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Working Material

Report of the Consultancy Meeting (F1-CS-1806963) on

Consultancy Meeting on Current Developments on Micro Dosimetry Detectors

Organized and hosted by
The International Atomic Energy Agency (IAEA)

Room C0217, IAEA Headquarters, Vienna, Austria

3-05 July 2019

Scientific Secretary: Mr Natko Skukan, NSIL/Physics/NAPC/IAEA

Chairperson: Mr Anatoly Rozenfeld (Australia)

Rapporteur: Mr Hans Rabus (Germany)

Contents

Executive summary

The meeting was organized by the IAEA Nuclear Science and Instrumentation Laboratory (NSIL), Physics Section (PS) of the International Atomic Energy Agency. The objectives of this meeting were to highlight, review and discuss the current state of the art and recent development in the field of microdosimetry, as well as receiving feedback and recommendations for future improvements and possible IAEA's activities.

The meeting was attended by four participants from four Member States (MS) (list of participants in Annex 1) who shared their work experiences and knowledge relevant to the scope of the Meeting (agenda in Annex 2). The presentations resulted in discussions on:

- Advanced semiconductors microdosimetry and its applications
- Experimental microdosimetry and ion-beam therapy
- Multi-scale approaches in micro-/nanodosimetry
- Role of microdosimetry in ion-beam therapy at Heavy Ion Medical Accelerator in Chiba, Japan (HIMAC)
- Radiation biology research in IAEA and possible connections to microdosimetry.

The participants concluded that the objectives of the meeting were accomplished through the wealth of information exchanged in presentations and discussions. In brief, the participants came to the following conclusions:

- Silicon microdosimetry might be more advanced than diamond detectors in development of dosimeters with micrometric size. Indeed, experiments with semiconductor microdosimetry were carried out in different medical high-energy ion beams, and results prove that these devices show no pile-up effect.
- Good conversion from silicon and diamond to tissue based on stopping power ratios confirms acceptable agreement of solid-state dosimetry and tissue equivalent proportional counter [1,2,3]. However, currently different approaches exist that require harmonization to get a univocal procedure so that users can trust the outcome and the significance of the results.
- There has been progress with thin diamond detectors [4,5,6], however continuation of the ongoing testing of such devices at high-energy particle accelerator is still needed.
- Currently there are no existing solid-state detectors for nanodosimetry. First approaches with DNA-based detectors may not be suitable for building practical detectors. Therefore, development of solid state nanodosimeters is worthwhile considering.
- Further work is needed on clarifying the link between nanodosimetry and microdosimetry for practical applications.
- First measurements for comparison of Relative biological effectiveness (RBE) for different cellular endpoints during in-vivo cell experiments with clinical ion beams (e.g. INFN-LNS,

CNAO, HIMAC) and microdosimetric measurements at the same points in water and plastic phantoms have shown good agreement.

- A potential follow-up technical meeting would need to involve ICRU in view of the upcoming revision of ICRU report 36 on microdosimetry concepts and quantities [7]. The revision of ICRU should also include nanodosimetry to obtain standardized definitions and concepts for this innovative field as well.

- A potential follow-up technical meeting would need to include technical topics and an in-depth expert discussion on the relation of the physical bases of Local effect Model (LEM) and Microdosimetric Kinetic Model (radial dose and microdosimetry in sites close to chromosome domains).

- Monte Carlo simulation techniques are an indispensable tool for developing microdosimetric detectors and for understanding their response. Indeed, Monte Carlo simulations are furthermore frequently used worldwide for microdosimetric and nanodosimetric studies including interpretation of radiobiological studies. Intercomparison exercises conducted within EURADOS Working group 6 [8] revealed that results of such simulations, even when restricted to physical aspects of microdosimetry and nanodosimetry, may have large deviations by factors rather than a few percent. Therefore, it is extremely important to develop a acceptability criteria (“gold standard”) for Monte Carlo simulations.

- Progress in the field of microdosimetry during the last years has led to development of novel types of detectors and different ways of application at different laboratories that was accompanied by individually developed data analysis procedures. Hence, measurement results cannot be easily compared to each other and the origin of discrepancies is often obscure. The situation requires a close exchange between different groups including an open exchange of the raw data produced. Experimentalists and simulators should be encouraged to share their raw data with the community on an open access basis to allow development of harmonized evaluation procedures and open discussion among the peers.

These conclusions resulted in the following recommendations to the IAEA:

- IAEA should organize a follow-up technical meeting bringing together the key players in clinical, pre-clinical and radiation-protection research to compile an overview of the current practice of clinical and preclinical use of microdosimetry and to elucidate the needs of the end users with respect to developments in micro- and nanodosimetry instrumentation and simulations. Furthermore, the issue of harmonization to get a univocal procedure should be a key aspect of this technical meeting.

- Experimentalists and simulators should be encouraged to share their raw data with the community on an open access basis to allow development of harmonized evaluation procedures. IAEA should facilitate this approach and assist via a collaborative IAEA SharePoint platform.

- IAEA should organize a follow-up consultancy meeting to facilitate an in-depth expert discussion on the relation of the physical and radiobiological bases of LEM and MKM.

Photograph of the participants to the Consultancy Meeting on Current Developments on Micro Dosimetry Detectors held in July 2019 taken in the lobby of IAEA.

