Final Publishable JRP Summary for JRP SIB06 BioQuaRT Biologically weighted quantities in radiotherapy

Overview

Cancer treatment increasingly uses proton and ion beams, since they can deliver a similar dose to tumours as conventional x-ray based radiotherapy, but with less damage to surrounding healthy tissue. These new radiotherapy modalities need a new dosimetric concept to be established that would allow a clear separation of the physical and biological factors that contribute to the effectiveness of ionising radiation. The measurable physical properties of the track structure (the path that the beam takes through the DNA) and cell structures, depend on the particle type and energy. The biological factors are independent of radiotherapy modality, and reflect how the cells and DNA respond to the imparted energy. This project laid the foundations for a new concept of dosimetry for proton and ion beam radiotherapy and investigated establishing a multiscale model as the basis of the new quantities.

Need for the project

In radiotherapy, or the treatment of cancer using ionising radiation, the dosage is generally prescribed in terms of the physical quantity absorbed dose, which is defined as the absorbed radiation energy per unit mass. A number of new irradiation modalities, such as protons and carbon ions, have been emerging that offer therapeutic advantages over the conventionally used high-energy x-rays. When using these particle beams, it is known that a lower value of absorbed dose will lead to the same biological effect as conventional x-ray based radiotherapy, so this is taken into account by applying biological weighting factors in the treatment planning.

These biological weighting factors are generally determined by performing expensive radiobiological tests at the radiotherapy centres, but there is variability between centres and methodologies. It is generally agreed that the diversity of methods being used to derive biological weighting factors leads to confusion in interpretation and ultimately possible risk to patients. A universally agreed approach for the weighting factors would facilitate exchange of information and improve collaboration between centres and within the radiation oncology community.

The biological weighting factors to convert an absorbed dose to a biological effective dose depend upon the physical interactions of the radiation with tissue and the biological response of the cells in the organism. The metrological challenge was to establish a new dosimetric quantity which would allow a transparent separation of the physical processes (dependent on radiotherapy modality) from the genuine biological ones (independent of modality). The Consultative Committee of Ionising Radiation (CCRI) of the Meter Convention has expressed strong support for defining such a new quantity, particularly for treatments involving the use of several multiplying factors to describe the corresponding biological effects of the absorbed dose.

Given the complexity of the initiation and occurrence of biological processes on various time and length scales, neither microdosimetry nor nanodosimetry on their own can fully describe the biological process occurring over time and distance. Therefore, a multiscale approach, which aims to combine the effects at the cell level (microdosimetry) and with the interaction at the DNA scale (nanodosimetry), is needed to get a full understanding of the effects. This will mean that the radiation can have maximum benefit with minimum damage to surrounding tissue.

Scientific and technical objectives

The first two objectives addressed the way the radiation penetrated the tissue at the cellular and DNA scales, using different types of radiation detectors to mimic tissue.

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- To develop micro-calorimeters directly measuring energy deposition spectra and to compare them with tissue-equivalent proportional counters and silicon based microdosimeters.
- To develop improved techniques for measuring ionising-particle track structure and its characteristics with nanometre resolution.

The third objective looked at the chemical reactions caused by the interaction between the radiation and the DNA.

- To develop methods for measuring the production rate and 3D distribution of reactive oxygen species in tissue exposed to proton and ion beams as a function of particle type and energy.

The fourth and fifth objective looked at simulation and modelling of radiation delivery and its effects on the body.

- To develop a numerical tool (based on DNA ionisation and fragmentation cross sections) for the multi-scale simulation of ionising particle track structure and biological effects of ionising radiation.
- To develop quantitative models to link the physical quantities with the biological outcome and to determine free parameters in the multi-scale model from biological assays.

Results

To develop micro-calorimeters directly measuring energy deposition spectra and to compare them with tissue-equivalent proportional counters and silicon based microdosimeters.

