings. Furthermore, at the nanometric level, the TEPC saturation function may be invariant with respect to radiation fields since the interaction is measured in the same site size where the initial biological damage occurs.
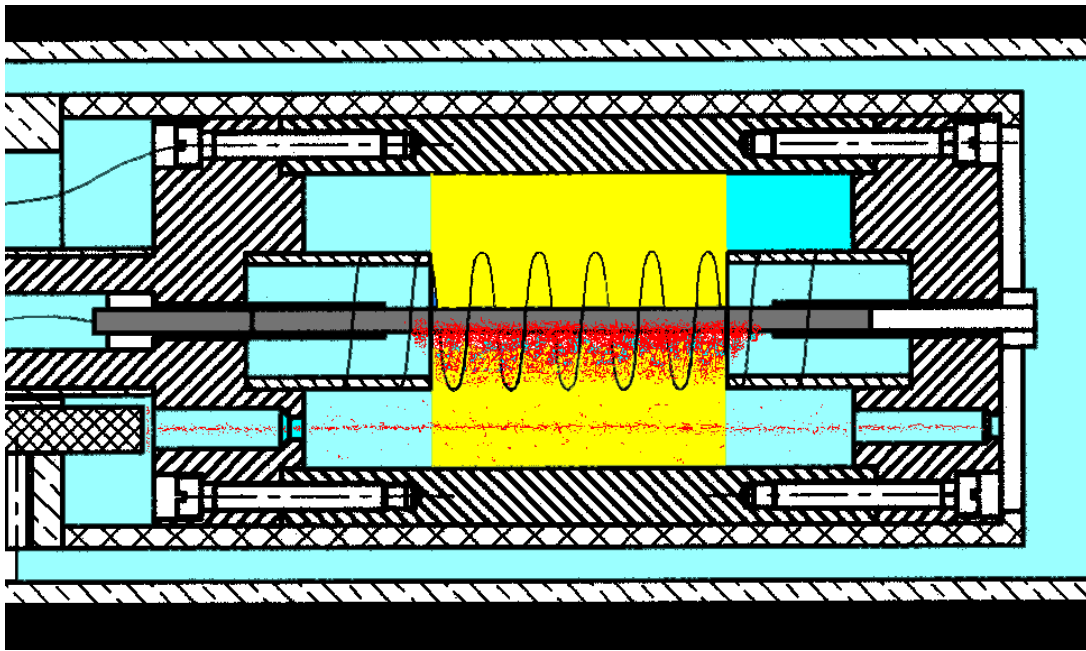
Fig. 18: Sketch of the avalanche-confinement TEPC. The electronic avalanche is forced inside the helix volume.

Agosteo also presented special avalanche-confinement TEPCs which have already been developed and can be operated down to few tens of nanometres. In these gas proportional counters, the electronic avalanche is forced to occupy a limited volume (a co-axial helix) around the anode wire.

The talk concluded with the proposal of constructing a new portable avalanche confinement TEPC with a smaller sensitive site size.

The session continued with **Gerhard Hilgers** giving an insight into **"Challenges in track structure nanodosimetry"**, which focused on the experimental aspects of nanodosimeters used to measure the track structure parameters of a primary particle track in a volume element of nanometre dimension. Since the direct measurement of individual interactions in a sufficiently small (i.e. nanometric) target volume in liquids and solids are not yet possible, the measurement of track structure parameters are conducted in larger targets consisting of rarefied gases.