1. Introduction

Microdosimetry is the subfield of radiation physics that regards the systematic study of the spatial and temporal distribution of the absorbed energy in microscopic structures within the irradiated matter, which are stochastic by nature. Although it originated more than fifty years ago, microdosimetry is still attracting high scientific interest nowadays in radiation medicine, radiation protection, radiation biology and other fields such as space research. In the field of radiation medicine, microdosimetry is particularly relevant for hadron therapy which is one of the most promising techniques to cure a number of tumors minimizing the damage on healthy tissue. In this medical application of ionizing radiation as well as in radiation protection, the conventional measurement quantity absorbed dose is not sufficient to explain the biological effects of the radiation in the human body such as the variation of radiobiological effectiveness along the path of a clinical ion beam. In radiation protection and in a number of modalities in radiation medicine, therefore, weighting factors are applied to the conventional dosimetric quantity absorbed dose in order to account for the biological effectiveness of the particular radiation quality. Examples include proton and ion beams, neutrons as well as kilovoltage X-rays as used in brachytherapy [9,10,11]. Micro- and nanodosimetry (a.k.a. structural microdosimetry, the extension of microdosimetry to smaller dimensions), have been developed to provide radiation quantities that capture the influence of the stochastic nature of radiation interactions and, hence, the properties of different radiation qualities responsible for their different relative biological effectiveness.

2. Objectives

The aim of this Consultancy Meeting is to gather up-to-date information and status of the field of microdosimetry, and in particular experimental microdosimetry, and to investigate the possible involvement of the IAEA, in order to enhance and boost the research and applications of microdosimetry in our member of states by contributing to the field of microdosimeter development. The main topics concern the current challenges and types of microdosimeters, state of the art of developments and instrumentation, as well as future perspectives and demands.

3. Work done

The opening words of the Consultancy Meeting were given by Mr Francois Foulon, Lab Head NSIL/PS, IAEA-NA. The Consultancy Meeting was attended by 4 participants from 4 MSs (Australia, Austria, Germany, Japan). The Agenda of the CM (see Annex 2) included individual presentations and discussion sessions.

The participants of the meeting agreed to elect Mr Anatoly Rozenfeld (Australia) as the Chairperson, and Mr Hans Rabus (Germany) as the rapporteur of the meeting.

The meeting included presentations from the participants. Each participant summarized results of their work in fields related to the topics covered by the meeting. Abstracts of each presentation are provided in Annex 3.

4. Minutes of the meeting

Anatoly Rozenfeld presents on Advanced Semiconductors Microdosimetry and its Applications:

- Centre for Medical Radiation Physics (CMRP) has collaboration with National Institute of Radiological Sciences (NIRS) and SINTEF (Norwegian semiconductor manufacturer) and many other collaborators.
- Reviews concepts of microdosimetry and differences with respect to conventional dosimetry
- Overview of Local Effect Model (LEM) and Microdosimetric Kinetic Model (MKM)
- Review of tissue equivalent proportional counter (TEPC), see e.g. Tsuda et al., PMB, 55, 5089-5101, 2010
- Microdosimetric spectra were used for quality factors in radiation protection (ICRP report 92)
- Establishing a new International Commission on Radiation Units and Measurements (ICRU) working group for revision of ICRU report 36 “Microdosimetry” is under consideration.
- Review of development of silicon microdosimetry at CMRP; present generation 8 contains an ensemble of detectors. [12]
- Review of the history of solid state microdosimeter development at CMRP and ‘mushroom’ technology design optimization. Planar geometry needs revised concept of path length instead of mean chord. Aspect ratio 1:2 gives almost constant mean path length with respect to depth in water in a clinical ion beam. State of the art detectors achieve lower detection threshold of 0.01 keV/µm.
- Relative biological effectiveness (RBE) and biological dose measurements at NIRS, recent work on the ability of multi-ion therapy by Tran et al. [13] received AAPM Award.
- Review of the RBE issue in proton therapy. Recent papers indicate increase of RBE at end of spread-out Bragg peak. See Prise et al, IJROBP 2017, Anderson et al., 2017 [14] , Tran et al., 2018 [15], Chuan-Jong Tung, 2015 [16]
- RBE prediction based on MKM, see paper by Debrot et al. [17]
- Combined radiobiology and Bridge Microdosimetry (collaboration with iThemba, SCK.CEN, dkfz, CMRP).
- OB comments that HSG tumor cells are not ‘normal’ due to their fast proliferation.

- Proton beam scanning work at Mayo clinics. Experiments of LET-based RayStation treatment plans at Groningen Uni (NL).
- Ion minibeam therapy (IMBT), see Debrot et al. [17]
- Wireless communication data acquisition system development and software development
- Space applications. Investigation of shielding materials using mushroom 10 µm thickness – 30 µm diameter. Microdosimetry important in these applications.
- Newest 8th generation mushroom microdosimeters operating at no bias. Noise level: 2 keV
- Single Event Upset (SEU) studies were performed with measurements in n-gamma-fields.
- Radon application with ANSTO. Pump air flow. OB mentions ongoing UNSCEAR – IRCP discussion on Rn that might benefit from these detectors.
- Development of low noise detector system for low dose rate measurements.
- Mushroom generation 9 with Si-detectors in polyethylene

Giulio Magrin report on experimental microdosimetry and ion-beam therapy at MedAustron, that has three pillars of microdosimetry research for ion beams:

1. Detector development
2. Collaboration with other groups and complementary disciplines
3. Revisiting the methodology (unidirectional vs. isotropic), correlation of lineal energy and LET, changing the prioritization of detector shapes.