The feasibility of micro-calorimeters based on micrometre-sized absorbers of tissue-equivalent material and on the measurement of the temperature rise by Superconductive Quantum Interference Devices (SQUID) was shown. A generic protocol of how to build the superconductive devices and make them operational to specifications has been established. Every device produced required extensive characterisation of its properties as a prerequisite for post-processing to make the device match the design goals. It was shown that the micro-calorimeter devices can be used successfully under broad beam conditions provided the dose rate of the radiation is below about 1 µGy/s.

As an alternative microdosimeter with micrometre-sized detectors, the technology of the silicon micro-telescopes was developed to make the devices operational under vacuum conditions, which is necessary to use them for characterising the incident ion beam at ion accelerator facilities. These novel devices have been used together with the third kind of microdosimeter, the miniature tissue-equivalent proportional counter (miniTEPC), to measure microdosimetric spectra of a clinical carbon ion beam. The conclusion is that measurements in a clinical ion beam are possible with both type of microdosimetric devices and that the microdosimetric spectra obtained with the two devices are in good qualitative agreement such that either approach can be used to characterise the change in radiation quality along the ion beam path.

While the principal feasibility of micro-calorimetric measurement of microdosimetric quantities could be shown, the originally planned measurements comparing the micro-calorimeter and the other two types of microdosimeter were not carried out and the determination of the correction for potential phase effects occurring with the miniTEPC could not be determined. The potential correction for tissue in-equivalence of silicon which occurs for microdosimetric spectra measured with silicon-technology detectors was also not derived. Although the objective was only partially achieved, it demonstrated for the first time that direct measurement of imparted energy using micro-calorimeters is feasible and that silicon micro-telescopes and miniTEPC can be used in a clinical environment to characterise ion beams and their biological effect.

To develop improved techniques for measuring ionising-particle track structure and its characteristics with nanometre resolution.

This objective was fully achieved. The three nanodosimeter devices developed at different institutes in Europe were further developed within the project. The Ion Counter instrument at PTB has been upgraded to position sensitive detection of the incident ions which allows measurement in broad beam conditions and determining the nanodosimetric quantity ionisation cluster size distribution for different distance of the ion track from the sensitive volume. By integrating a silicon micro-telescope in the Ion Counter set-up, a prototype device for multi-scale measurement of particle track structure properties has been realised. It was used during this project to characterise the track structure of the ion beams for the cell experiments performed to establish radiobiological reference data. For the StarTrack nanodosimeter of INFN, it could be shown that measurements simulating site sizes of about 10 nm (instead of the original and conventionally used design value of 20 nm) are also feasible. With the Jet Counter nanodosimeter at NCBJ the measures taken to increase the overall detection efficiency resulted in a smaller than expected enhancement.

The three nanodosimeters simulate different target sizes and they have different detection principles and approaches for defining the target volume geometry. Nevertheless, the comparisons performed within the project identified universal relations between the ionisation cluster size distributions. When the cumulative probabilities for ionisation cluster sizes exceeding a certain value *k* are plotted versus the mean ionisation cluster size, the measurements performed with different nanodosimeters in ion beams of different radiation quality all fall on the same curve. This finding is an experimental proof of the theoretical scaling principle underlying the nanodosimetric approach, and is a validation of the methodology.

The shape of the universal nanodosimetric curves could be linked to the radiobiological effectiveness of the ion beam radiation qualities. It was shown that there is a nanometric target size (in the order of magnitude 1 nm) for which the biological cross section for inactivation of the cells becomes proportional to the cumulative probability for a certain ionisation cluster size. These findings indicate that at least for single cells the biological consequences of the irradiation are predominantly determined by the initial physical radiation interaction.

To develop methods for measuring the production rate and 3D distribution of reactive oxygen species in tissue exposed to proton and ion beams as a function of particle type and energy.

Like all kinds of ionising radiation, ion beams break water molecules, thus producing radicals. This objective aimed to use 'indicator' molecules that would change colour when reacting with the radicals created by the ion beam. By monitoring the colour intensity and distribution of the molecules, the path of the radiation could be studied. The hydroxyl (OH) and superoxide (O_2^-) radicals were identified as the key species to monitor the effect of radiation exposure on biological systems. The molecules coumarin and hydroethidine were identified as potential candidates for monitoring the radiation-produced yield of these radicals, as they form fluorescent compounds when reacting with the OH and O_2^- radicals, respectively.