Generally, there are three different nanodosimeter devices that allow the direct measurement of ionisations produced inside small gas volumes by ionising particles directly crossing them, or passing nearby at given impact parameter d (distance between the particle track and centre of the measuring volume related to a density of 1 g/cm³). Two of the devices are based on single-ion counting (NCBJ, PTB) and the third, a track-nanodosimeter (LNL), is based on single-electron counting.
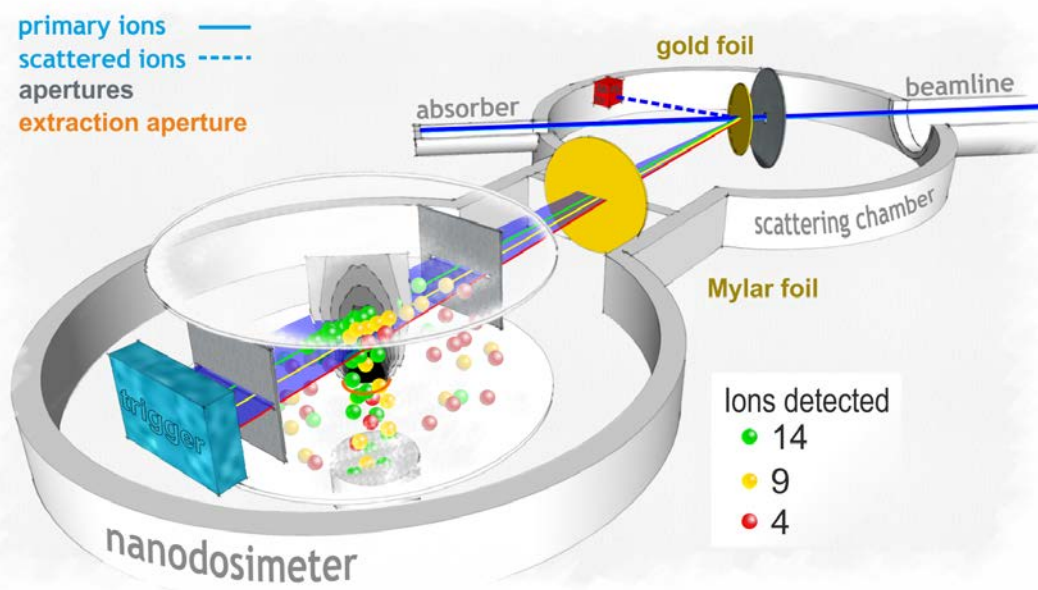
Fig. 19: Outline of the PTB-nanodosimeter.

The nanodosimeter operated at PTB was used to discuss the experimental problems of the three setups, which are of a similar nature. Hilgers then went on to explain the fundamental nanodosimetric quantities and various experimental aspects, such as the collection of secondary ions created along the primary particle track as well as the determination of primary particle track parameters and size of the sensitive volume element. The presentation concluded with recent measurement data from carbon ion beams.

Valeria Conte presented the results of several measurement campaigns at Legnaro National Laboratories (LNL) in her talk **"Experimental nanodosimetry of carbon ions."** Owing to increased interest for carbon ions in radiotherapy at energies close to the Bragg peak, ionisation cluster size distributions produced by 96 MeV, 150 MeV and 240 MeV ^{12}C-ions have been measured for various impact parameters d. The work focused on track structure parameters derived from measured ionisation cluster size distributions, such as the mean ionisation cluster size M_1 and the cumulative probability F_k of measuring cluster sizes $\nu \geq k$. The quantity F_k is of interest from a radiobiological point of view as an increase in k corresponds to a damage of higher complexity.

The mean ionisation cluster size distributions with respect to the impact parameter were presented. A clear correlation between the mean ionisation cluster size (when d equals zero) and the quotient D_{eff}/λ_{ion} can be seen, where D_{eff} is the effective diameter of the sensitive target volume with $\rho = 1$ g/cm^3 and λ_{ion} is the corresponding primary ionisation mean free path length. The quotient itself could then be considered as the mean number of primary ionisations along a length D_{eff}. In general, not only M_1 ($d = 0$) but all mean ionisation cluster size distributions as a function of d could be scaled "almost perfectly" by D_{eff}/λ_{ion}.

For small impact parameters, the cumulative distribution F_2 exhibits a saturation effect, whereas for larger impact parameters F_2 seems to be proportional to D_{eff}/λ_{ion}.