- Review of specificities of ion beams with respect to microdosimetry: Well defined beam energy, single ion species, unidirectional, very intense with up to 10^{10} particles per s.
- Diamond detectors were developed together with Tor Vergata University in Rome and tested also in Zagreb with microbeam ion-beam induced charge (IBIC) measurements.
- Review of the performed investigations on the detectors and the evolution of the different prototype detectors. Final prototype has a sandwich structure of commercial diamond substrate with a boron-doped deep electrode, CVD diamond blanket and a superficial electrode.
- Non-uniformity of response found is due to bad polishing of substrate. Radiation hardness is on the order of 3% after 50 kGy (equivalent to irradiation of about 1000 patients) and depends on the quality of the diamond. Energy in deposited diamond is proportional to electronic stopping power.
- Collaboration with Politecnico Milano on testing silicon micro-telescope detectors. Characterization again with IBIC at the Rudjer Boskovic Institute (RBI) microbeam. Studies for different incidence angles to determine dead layer thickness. (See thesis of Sofia Colombi [18]). Additionally, silicon microtelescope was tested in proton therapeutic beam in Loma Linda proton therapy center and the Heidelberg Ion Therapy Center and compared with Monte Carlo simulations giving good agreement.

- Lateral electrical field border width is about 1 µm. Uniformity of response: standard deviation per pixel about 7%, scatter of mean values of pixels about 1%. Ageing studies show that in the energy range investigated silicon is as radiation hard as diamond. Furthermore, the damage can be annealed.

- Giulio Magrin makes proposal for investigating the community's view of microdosimetry.

- Review of use of microdosimeters in ion-beam therapy. Need to obtain microdosimetric spectra independent on the detector type, shape and material. Discussion of differences induced by shapes and conversion from slab to general shapes. Additional issue of material conversion is discussed. Examples shown for conversion from diamond slab to propane cylinder that agreed well with mini-TEPC measurements.

- Open questions in community:

  - General: best shape, best material, which parameter for characterizing radiation quality in ion beam therapy (spectra, mean values, *L*).

  - Spectra transformation (equivalence of shapes, of materials, self-calibration parameters, extrapolation below noise threshold)

  - Correlation microdosimetric spectra and Linear energy transfer (LET). There are different LET averages used in radiobiological data L_T, L_D

  - Saturation values of lineal energy, y^*, also sometimes used as physical parameter.

- Anatoly Rozenfeld notes that microdosimetry was originally developed by assuming cells be spherical. Giulio Magrin states that comparison between different detectors that gave differences on the order of 20%.

- Oleg Belyakov mentions program from Michael Hayek (IAEA) to go from dosimetry to microdosimetry to biodosimetry.

Hans Rabus reports on multi-scale approaches in micro-/nanodosimetry:

- Review of the multi-scale approach of the BioQuaRT EU project to link physical and biological radiation effects based on measurable properties of ionizing radiation at the microscopic level.

- Motivation was IAEA TRS 461 "Relative Biological effectiveness in Ion beam Therapy" where the need for microdosimetry and for approaches to a three-dimensional characterization of ionizing radiation particle track structure was highlighted.

- Nanodosimetry considers the stochastics of ionizations in nanometric targets. These are smaller than the particle tracks so that additional geometrical parameters come into play.

- In the context of the BioQuaRT project [19], an intercomparison of the three gas-counter nanodosimeters existing in Europe was performed and led to the discovery of a universal relation among the statistical parameters of the frequency distributions of ionization cluster sizes in different nanometric target volumes [20].

- This universal curve showed also a close relation with the dependence of the yield of biological endpoints observed in cell irradiations by ions [20, 21].

- In BioQuaRT and in parallel, independent research, multi-scale approaches encompassing micro- and nanodosimetry [19, 22, 23] have been investigated and the application of nanodosimetric track parameters in treatment planning has been explored [24, 25].

- Another project (LET-Verbund) found experimental evidence for the relevance of different length scales for cellular damage [26].

- Current development of experimental nanodosimetry: 1. condensed-phase nanodosimetric detectors [27], 2. measurement of correlations of track parameters for different targets in proximity [28], 3. Extension of microdosimetric measurements into the nanometer regime [29].

- Current development of nanodosimetric simulations: 1. extending nanodosimetry for use in clinical situations, e. g. by considering multi-target situations [30]; 2. developing 3D models of particle tracks from simulations [31].

- Overarching challenge is establishment of uncertainty budgets for nanodosimetric track structure parameters obtained by measurement [32] or simulation [33].

Naruhiro Matsufuji present the role of microdosimetry in ion-beam therapy at HIMAC and emerging aspects

- Heavy Ion Medical Accelerator in Chiba (HIMAC) performs C-ion treatments since 1994, >11000 patients, 10^9 C per s, energy 430 MeV/u. Actually 600-800 patients per year.

- Overview of Japanese carbon ion facilities and the medical indications where ion beams are applied.

- Review of recent developments for moving targets. Rotating superconducting gantry was installed recently.

- Review of modeling requirements. Recipe of the original model is described. Human salivary gland (HSG) tumor cells are considered due to their moderate radiosensitivity. Model is based on the LQ model, where alpha and beta values are tabulated and RBE for 10% survival in each faction is used.