Direct Stochastic Optical Reconstruction Microscopy (dSTORM) was shown to enable theoretical imaging of the radical species in an ion track. However, the process was more complex than expected. It was difficult to stop the chemical agents migrating or diffusing before the measurements were taken. Attempts to 'fix' the chemicals stopped them producing the fluorescent compounds after irradiation, even with photon radiation.

Therefore, the objective was only partially achieved; chemicals were identified and the imaging technique was demonstrated, however full imaging of the ion beam paths was not achieved.

To develop a numerical tool (based on DNA ionisation and fragmentation cross sections) for the multi-scale simulation of ionising particle track structure and biological effects of ionising radiation.

This objective has been fully achieved. A generic mathematical model was developed which consists of two parts (cf. Ref. [16]): The first part describes the relation between the microscopic pattern of the (physical) radiation interaction and the track structure characteristics obtained with microdosimetric and nanodosimetric

measurements. The second part then relates this track structure to biological consequences of the irradiation within a cell. Computational tools for numerical modelling of the particle track structure of ion beams have been developed. The new simulation tool offers capabilities beyond the conventional GEANT4-DNA code, which only used interaction cross sections of liquid water, by simulating the direct radiation interaction with the DNA molecule based on interaction cross sections of DNA constituents. These cross sections for the ionisation of model molecules for DNA ingredients by electrons and protons have been measured within the project, and also the cross sections for the fragmentation of these molecules after ionisation.

In addition, a detailed geometrical model of the DNA at the molecular level was implemented in the simulation. The use of this realistic target description was essential for an accurate modelling of the chemical reactions between radical species and DNA, which give rise to indirect effects (that account for more than 70 % of the total DNA damage). Thus, it has become possible to perform more realistic simulation of radiation damage to biological systems where the physical properties of the radiation can be traced to and benchmarked with measurable microdosimetric and nanodosimetric quantities. The simulation tools developed within the project have become part of the open-access GEANT4-DNA distribution, so that the augmented capabilities can be used by all researchers in the field.

This objective showed that the radiation interacted more with the DNA than expected. Better simulation of radiation damage can therefore be done by including the realistic properties of DNA, rather than assuming that the human body can be approximated to consist completely (rather than just 80%) of water.

To develop quantitative models to link the physical quantities with the biological outcome and to determine free parameters in the multi-scale model from biological assays.

A protocol for performing targeted irradiation of cells with an ion microbeam has been established. From the measurements, data for the induction of DNA double strand breaks (DSBs) have been obtained for primary human cells and three radiation qualities (“early effects”). Data for the induction of chromosomal aberrations (“late effects”), i.e. genetic changes of the cells after irradiation, have been taken on Chinese hamster ovary cells for the same three radiation qualities and a fourth one mimicking the effects of a clinical spread-out carbon ion Bragg peak. A protocol that allows the simultaneous scoring of micronuclei and di-centric chromosomes, i.e. of different types of chromosomal aberration, has been developed which provides a basis for the harmonisation of different approaches in biological dosimetry.

Both data sets have been compared to predictions of the multi-scale model. Regarding the “late” effects the research results supported the hypothesis that the chromosomal aberrations are due to a combination of clustered damage at the DNA scale (nanometres) and the interaction of different DNA lesions at the µm-scale (“proximity effects”). For the “early” effects it could be shown that the details of the micro-beam irradiation have to be taken into consideration in order to compare the simulation results with the radiobiological assays.

This objective was fully achieved and it is now possible to model what happens after the radiation has impacted, and how the cells react to radiation damage.

Actual and potential impact

Dissemination of results

The project outputs have been shared widely with the metrology, instrumentation and clinical communities. There were 108 presentations at international scientific conferences, 42 articles published in peer reviewed journals, 16 training courses, 4 workshops, 8 reports to international standards committees, and 37 other dissemination activities such as web sites and seminar or workshop presentations. Collaborators and stakeholders were regularly updated formally and informally. Discussions were held with the International Commission for Radiological Units and Measurements about establishing a reporting committee based on the outcomes of the project. A representative of the International Atomic Energy Agency was invited to PTB for a presentation of the project results and consultation about potential uptake. A symposium was held as part of the 3rd ESTRO forum with an audience of about 200 people.

