EMPIR Call 2015 – Health, SI, Normative and Research Potential

Selected Research Topic number: **SRT-h21**
Version: 1.0

Title: Biologically relevant metrology of ionising radiation

Abstract

A long-term approach is needed to develop biologically-relevant and personalised radiation metrology in Europe. This should encompass the realisation of radiation quantities that establish a clear link between the physical effects of radiation at the microscopic and nanoscopic scale and the resulting biological effects, which are of paramount importance for the future development of radiation therapy with combined treatment modalities. They are also a prerequisite for a metrological underpinning of radiobiological techniques which are the key to determining individual radiation sensitivity in radiotherapy and radiation protection. To achieve these goals, detectors should be developed which are capable of measuring all of the biologically-relevant multi-scale characteristics of particle track structure, including the correlation between multiple targets and measurement in mixed radiation fields. Also, the multi-scale approach should be extended from initial radiation damage to late biological consequences and towards its integration into radiation transport calculations. Finally, the uncertainty associated with the measured and simulated micro- and nanodosimetric parameters of track structure should be assessed.

The specific objectives aim at laying the foundation for the long-term development of a metrological support for radiobiological methods and radiation quantities based on the micro- and nanoscopic pattern of radiation interactions. They build on the achievements made in the EMRP project SIB06 BioQuaRT, in particular the multi-scale approach to characterising charged particle track structure.

Keywords

Ionising radiation metrology, biological multi-scale model, particle track structure, radiation quality, radiobiology, radiation protection, radiotherapy, microdosimetry, nanodosimetry

Background to the Metrological Challenges

A harmonised metrological basis for the quantitative characterisation of the effects of ionising radiation, at µm to nm scales needs to be developed in alignment with the EURAMET TC-IR Road Map “Novel dosimetry concept for ionising radiation interaction with matter”. This need is being driven by the European Society of Therapeutic Radiation and Oncology (ESTRO) 2020 vision of a multi-disciplinary approach to individualised radiotherapy [1] and the Multidisciplinary European Low Dose Initiative (MELODI) [2,3], which requires a proper assessment of the low-dose radiation risk for radiation protection. Individual radiation sensitivity also needs to be considered, i.e. balancing the chance of curing a tumour, with the risks of imposing adverse side effects or of inducing cancer or other diseases by involuntary exposure to ionising radiation.

There were an estimated 3.45 million new cases of cancer in Europe in 2012 [4] and about 50 % of these patients underwent radiotherapy, mostly using high energy (MeV) photon or electron beams. Alternative approaches, for example brachytherapy, targeted radionuclide therapy and treatment modalities using proton or carbon ion beams that are completely stopped in the body, have therapeutic advantages for specific types of tumours. In the future, combining different irradiation modalities is expected to lead to higher cure rates but, the correct combined radiotherapy dose (absorbed dose to water) would need to be prescribed. For example, using these alternative approaches the same biological effect can generally be obtained with a smaller absorbed dose (i.e. the absorbed dose is a macroscopic average whereas the biological effect is due to radiative energy transfer at the DNA, cell, cytoplasm and tissue scale) [5,6]. Therefore, additional weighting factors have to be employed to convert the absorbed dose into quantities that are better suited for predicting the biological outcome (e.g. the relative biological effectiveness). The different methodologies that have been used for this need to be harmonised based on new, still to be developed radiation quantities that give a clear separation between the physical effects of a radiation exposure, which depend on the modality, and the genuine biological effects, which are independent of the modality [7]. This will require a comprehensive investigation of the relationship between the characteristics of the particle track structure and the biological radiation effects for different endpoints. Measurement and simulation techniques for

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determining the micro- and nanoscopic distributions of radiation interactions (i.e. at the cellular and DNA level) will also need to be further developed towards a metrological level with traceability to standards and uncertainty budgets established.