- Fast neutron data on HSG and HeLa cells for additional information with ample clinical data. @80 keV/µm dose averaged LET of carbon and neutron 2.1 → assumption that clinical RBE 3.0 is also same.

- They used look-up tables to get LET_d averaged values and then superimpose pristine peaks to produce spread-out Bragg peak (SOBP). Normalization with neutron data done at 80 keV/µm, i.e. close to the end of the SOBP [34].

- Cons of this approach: Parameter driven, difficulty in prospective estimation, oversimplified approximation on fragments (C only).

- New mechanistic approach to be harmonized with the old approach, based on the Microdosimetric Kinetic Model (MKM) [35, 36, 37, 38]

- Explanation of the parameters in MKM. Domain size is free parameter. Verification with TEPC measurements shows y_D is more important than LET_d (no more differences between ion species) and with radiobiological data on HSG cells.

- Summary overview of the current model based on HSG cell system and MKM.

- Emerging aspects for microdosimetry: Measurements with CMRP microdosimeters. Due to high dose rate in therapeutic beams, particle flux reduction by factor of 100 necessary.

- Report on first experiments with in vivo dosimeter. [39] It would be desirable to have it also as microdosimeter.

- For intensity modulated composite particle therapy or multi-ion therapy and Oxygen Enhancement Ratio (OER) issue, first approaches have been undertaken to modify MKM for OER [40,41].

- Attempts on dosimetry in MRI-RT and magneto-particle therapy [42]. There is an enhancement of RBE that is not explained by track shrinkage.

- Discussion on inclusion of (in vivo) microdosimetry in clinical QA procedures. Probably only possible for selected patients.

Oleg Belyakov reports on the activities of the IAEA Adaptive Radiation Biology and Radiotherapy Section

- IAEA radiobiology projects
  - CRP E33032: Stem cells therapeutics for radiation induced damage to normal tissue 230 k€ for 13 institutions from ten member states
  - New project on mesenchymal stem cell therapy planned for 2020-2023 (estimated budget 350 k€)
  - CRP E31006 Safety and Optimization of Radiation Sterilization in Tissue Banking, 16 participants from 15 member states, 292 k€
  - CRP F23030-E31007 Tissue Engineering, in cooperation with IAEA Division of Physical and Chemical Sciences. Engineering instructive scaffold and surfaces using radiation technology to produce artificial tissues, 485 k€ → IAEA Technical document and special issue in journal
  - IAEA Consultancy meeting on particle therapy in the 21st century. Paper Rosenblatt et al., Int J Radiat Oncol Biol Phys 95, 25-29 (2016)
  - IAEA Tech Meeting on Radiobiology of Charged Particle Therapy 11-13 November 2015, report was produced and paper pending

- New CRP on Ion beam radiobiology and/or clinical trials planned. Consultants meeting in 2020 to formulate new CRP.

- Biodosimetry projects and Biodosimetry Model Dosimetry laboratory

  - Reconstruction of dose of radiation. PNA-FISH, mFISH, mBAND-FISH → intrachromosomal dislocations. Prof. Hande (Natl Uni Singapore)

  - Joint IAEA, PACO and WHO Manual Cytogenetic Dosimetry - Application in Prepareness for and Response to Radiation Emergencies

  - CRP E35008 (2012-2017) Strengthening of Biological Dosimetry in IAEA member states, 25 participating institutes from 15 member states, 543 k€ (incl. 239 k€ from Peace Use Initiative); 19 proceedings papers in special issue Genome Integrity Journal plus IAEA Human Health Series Report "Application of Biomarkers of Radiation Exposure in Radiological Clinical Practise" was prepared.

  - CRP E35010 (2017-2021) Bioogical Dosimetry methods in Radiation Medicine, 34 participating institutions in 29 MSs (427 k€, 150 k€ unfunded)

  - Retrospective and clinical biodosimetry

  - Plans for IAEA Biodosimetry / Radiobiology lab. Irradiation facilities, dosimetric facilities, biodosimetric facilities, data center. Liaised with variety of institutions and networks.

- Non-targeted effects

  - Non-targeted effects. UNSCEAR 2006 report on Effects of Ionizing Radiation Volume II, Annex C "Non-targeted and delayed effects of exposure to ionizing radiation" (published 2009)

  - NOTE EURATOM project; Special Issue Mutation research 687 (1-2) in 2010 + position paper in Mutation Research 2013

- Individual radiosensitivity and susceptibility

  - Radiation Safety Standards Committee (RASCC) meeting 2015 "Individual Susceptibility to Radiation" → IAEA and NIH-NCI considering new CRP "Development of a Technical manual for Intrinsic Radiation Sensitivity based on standardized Clonogenic Cell Survival assay.

  - August 2018 Workshop on understanding high-dose, ultra-dose-rate and spatial fractionated radiotherapy. Better tumour control and less side effects. → spatially fractionated radiotherapy mechanisms needs micro-/nanodosimetry.

  - Discussion on FLASH and microdosimeters. Collection times order of magnitude of 2.5 µs.

5. Conclusions

- Silicon microdosimetry might be more advanced than diamond detectors in development of dosimeters with micrometric size. Indeed, experiments with semiconductor microdosimetry were carried out in different medical high-energy ion beams, and results prove that these devices show no pile-up effect.

- Good conversion from silicon and diamond to tissue based on stopping power ratios confirms acceptable agreement of solid-state dosimetry and tissue equivalent proportional counter [43,44,45]. However, currently different approaches exist that require harmonization to get a univocal procedure so that users can trust the outcome and the significance of the results.