Early Impact.

The project brought together the clinicians, biologist and physicists in this field and generated a collaborative approach to the problem. It demonstrated the importance of understanding both the physics and biological processes in order to characterise the ion beam radiation fully and accurately.

The project has had a significant impact on European research institutions active in the field of ionising radiation metrology. PTB has created a new department within its ionising radiation division to focus on radiation effects. The results have been shared with IAEA and ICRU, who are the standardising bodies active in this area.

The results are being used in studies in the US into the potential benefits of carbon ion therapy, previously only used in Europe and Japan. Further investigation into the link between physical and biological radiation effects and development of track-structure based radiation quantities is a key priority for the European Joint Programme for the Integration of Radiation Protection Research.

Potential future impact

The project developed the methodology for determining the weighting factors to convert an absorbed dose to a biological effective dose, and the multiscale approach has given a better understanding of the measurement techniques and how to characterise the beams. This will pave the way for the future development of radiation treatment planning tools. Optimised radiotherapy plans, in terms of physical dose and the predicted treatment outcome, will enable clinical radiotherapy plans from different radiotherapy centres in Europe to be compared. Since the number of patients treated at any given centre for a particular indication is often small, multi-centre studies will increase statistical power and improve utilisation of clinical data. The project may reduce the need for expensive radiobiological cell experiments, and reduce biological waste and animal experiments.

The future treatment planning tools will allow different radiotherapy modalities to be combined, providing radiotherapy researchers with improved capabilities based on sound metrological principles and dosage quantification. This will strongly support the realisation of the ESTRO 2020 Vision of individualised radiotherapy; and will have a wide impact on clinical practice and the radiotherapy technology industry. The project will contribute to increasing cure rates for the predicted 50 million European citizens that will be diagnosed with cancer and treated with radiotherapy over the next two decades, and reduce the side effects of cancer treatments and post-treatment patient care.

The concepts developed within the project could also be extended to a wider range of applications such as secondary cancer risks due to exposure of non-target regions in radiotherapy, health risks from low-dose environmental exposure (e.g. Radon gas), exposure of occupational radiation workers, accidental exposure and space radiation effects.

List of publications

[1] S. Pszona, B. Grosswendt, A. Bantsar, I. Cieszykowska, W. Czarnacki: *Nanodosimetry of ^{125}I – Auger electrons – Experiment and modeling*. Radiation Measurement 47, 1092-1096 (2012).

[2] W. Y. Baek, A. Arndt, M. U. Bug, H. Rabus, M. Wang: *Total electron scattering cross sections of pyrimidine*. Physical Review A 88, 032702 (2013). doi: dx.doi.org/10.1103/PhysRevA.88.032702

[3] M. U. Bug, E. Gargioni, H. Nettelbeck, W. Y. Baek, G. Hilgers, A. B. Rosenfeld, H. Rabus: *Ionization cross section data of nitrogen, methane, and propane for light ions and electrons and their suitability for use in track structure simulations*. Physical Review E 88, 043308 (2013). doi: 10.1103/PhysRevE.88.043308

[4] D. Moro, P. Colautti, V. Conte, G. Hilgers, A. Pausewang, W. Helms, B. Lambertsen, H. Rabus: *ILITS Experiment at TANDEM-ALPI accelerator*. INFN-LNL Report 239, 178-179 (2013).