Furthermore, for all measured beam qualities the cumulative distribution F_2 versus M_1 would produce an "almost perfect universal curve" that would exhibit a saturation effect similar to radiobiological cross sections as a function of LET. Several measured distributions were presented in which the ratios F_2/M_1 behave almost as unique functions of M_1, and the ratios F_k/M_1 versus M_1 are expected to mimic the behaviour of RBE_α as a function of LET.
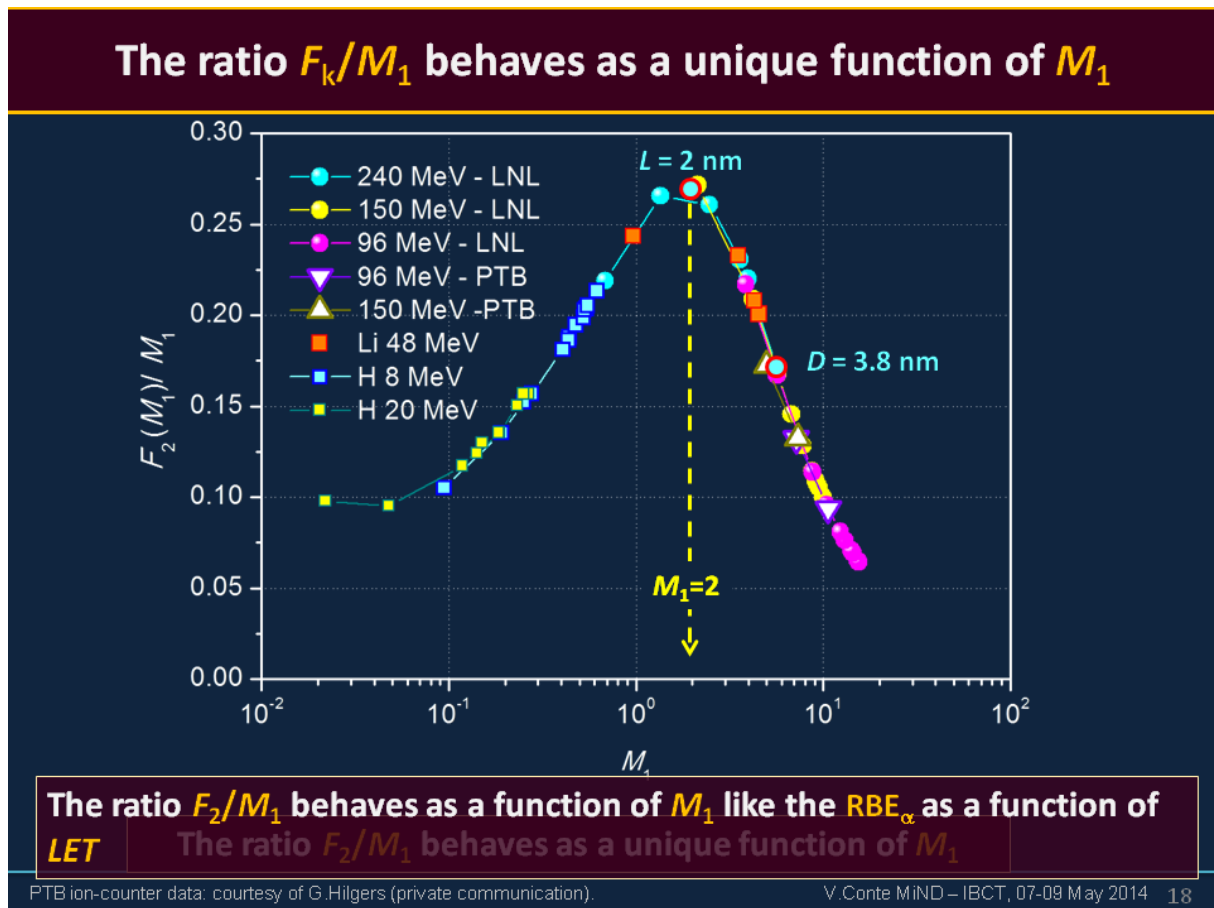

Fig. 19: Ratios F_2/M_1 of measured distributions as functions of M_1.

Conte concluded that the biological efficiency of ionising particles would be clearly related to their track structure properties on the nanometric scale, where these properties can not only be simulated but also measured directly. Furthermore, M_1 reflects the ionisation density D_{eff}/λ_{ion} which is measurable. A great challenge of track structure nanodosimetry is a portable detector which is feasible for use in clinics, such as a TEPC operated at a nanometric level.