- There has been progress with thin diamond detectors [46,47,48], however continuation of the ongoing testing of such devices at high-energy particle accelerator is still needed.

- Currently there are no existing solid-state detectors for nanodosimetry. First approaches with DNA-based detectors may not be suitable for building practical detectors. Therefore, development of solid state nanodosimeters is worthwhile considering.

- Further work is needed on clarifying the link between nanodosimetry and microdosimetry for practical applications.

- First measurements for comparison of Relative biological effectiveness (RBE) for different cellular endpoints during in-vivo cell experiments with clinical ion beams (e.g. INFN-LNS, CNAO, HIMAC) and microdosimetric measurements at the same points in water and plastic phantoms have shown good agreement.

- A potential follow-up technical meeting would need to involve ICRU in view of the upcoming revision of ICRU report 36 on microdosimetry concepts and quantities [49]. The revision of ICRU should also include nanodosimetry to obtain standardized definitions and concepts for this innovative field as well.

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- Monte Carlo simulation techniques are an indispensable tool for developing microdosimetric detectors and for understanding their response. Indeed, Monte Carlo simulations are furthermore frequently used worldwide for microdosimetric and nanodosimetric studies including interpretation of radiobiological studies. Intercomparison exercises conducted within EURADOS Working group 6 [50] revealed that results of such simulations, even when restricted to physical aspects of microdosimetry and nanodosimetry, may have large deviations by factors rather than a few percent. Therefore, it is extremely important to develop a acceptability criteria (“gold standard”) for Monte Carlo simulations.

- Progress in the field of microdosimetry during the last years has led to development of novel types of detectors and different ways of application at different laboratories that was accompanied by individually developed data analysis procedures. Hence, measurement results cannot be easily compared to each other and the origin of discrepancies is often obscure. The situation requires a close exchange between different groups including an open exchange of the raw data produced. Experimentalists and simulators should be encouraged to share their raw data with the community on an open access basis to allow development of harmonized evaluation procedures and open discussion among the peers.

6. Recommendations to the IAEA

- IAEA should organize a follow-up technical meeting bringing together the key players in clinical, pre-clinical and radiation-protection research to compile an overview of the current practice of clinical and preclinical use of microdosimetry and to elucidate the needs of the end users with respect to developments in micro- and nanodosimetry instrumentation and simulations. Furthermore, the issue of harmonization to get a univocal procedure should be a key aspect of this technical meeting.

- Experimentalists and simulators should be encouraged to share their raw data with the community on an open access basis to allow development of harmonized evaluation procedures. IAEA should facilitate this approach and assist via a collaborative IAEA SharePoint platform.

- IAEA should organize a follow-up consultancy meeting to facilitate an in-depth expert discussion on the relation of the physical and radiobiological bases of LEM and MKM.

Annex 1: List of participants

Anatoly Rozenfeld (AR)	*Australia*	*University of Wollolong*	*anatoly@uow.edu.au*
Naruhiro Matsufuji (NM)	*Japan*	*NIRS/QST*	*matsufuji.naruhiro@qst.go.jp*
Giulio Magrin (GM)	*Austria*	*MedAustron*	*giulio.magrin@medaustron.at*
Hans Rabus (HR)	*Germany*	*Physikalisch-Technische Bundesanstalt (PTB)*	*hans.rabus@ptb.de*
Natko Skukan (NS)	*Int*	*IAEA*	*n.skukan@iaea.org*
Oleg Belyakov (OB)	*Int*	*IAEA*	*o.belyakov@iaea.org*

Annex 2: Meeting agenda

Wednesday 3		
08:30 – 09:15	Registration	
09:15 – 09:30	Official Opening:	*Mr Francois Foulon, Lab Head NSIL/PS, IAEA-NA*
09:30 – 09:40	Brief self-introduction of the participants	
09:40 – 9:50	Organizational arrangements	*Mr Natko Skukan* *NSIL, IAEA-NA*
9:50 – 10:40	NSIL activities and the modalities for networking and collaborations within the IAEA	*Mr Natko Skukan* *NSIL, IAEA-NA*
10:40 – 10:55	***Coffee Break***	
10:55 – 12:35	Advanced Semiconductors Microdosimetry and its Applications	*Mr Anatoly Rozenfeld* *University of Wollongong, Australia*
12:35 – 14:00	***Lunch Break***	
14:00 – 15:30	Experimental microdosimetry and ion-beam therapy: are there new links?	*Mr Giulio Magrin* *MedAustron, Austria*
15:30 – 17:00	Multi-scale approaches in micro-/nanodosimetry: BioQuaRT and beyond	*Mr Hans Rabus* *Physikalisch-Technische Bundesanstalt (PTB), Germany*
20:00	Social event	