[5] G. Hilgers, M. U. Bug, E. Gargioni, H. Rabus: *Comparison of measured and Monte-Carlo simulated track structure parameters in nanometric volumes*. Radiation Protection Dosimetry 161, 441-444 (2014). doi: 10.1093/rpd/nct265

[6] M. U. Bug, E. Gargioni, W. Y. Baek, G. Hilgers, H. Nettelbeck, H. Rabus: *Proton-impact ionization cross sections for nanodosimetric track structure simulations*. Radiation Protection Dosimetry 161, 474-477 (2014). doi: dx.doi.org/10.1093/rpd/nct317

[7] D. Moro, S. Chiriotti, P. Colautti and V. Conte: *TEPC gas gain measurements in propane*. Radiation Protection Dosimetry 161, 459-463 (2014). doi: 10.1093/rpd/ncu005

[8] Aliaksandr Bantsar, Marcin Pietrzak, Marian Jaskóła, Andrzej Korman, Stanisław Pszona, Zygmunt Szefliński: *Status report: Nanodosimetry of carbon ion beam at HIL*. Reports of Practical Oncology & Radiotherapy 19, S42-S46 (2014).

[9] G. Hilgers, W. Helms, B. Lambertsen, A. Pausewang, H. Rabus, A. Bantsar, S. Pszona, Z. Szeflinski: *ILITS Experiment: First Results*. HIL Annual Report 2013, 46-48 (2014).

[10] G. Hilgers, D. Moro, A. Pausewang, W. Helms, B. Lambertsen, H. Rabus, P. Colautti, V. Conte: *ILITS Experiment: First Results*. INFN-LNL Report 240, 129-130 (2014).

[11] D. Bianco, C. Villagrasa and M. Dos Santos: *Multi-Scale Analysis of Simulated Proton and Alpha Irradiation*. Radiation Protection Dosimetry 164, 444-448 (2014). doi: 10.1093/rpd/ncu187

[12] W. Y. Baek, M. U. Bug, H. Rabus: *Differential elastic electron scattering cross sections of pyrimidine in the energy range between 20 eV and 1 keV*. Physical Review A 89, 062716 (2014). doi: 10.1140/epjd/e2014-40829-8

[13] C. Champion, M. A. Quinto, M. U. Bug, W. Y. Baek and P. F. Weck: *Theoretical and experimental quantification of doubly and singly differential cross sections for electron-induced ionization of isolated tetrahydrofuran molecules*. European Physics Journal D, 68: 205, 1-7 (2014). doi: 10.1140/epjd/e2015-60095-6

[14] Marion U. Bug, Gerhard Hilgers, Woon Yong Baek, Hans Rabus: *Nanodosimetric characterization of ion beams*. European Physics Journal D 68: 217, 1-10 (2014). doi: 10.1140/epjd/e2014-50015-9

[15] H. Rabus, H. Palmans, G. Hilgers, P. Sharpe, M. Pinto, C. Villagrasa, H. Nettelbeck, D. Moro, A. Pola, S. Pszona, P. Teles: *Biologically Weighted Quantities in Radiotherapy: an EMRP Joint Research Project*. EPJ Web of Conferences 77: 00021, 1-7 (2014); doi: 10.1051/epjconf/20147700021

[16] H. Palmans, H. Rabus, A. L. Belchior, M. U. Bug, S. Galer, U. Giesen, G. Gonon, G. Gruel, G. Hilgers, D. Moro, H. Nettelbeck, M. Pinto, A. Pola, S. Pszona, G. Schettino, P. H. G. Sharpe, P. Teles, C. Villagrasa and J. J. Wilkens: *Future development of biologically relevant dosimetry*. British Journal of Radiology 88:20140392, 1-19 (2015). doi: 10.1259/bjr.20140392

[17] Marion Bug: *Nanodosimetric Particle Track Simulations in Water and DNA Media*. University of Wollongong, Wollongong, NSW, Australia 13 November 2014, http://ro.uow.edu.au/theses/4150/

[18] A. Arndt, W. Y. Baek, M. U. Bug, T. Buhr, G. Hilgers, H. Nettelbeck, H. Rabus, J. Rahm, M. Wang: *Progress Report of the Department 'Fundamentals of Dosimetry'*. Report CCRI(I)/13-10, 29-41 (2015). http://www.bipm.org/cc/CCRI(I)/Allowed/21/CCRI(I)_ProgressReport_PTB_2013.pdf