Acknowledgements

References /Full List of Contributions

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The role of microdosimetry and nanodosimetry for biologically relevant radiation quantities:	H. Rabus[1], H. Palmans[2,3], G. Hilgers[1], P. Sharpe[2], M. Pinto[4], C. Villagrasa[5], Th. Schneider[1], D. Moro[6], A. Pola[7], S. Pszona[8], P. Teles[9]	[1] Physikalisch-Technische Bundesanstalt (PTB), Braunschweig, Germany [2] National Physical Laboratory (NPL), Teddington, UK [3] EBG MedAustron GmbH, Wiener Neustadt, Austria [4] Istituto Nazionale di Metrologia delle Radiazioni Ionizzanti (ENEA-IMRI), Santa Maria di Galeria, Italy [5] Institut de Radioprotection et de Sûreté Nucléaire (IRSN), Fontenay-aux-Roses, France [6] Istituto Nazionale di Fisica Nucleare (INFN), Legnaro, Italy [7] Politecnico di Milano (PoliMi), Milan, Italy [8] National Centre for Nuclear Research (NCBJ), Otwock-Swierk, Poland [9] Universidade Tecnica de Lisboa, Instituto Tecnológico e Nuclear (IST-ITN), Sacavém, Portugal
Radiation quality measurements of ion beams: clinical feasibility and possible implementations	G. Magrin, R. Mayer	EBG MedAustron, Wiener Neustadt, Austria
Dose modifiers with particle beams from track structure to treatment planning: Oxygen effect and nanoparticle sensitization	E. Scifoni[1], C. Wälzlein[1], M. Durante[1,2] and M. Krämer[1]	[1] GSI Biophysics, Darmstadt, Germany [2] TUD Darmstadt, Germany
The dependency of the alpha and beta parameters from the LQ model on LET: a bayesian model selection perspective	G. Cabal[1], A.Trende[1], E. Blakely[2], K. Parodi[1]	[1] Faculty of Physics, Ludwig-Maximilians-Universität München, Munich, Germany [2] Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA
RBE for Therapy: Development of the Local Effect Model and uncertainty assessment based on the PIDE data base	T. Friedrich[1], R. Grün[1], M. Durante[1,2], M.Scholz[1]	[1] GSI Helmholtzzentrum für Schwerionenforschung, Darmstadt, Germany [2] Institut für Festkörperphysik, Technische Universität Darmstadt, Darmstadt, Germany
Understanding spatial and temporal track structure effects with clinically relevant ion beam studies in biological systems	K. M. Prise	Centre for Cancer Research and Cell Biology, Queen's University Belfast, 97 Lisburn Road, Belfast BT9 7AE, UK
A biophysical model linking DNA damage, chromosome aberrations and cell death	F. Ballarini, M. Carante	University of Pavia and INFN
Track structure and initial DNA damage simulation for ion energies around the Bragg peak	W. Friedland, E. Schmitt, P. Kundrát	Helmholtz Zentrum München, Department of Radiation Sciences, Institute of Radiation Protection
Carbon ion beam quality: LET spectra calculated by Geant4 at different positions along and around ion beam	M. Šefl[1,2], V.Štěpán[3,1], I. Ambrožová[1], K. P. Brabcová[1,4], O. Ploc[1], S. Incerti[3], M. Davídková[1,2]	[1] Nuclear Physics Institute, ASCR, Prague, Czech Republic [2] Faculty of Nuclear Sciences and Physical Engineering, CTU in Prague, Czech Republic [3] Université de Bordeaux, CNRS/IN2P3, Centre d'Etudes Nucléaires de Bordeaux Gradignan, Gradignan, France [4] Dept. of Applied Physics, Chalmers University of Technology, Göteborg, Sweden
Simulation of electron tracks in water and DNA medium	M. U. Bug, W. Y. Baek, H. Rabus	Physikalisch-Technische Bundesanstalt, Braunschweig, Germany
Track structure calculations with the Geant4-DNA toolkit and on-going developments	C. Villagrasa (Geant4-DNA collaboration)	IRSN/PRP-HOM/SDE/LDRI, Institut de Radioprotection et Sûreté Nucléaire. BP 17, 92262 Fontenay-aux-Roses Cedex, France
A novel approach to particle therapy radiation metrology based on nanodosimetry - concepts and first results	R. Schulte	Loma Linda University Medical Center, Loma Linda, California, USA
Microdosimetry of Ion Beams	P. Colautti[1], D. Moro[1], V. Conte[1], S. Chiriotti[1,2]	[1] INFN Laboratori di Legnaro, I-35020 Legnaro, Italy [2] SCK-CEN, B-2400, Belgium
Critical assessment of physical data to calibrate microdosimetric spectra	S. Chiriotti[1,2,3], D. Moro[3], V. Conte[3], P. Colautti[3], B. Grosswendt[4], E. Sterpin[2], S. Vynckier[2,5]	[1] Belgian Nuclear Research Centre, SCK•CEN, Mol, Belgium [2] Center of Molecular Imaging, Radiotherapy and Oncology, Université catholique de Louvain (UCL), Brussels Belgium [3] Laboratori Nazionali di Legnaro, INFN-LNL, Legnaro, Italy [4] Guest at LNL-INFN, Legnaro, Italy [5] Cliniques universitaires Saint-Luc, Université catholique de Louvain, Brussels, Belgium

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