Thursday 4		
09:30- 11:20	Role of microdosimetry in ion-beam therapy at HIMAC and emerging aspects	*Mr Naruhiro Matsufuji* *National Institute of Radiological Sciences (NIRS) /QST, Japan*
11:20 -13:00	Radiation Biology research in IAEA and possible connections to microdosimetry	*Mr Oleg Belyakov, NAHU, IAEA*
13:00 – 14:00	***Lunch Break***	
14:00 – 15:00	Discussion on possible involvement of the IAEA	
16:00 – 21:00	Visit to MedAustron: *15:00 – Leave from IAEA* *16:45 - Arrive at MedAustron* *17:00 to 18:00 -Discussion in room Wilson: Markus Stock, Head Medical Physics, will describe the facility and will illustrate some unresolved issues in ion beam therapy which could benefit from an improved characterization of the LET/microdosimetry; Thomas Schreiner, Coordinator of the non-clinical research, will describe the research program of MedAustron.* *18:00 to approximately 19:00 – Thomas Schreiner and Giulio Magrin will guide the visit of the facility starting from the non-clinical research laboratories and then continuing to the clinical area. We will be able to visit the irradiation rooms, at least the room dedicate to the research activity and the room with the proton gantry which is not used yet for patients.*	

Friday 5		
09:30 – 10:30	Session 3: Drafting meeting report	
10:30 – 10:45	***Coffee Break***	
10:45 – 11:45	Drafting meeting report (cont'd)	
11:45 – 13:30	***Lunch Break***	
13:30 – 15:00	Session 4: Finalizing meeting report	
15:00 – 15:30	***Coffee Break***	
15:30 – 16:30	Final remarks and closing of the meeting	

Annex 3: Abstracts of participant presentations

Advanced Semiconductor Microdosimetry and its Applications

Anatoly ROZENFELD, *Australia, Centre for Medical Radiation Physics, University of Wollongong*

The Centre for Medical Radiation Physics (CMRP) at University of Wollongong, has successfully developed a microdosimetric probe which is based on a Silicon on Insulator (SOI) detectors with 3D micron sized sensitive volumes (SVs). These detectors mimicking array of biological cells, known as the “Bridge” and “Mushroom” microdosimeters are operating under less than 10V bias (or no bias), small size in contrast to the Tissue Equivalent Proportional Counter (TEPC) which is required high voltage operation, TE gas and usually large in size. Fig 1 shows the MicroPlus probe developed at CMRP connected to the SOI Mushroom microdosimeter.

The silicon microdosimeter provide extremely high spatial resolution (better than 1mm) and were used to measure the microdosimetry spectra in different heavy ions fields at Heavy Ion Medical Accelerator in Chiba (HIMAC), Japan and in a proton field delivered with pencil-beam scanning (PBS) and passive scattering at different accelerator facilities. Measured microdosimetric parameters were used for derivation of RBE10 using modified Microdosimetric Kinetic Model (MKM) allowed determination of α parameter in Linear Quadratic Model (LQM) vs measured dose averaged lineal energy y_d. Example of derived RBE10 values in response to 290 MeV/u carbon-ion SOBP is presented in Fig. 2. The RBE10 values obtained with the SOI microdosimeters match very well with those obtained from the TEPC measurements. Due to the high spatial resolution of the microdosimeter, a more detailed RBE10 distribution was obtained at the end of the SOBP compared to the TEPC.

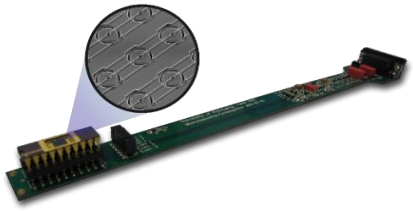

Fig. 1 MicroPlus probe connected to the microdosimeter with SEM image of the mushroom microdosimeter

Fig. 3 shows the comparison of absorbed dose and derived from measured microdosimetric spectra RBE10 for the 400 MeV/u 16O beam in water. Due to submillimeter spatial resolution, it was possible to demonstrate that the peak of physical dose does not necessary in coincidence with the RBE10 maximum as was predicted previously by Kraft (GSI).

Application of “mushroom“ and “bridge“ microdosimeters were used for RBE studies in a proton therapy and reveal that RBE is essentially changing along the Bragg Peak and reaching 1.4 to 1.8 at distal part of the BP for passive and PBS spot beam, respectively. Experiments with biological cells and SOI microdosimeters in a proton therapy field reveal good agreement in RBE_{10} and RBE_d obtained from clonogenic cell survival studies and derived with SOI microdosimeters at the same position along the SOBP.

The developed SOI microdosimeters can be very useful for dose equivalent measurements in Solar Particle Events (SPE) and Galactic Cosmic Rays (GCR) mixed radiation fields for radiation protection of astronauts and evaluation of radiation shielding. The experiments with 400 MeV/u 16O, 500 MeV/u 56Fe, 400 MeV/u 20Ne and 490 MeV/u 28Si ions incident on a slab with different thicknesses and composition of materials mimicking the wall at the International

Space Station (ISS) was carried out at HIMAC. The average quality factor, $\bar{Q}$ and the dose equivalent, Hp per incident ion per cm2 at different depths in a water phanotm (mimicking astronaut) downstream of the wall was derived. Fig 4 shows the microdosimetric spectra and corresponding to them $\bar{Q}$ for different scenarios for 500 MeV/u 56Fe ion beam as an example.

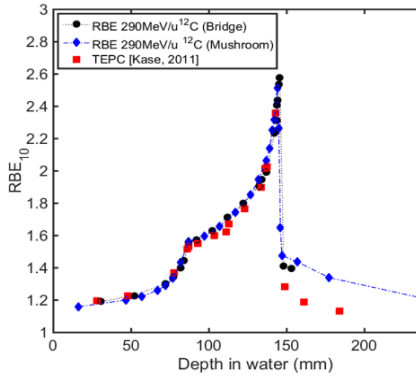

Fig. 2 Derived RBE_{10} along the central axis of the SOBP of ^{12}C ion beam, obtained by SOI bridge and mushroom microdosimeter and TEPC at NIRS.