[19] C. Patrono, O. Monteiro Gil, U. Giesen, F. Langner, M.Pinto, H. Rabus, A. Testa: *"BioQuaRT" project: design of a novel in situ protocol for the simultaneous visualization of chromosomal aberration and micronuclei after irradiation at microbeam facilities*. Radiation Protection Dosimetry 166, 197-199 (2015). doi: 10.1093/rpd/ncv160

[20] D. Moro, S. Chiriotti, V. Conte, P. Colautti and B. Grosswendt: *Lineal energy calibration of a spherical TEPC*. Radiation Protection Dosimetry 166, 233-237 (2015), doi: 10.1093/rpd/ncv153

[21] S. Chiriotti, D. Moro, V. Conte, P. Colautti, B. Grosswendt, E. Sterpin, S. Vynckier: *Influence of the Physical Data to Calibrate TEPCs*. Radiation Protection Dosimetry 166, 238-241 (2015). doi: 10.1093/rpd/ncv140

[22] A. Bantsar, G. Hilgers, S. Pszona, H. Rabus and Z. Szeflinski: *Experimental investigation of ionization track structure of carbon ions - experiments at HIL Warsaw.* Radiation Protection Dosimetry 166, 253-256 (2015). doi: 10.1093/rpd/ncv191

[23] Thorsten Schneider, Hans Rabus, Marion U. Bug: *A database application to investigate the validity of the nanodosimetric approach*. Radiotherapy & Oncology 115 (Suppl. 1), S734-S735 (2015). doi: 10.1016/S0167-8140(15)41355-6

[24] Hans Rabus: *Requirements for multi-scale models of radiation action – activities in European projects Nano-IBCT and BioQuaRT*. Radiotherapy & Oncology Oncology 115 (Suppl. 1), S107 (2015). doi: 10.1016/S0167-8140(15)40210-5

[25] Marion U. Bug, Woon Yong Baek, Hans Rabus: *Calculation of electron track structure in water and DNA medium*. Radiotherapy & Oncology 115 (Suppl. 1), S76 (2015).doi: 10.1016/S0167-8140(15)40154-9

[26] C. Villagrasa, G. Gruel, G. Gonon, S. Meylan, M. Bug, U. Giesen, M. Bueno, W. Y. Baek, A. Arndt, H. Rabus: *Characterisation of interaction of radiation with cells- track structure modelling and*

biodescriptors of the topology of energy deposition. Radiotherapy & Oncology 115 (Suppl. 1), S106-S107 (2015). doi: 10.1016/S0167-8140(15)40209-9

[27] D. Moro: *Experimental methods for microdosimetry, nanodosimetry and track structure determination: state of the art*. Radiotherapy & Oncology 115 (Suppl. 1), S106-S107 (2015). doi: 10.1016/S0167-8140(15)40208-7

[28] F. Alexander, C. Villagrasa, H. Rabus, J.J. Wilkens: *Exploring the potential of nanometric track structure based quantities for particle beam treatment planning*. Radiotherapy & Oncology 115 (Suppl. 1), S796 (2015). doi: 10.1016/S0167-8140(15)41460-4

[29] U. Kamierczak, A. Bantsar, D. Banas, J. Braziewicz, J. Czub, M. Jaskóla, A. Korman, M. Kruszewski, A. Lankoff, H. Lisowska, M. Pietrzak, S. Pszona, T. Stepkowski, Z. Szeflinski, M. Wojewódzka: *Heavy Ion Beams for Radiobiology: Dosimetry and Nanodosimetry at HIL*. Acta Physica Polonica A 127, 1516-1519 (2015). doi: 10.12693/APhysPolA.127.1516

[30] A.Bantsar, S.Pszona: *Nanodosimetry of Electons: Analysis by Experiment and Modelling*. Radiation Protection Dosimetry 166, 210-213 (2015). doi: 10.1093/rpd/ncv301

[31] S. Chiriotti, D. Moro, P. Colautti, V. Conte, B. Grosswendt: *Equivalence of Pure Propane and Propane TE Gases for Microdosimetric Measurements*. Radiation Protection Dosimetry 166, 238-241 (2015). doi: 10.1093/rpd/ncv293