Within the EMRP project SIB06 BioQuaRT, the ground work has been done for the development of a multi-scale approach for the characterisation of the particle track structure of ion beams. Advanced types of microdosimeters and different approaches to nanodosimetry, simulating a single target, have been developed and compared for radiation qualities of mono-energetic ions. An integrated micro- and nanodosimeter has been built and radiobiological reference data have been produced for cell irradiations at an ion microbeam for which the radiation quality of the mono-energetic ions was characterised using this instrument. A numerical tool for simulating particle track structure and radiation effects at the cellular and sub-cellular scale, down to the DNA molecule, has been developed and used to interpret the outcome of radiobiological assays on early biological radiation effects. Based on this tool, a potential pathway towards the application of the multi-scale approach in treatment planning has been investigated for the special case of ion beam therapy. In parallel, complementary experimental approaches for the characterisation of ionising particle track structure and the linking of micro- and nanodosimetry have been developed and alternative multi-scale approaches for predicting the biological consequences of ion beams in biological cells have also been formulated. The proper assessment of the uncertainty of micro- and nanodosimetric quantities obtained by simulations of track structure has been recently identified as an important issue by several EURADOS working groups.

Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the JRP-Protocol.

The JRP shall focus on the biologically relevant and personalised radiation metrology of novel dosimetry.

The specific objectives are

1. To develop measurement instruments with novel detectors for the multi-scale characterisation of ionising particle track structure. This should include the analysis and comparison of existing detector technologies and the investigation of advanced detection schemes based on nano-structure technologies with respect to their potential to build easy-to-use detectors for field use.
2. To extend the multi-scale simulation tool, from initial biological radiation effects to incorporate modelling of cell killing and functional changes in single cells and tissue, by developing existing radiobiological models.
3. To extend the multi-scale approach to all forms of radiation therapy and to integrate it into treatment planning. This should go beyond the Monte-Carlo approach, with analytical descriptions of track structure and alternative techniques for simulation being built into a prototype simulation tool.
4. To establish an uncertainty budget for the particle track structure characteristics obtained by micro-dosimetric and nano-dosimetric measurement and by multi-scale simulations.
5. To facilitate the take up of the technology and measurement infrastructure developed by the project by healthcare professionals (radiotherapy centres) and industry (instrumentation manufacturers).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this. In particular, proposers should outline the achievements of the EMRP project SIB06 BioQuaRT and how their proposal will build on those.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution to the project. Any deviation from this must be justified.

Any industrial partners that will receive significant benefit from the results of the proposed project are expected to be unfunded partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the "end user" community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the "end user" community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the radiology sector.

You should detail other impacts of your proposed JRP as specified in the document "Guide 4: Writing Joint Research Projects (JRPs)".

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.

Additional information

The references were provided by PRT submitters; proposers should therefore establish the relevance of any references.

[1] Vincenzo Valentini, Jean Bourhis, Donal Hollywood, (2012) ESTRO 2012 Strategy Meeting: Vision for Radiation Oncology, Radiotherapy and Oncology 103 99-102.

[2] High Level and Expert Group (HLEG), Report of High Level and Expert Group on European Low Dose Risk Research, (2009). URL: http://www.hleg.de/fr.pdf. Accessed 12 March 2015.

[3] URL: http://www.melodi-online.eu/index.html. Accessed 12 March 2015.

[4] J. Ferlay et al., (2013) Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012, European Journal of Cancer 49, 1374– 1403.

[5] Bernard W. Stewart and Christopher P. Wild (Eds.), (2014) World Cancer Report, World Health Organisation, Lyon.

[6] IAEA, (2008) "Relative Biological Effectiveness in Ion Beam Therapy", Technical Report Series Vol. 461 International Atomic Energy Agency, Vienna.

[7] BIPM-CCRI. (2005) Report of the 19th Meeting, BIPM. Consultative Committee for Ionizing Radiation Report, BIPM. Published online at http://www.bipm.org/utils/common/pdf/CCRI19.pdf.