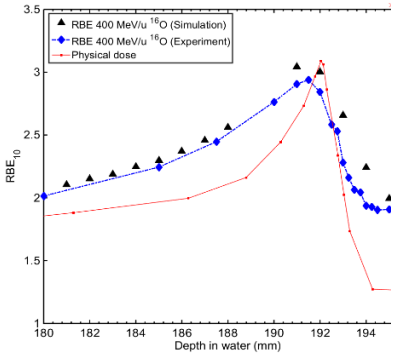

Fig. 3 Detailed view of RBE_{10} distribution obtained with the mushroom microdosimeters (μ^+ probe) as a function of depth in water for the 400 MeV/u ^{16}O pristine BP

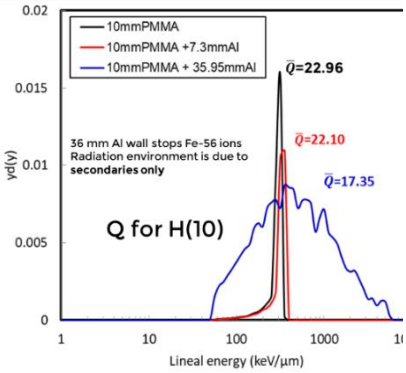

Fig. 4 Microdosimetric spectra obtained during 500MeV/u ^{56}Fe irradiations in free air

Applications of SOI microdosimetry detectors for dose equivalent measurements in radiation field of ^{222}Rn gas as well as for mixed gamma-neutron isotopic sources were demonstrated suggesting that SOI microdosimetry can be utilized for personal radiation protection.

Fig 5 is an example of IBIC studies of charge collection efficiency in 10µm thick SOI mushrooms measured with 5.5 MeV He^{2+} ion microbeam at ANSTO Sirius accelerator in developed.

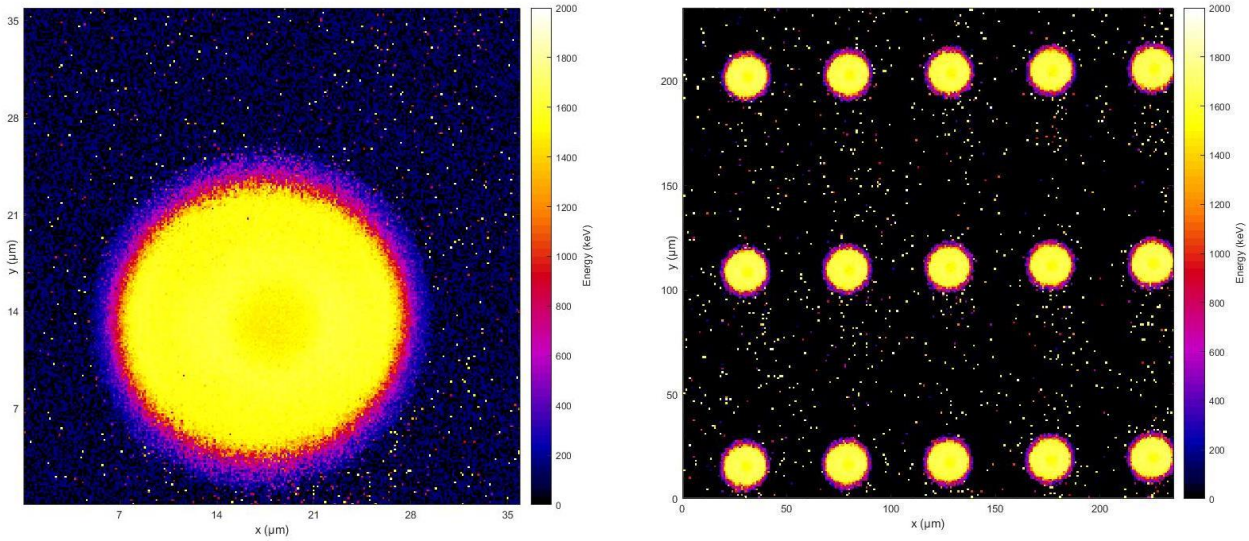

Fig 5. Charge collection efficiency map in SOI mushroom detector obtained with 1 µm scanning He^{2+} ion microbeam

Useful references to recent publications on SOI microdosimetry:

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Experimental microdosimetry and ion-beam therapy: are there new links?

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The talk presented the three actions preformed in the past eight years at MedAustron for the implementation of microdosimetry in ion-beam therapy. MedAustron is the Austrian center for proton and carbon ion-beam therapy located in Wiener Neustadt.

The three actions are the following.

The first action concerns the study and development of microdosimeters adapted to the characteristics of the ion beams used in therapy.

Two types of solid-state microdosimeters were tested using several ion beams including the micro beam of the Ruder Boskovic institute in Zagreb. The first type of detector is the Chemical Vapor Deposition diamond microdosimeters developed in collaboration with University of Rome Tor Vergata [**Error! Bookmark not defined.**]. The second type of detector is the silicon telescope developed by Politecnico di Milano [18]. Both detector types were investigated to assess the geometrical and electrical characteristics of the sensitive volume and the radiation hardness.