[32] G. Hilgers, D. Moro, A. Pausewang, W. Helms, B. Lambertsen, H. Rabus, P. Colautti, V. Conte: *ILITS experiment: track structure of carbon ions*. INFN-LNL Report 241, 132-133 (2015)

[33] S. Chiriotti, D. Moro, E. Motisi, M. Ciocca, P. Colautti, V. Conte, B.Grosswendt. : *First Microdosimetric Measurements at CNAO*. INFN-LNL Report 241, 141-142 (2015)

[34] V. Conte, D. Moro, P. Colautti, B. Grosswendt, G. Hilgers and H. Rabus: *The Ion Counter and the StarTrack Counter: consistent nanodosimetry of track structure for carbon ions*. INFN-LNL Report 241, 164-165 (2015)

[35] G. Hilgers, W. Helms, B. Lambertsen, A. Pausewang, H. Rabus, A. Bantsar, S. Pszona, Z. Szeflinski: *ILITS experiment: scaling of cluster size distributions.* HIL Annual Report 2014, 48-51 (2015)

[36] M. Pietrzak, A. Bantsar and S. Pszona: *Nanodosimetry of Carbon Ions at HIL - study of the wall effect in the Jet Counter.* HIL Annual Report 2014, 54-56 (2015)

[37] A. Bantsar, G. Hilgers, M. Pietrzak, S. Pszona and H. Rabus: *Nanodosimetry of carbon ions - comparison of the experiments with Ion Counter and Jet Counter.* NCBJ Annual Report 2014, 59 (2015)

[38] F. Alexander, C. Villagrasa, H. Rabus J. Wilkens: *Energy dependent track structure parametrisations for protons and carbon ions based on nanometric simulations*. European Physics Journal D 69:237, 1-7 (2015). doi: 10.1140/epjd/e2015-60206-5

[39] B. Rudek, D. Bennett, M. Wang, A. Arndt, H. Rabus: *Ion induced fragmentation cross-sections of DNA constituents*. European Physics Journal D 69:237, 1-9 (2015). doi: 10.1140/epjd/e2015-60204-7

[40] G. Hilgers, M. U. Bug, E. Gargioni, H. Rabus: *Effect of secondary ionizations on the comparison of measured and simulated track structure parameters in nanometric volumes*. European Physics Journal D 69:239, 1-18 (2015). doi: 10.1140/epjd/e2015-60176-6

[41] F. Alexander, C. Villagrasa, H. Rabus, J. J. Wilkens: *Local weighting of nanometric track structure properties in macroscopic voxel geometries for particle beam treatment planning.* Physics in Medicine and Biology 60, 9145-9156 (2016), doi: 10.1088/0031-9155/60/23/9145

[42] S. Chiriotti, D. Moro, V. Conte, B. Grosswendt, F. Vanhavere and S. Vynckier: *Indirect method to monitor the site size of sealed spherical TEPCs.* Radiation Measurements 85, 26-31 (2016),

[43] M. Wang, B. Rudek, T. Buhr, D. Bennett, M. Bug, P. de Vera, W. Y. Baek, G. Hilgers and H. Rabus: *Cross sections for ionization of tetrahydrofuran by protons at energies between 300 and 3000 keV*. Physical Review A 93, 052711, 1-16 (2016). doi: 10.1103/PhysRevA.93.052711

[44] B. Rudek, D. Bennett, M. Bug, M. Wang, W. Y. Baek, T. Buhr, G. Hilgers, C. Champion, H. Rabus: *Double differential cross sections for proton induced electron emission from molecular analogues of DNA constituents for energies in the Bragg peak region*. The Journal of Chemical Physics, 145, 104301, 1-12 (2016), doi: 10.1063/1.4962171

[45] M. Bug, W. Y. Baek, H. Rabus, C. Villagrasa, S. Meylan, A. B Rosenfeld: *An electron-impact cross section data set (10 eV - 1 keV) of DNA constituents based on consistent experimental data: a requisite for Monte Carlo simulations*. Radiation Physics and Chemistry 130, 459–479 (2017), doi: 10.1016/j.radphyschem.2016.09.027

SIB06 BioQuaRT

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