The second action focuses on understanding how other centers of ion-beam therapy foresee the implementation of microdosimetry. The talk presented few examples of microdosimetry detectors and concepts used for the characterization of the therapeutic beam, the assessment of biological effectiveness, and the collection of information, before and during the treatment, on non-targeted radiation. A complete survey of the activities concerning the microdosimetry carried out in the proton an ion-beam centers is proposed as one important task which could be coordinated by IAEA.

The third action concerns the elaboration of the methodology and formalism to provide, starting from the experimental data collected with microdosimeters which are different in shape, material, and working characteristics, univocal and detector-independent outcomes. This action has started few years ago and it is entering now a phase of discussion in the community. Converging to commonly agreed procedures and homogeneous representation of the detector outcomes is a prerequisite for microdosimetry to be accepted by the ion-beam therapy users as a valuable tool. For this scope, the role of IAEA is fundamental.

Multi-scale approaches in micro-/nanodosimetry: BioQuaRT and beyond

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HR reviews the multi-scale approach of the BioQuaRT project to link physical and biological radiation effects based on measurable properties of ionizing radiation at the microscopic level. The motivation for such developments was IAEA TRS 461 “Relative Biological effectiveness in Ion beam Therapy” where the need for microdosimetry and for approaches to a three-dimensional characterization of ionizing radiation particle track structure was highlighted. In contrast to microdosimetry where the stochastics of energy deposition is considered, nanodosimetry (aka structural microdosimetry) considers the stochastics of ionizations in nanometric targets that are smaller in extension than the penumbra of particle tracks so that additional geometrical parameters need be considered.

While the basic concept of nanodosimetry as a tool for the characterization of charged particle track structure dates back to 1975 [51], for a long investigations of track structure were dominated by simulation approaches [52, 53], until around the beginning of the 21st century experimental methods were developed that allowed track structure details to be measured in gas counters simulating target sizes of nanometric dimensions [54]. In the context of the European project BioQuaRT [19], an intercomparison of the three gas-counter nanodosimeters existing in Europe was performed and led to the discovery of a universal relation among the statistical parameters of the frequency distributions of ionization cluster sizes in different nanometric target volumes [20]. This universal curve showed also a close relation with the dependence of the yield of biological endpoints observed in cell irradiations by ions [20,21]. Within BioQuaRT as well as in parallel, independent research, so-called multi-scale approaches encompassing micro- and nanodosimetry [19,22,23] have been investigated and the application of nanodosimetric track parameters in treatment planning has been explored [24,25].

The current development of experimental nanodosimetry is characterized by endeavours to develop condense-phase nanodosimetric detectors [27], to measure correlations of track parameters for several nanometric targets in spatial proximity [28], and to extend microdosimetric measurements into the nanometer regime [29]. On the simulation side, the focus is on extending the concepts of nanodosimetry for use clinical situations, e. g. by considering multi-target situations [30] or by developing 3D models of particle tracks from simulations [31]. An overarching challenge is the establishment of uncertainty budgets for nanodosimetric track structure parameters obtained by measurement [32] or simulation [33].

Role of microdosimetry in ion-beam therapy at HIMAC and emerging aspects

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The change in biological effectiveness (RBE) of carbon-ion beam is one of the attractive characteristics of C-ion RT. Microdosimetry plays crucial role there. Originally the RBE was estimated by a pragmatical model with using LET as an index of the radiation quality. Particle-species dependency remained there and treated as parameter-driven manner. Microdosimetry enables to bridge the physical characteristics of the therapeutic beam that can be measured (absorbed dose and lineal energy) and RBE mechanistically. It is advantageous in modern ion-beam therapy where the composition of the therapeutic beam tends to be highly complex.

As a microdosimetric detector, commercially available TEPC was long used, however, its actual geometrical size (~2cm) and low counting rate made it difficult to measure the real therapeutic beam. Recently developed solid microdosimeter (Prof. Rozenfeld) is highly attractive device with its small geometrical size (less than 10 um). With respect to the emerging aspects of future ion-beam therapy, the following points will be a challenge for microdosimetry detector.

- Intensity: Modern scanning system delivers high-dose rate locally. The reduction in intensity of the beam for measurement is limited especially on commercial accelerator. In addition, instantaneous high dose-rate irradiation (FLASH) gains high attention to spare normal tissue in radiotherapy. It is expected the microdosimetry detector can be used under such high dose-rate irradiation.

- Compactness: in-vivo dosimeter, a dosimeter small enough to insert to patient body during therapeutic irradiation, has been under development for QA in ion-beam therapy, however, absorbed dose alone is not sufficient to evaluate the biological effectiveness of the beam. The comparable size of in-vivo microdosimeter detector is needed for QA in selected case.

- Coverage: Currently carbon ion is the sole choice in ion-beam therapy, however, the other ion species will be enrolled in near future. On the other hand, targeted radiotherapy such as radioimmunotherapy or BNCT may be concomitantly used in future ion-beam therapy. The microdosimetry detector that can be served in such wide variety of the radiation field will be necessary.

- Magnetic field: Magnetic field modulates the trajectory of electrons therefore affects to ion-chamber dosimetry and likely to microdosimetric measurement. On the other hand, concomitant use of the MRI device during radiotherapy will be popular as it enables to monitor internal organ structure and motion during radiotherapy without extra radiation. In addition, recent study reports that the magnetic field tends to enhance the biological effectiveness of the ion beam. It is expected that the future microdosimetry detector works properly even under the magnetic field.

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