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## 3. TC-IR Roadmap

### Novel dosimetry concept for ionising radiation interaction with matter (Hans Rabus, PTB)

#### Drivers and Challenges

##### a. ESTRO 2020 Vision of a multi-disciplinary approach to individualised radiotherapy:

In the past (and for several treatment modalities also still in the present), the major metrological challenge for medical applications of ionising radiation for therapeutic purposes was to establish a QA system based on standardised protocols for dosage quantification and their traceability to primary standards of absorbed dose to water. The extensive progress made in improving the traceability chain by reducing the gap between clinical and reference irradiation conditions during recent years has led to a situation where today, for mainstream treatment modalities, further efforts to reduce uncertainties of measurement standards of absorbed dose to water will not lead to an improvement of the treatment capabilities.

This preceding statement does not apply to a series of advanced and sophisticated treatment modalities using external radiation fields that are very inhomogeneous such that the specification of absorbed dose becomes problematic [1]. Similarly absorbed dose specification radionuclide therapy is still an ongoing challenge [2] particularly when the radiopharmaceutical is a radionuclide emitting short-range alpha particles or an Auger emitter. In some techniques such as, in particular, ion beam radiotherapy absorbed dose is not the relevant quantity for the treatment and needs to be modified by factors taking into account the different relative biological effectiveness (RBE) of different kinds of radiation [3][4][5]. Hence, the comparison of different treatment modalities based on absorbed dose to water protocols is still very difficult to impossible (e.g. for radionuclide therapy where the treatment is generally administered in terms of activity and not absorbed dose). Major hampering factors are:

- The different biological effectiveness of different radiation qualities on cancerous and healthy tissue.
- The large span of different irradiation conditions when comparing external beam therapy with photons and boron neutron-capture therapy (BNCT) or radionuclide therapy using alpha emitters.
- Different patient radio-sensitivity owing to which equivalent dosage (in terms of absorbed dose to water) does not imply equivalent treatment.

This dissatisfactory situation has prompted the ESTRO to formulate her 2020 vision [6] of individualised radio-therapeutic treatment using a multi-disciplinary approach which involves couple of metrological challenges:

- A dosimetric concept that facilitates the combination of different treatment modalities, particularly of radionuclide therapy and external beam therapy (EBT), and which also allows to properly take into consideration the confounding influence of imaging techniques in image-guided radiation therapy (IGRT), such as ionising radiation effects in magnetic fields.
- Providing metrology support for improved individualised treatment planning based on the virtual human approach, where also basic parameters entering the treatment planning may be individually derived from the diagnostic measurements preceding the treatment (e.g. conversion of Hounsfield units into radiation transport quantities).
- Development of a unified dosimetric concept for radiation quality that is not based on the global-view specification how the radiation is produced or administered but rather reflects the local properties of the radiation field and thus allows quantifying radiation effects at the microscopic level and at the level of individual cells or small compartments of tissue including early biological effects.

- Developing a measurement protocol for biological effects, e.g. quantifying the ‘efficiency’ of cell repair mechanisms, to provide a metrology support for the application of dose fractionation and radio-sensitizers.
- Measuring individual radio-sensitivity, enabling treatment plans based on patient-specific rather than population-averaged dose-effect curves.

Providing metrology support for the realisation of the ESTRO 2020 vision will result in higher cure rates in radiotherapy with a simultaneous reduction of side effects (detriments on healthy tissue), sustained improvements of patients’ quality of life after treatment and an overall cost-reduction to the health system.

#### b. Proper assessment of low-dose radiation risk for radiation protection

The present system of dosimetric quantities in radiation protection is based on phenomenological weighting factors for cancer risk that are almost exclusively based on epidemiological evidence. The tissue weighting factors take into account the different susceptibility of different tissues and organs for developing health detriment after radiation exposure. The radiation quality factors take into account that the risk for developing cancer after exposure to a certain dose depends on the kind of radiation (radiation quality) to which the organs were exposed [7]. These radiation weighting factors are generally based on the induction of chromosomal aberrations. Both type of weighting factors are obtained from studies with “high dose” exposure (in excess of about 100 mSv) and require an extrapolation into the low-dose exposure regime based on model assumptions that are very difficult to test experimentally, as the range of applicability of biological dosimetry is also limited to sufficiently high doses. Determination of the dose-response curve for low dose exposure has been identified in the 2009 *Report of High Level and Expert Group on European Low Dose Risk Research* [8] as one of the major issues in this field and became one priority area of the strategic research agenda of MELODI [9].

Other areas of concern are the dependence of risk on radiation quality [10] and incorporated radionuclides emitting alpha particles [11]. Generally for densely ionising charged particles the exposure is strongly inhomogeneous and characterised by a pronounced track structure such that a dosimetry concept based on macroscopic averages is of limited use. This applies to radiation exposure in space, where already different approaches are under discussion [12][13] as well as to all radioactive agents emitting short-range alpha particles, such as the ubiquitous Radon and its progeny [14][15].

Metrological challenges:

- Development of measurement techniques for radiation effects at the microscopic level, including the spatial and temporal correlations of radiation interactions within individual charged-particle tracks.
- Extension of the range of applicability of biological dosimetry toward lower doses by enhancing the through-put and reliability of biological assays through better control of experimental conditions by application of metrology.
- Establishing a traceability chain of biological dosimetry to physical standards of ionising radiation or, alternatively, develop biological standard systems.

#### c. Radiation damage to nanometric electronic structures

The advance of new materials in nano-technology and the development of advanced electronics produce structures of geometrical dimensions which are comparable with particle track diameters. These structures are potentially very vulnerable when exposed particularly to densely ionising radiation fields as are present in space application, at fusion reactor experiments but also in accelerator-based treatment units in clinics. A

quantitative measure of the risk of inducing a severe damage that can lead to component failure or loss does not exist. Radiation hardness or reliability of such components is typically assessed on a phenomenological basis in destructive tests. A measurand quantifying damage due to radiation interaction in nano-tech components, electronics and bio-systems would give a means to characterise the potential of different radiation qualities to damage such systems and would allow a targeted development of more radiation-robust components and hence have a significant impact on the speed of progress in this fields as well as on financial resources hitherto wasted in destructive testing.

## Targets

- ❖ To facilitate the combination of different treatment modalities in radiotherapy

This overarching target comprises the following main objectives:

- Development of a unified concept of radiation quality that is not only based on specifying the spectrum of photon and particle energies but on the microscopic distribution of interaction events, the associated energy transfers and the effects on the irradiated biological systems. Specifying radiation effects at the microscopic level, this radiation quality concept would apply to external irradiation of the human body as well as for internal exposure by administered radionuclides. It could also help the optimisation of image-guided techniques in radiotherapy, particularly for MRI-guided radiotherapy where the magnetic field influences the secondary electron distribution. This approach of considering the radiation effects at the microscopic level also will be most appropriate for the further development of radio-sensitizers as these often are based on nanoparticles or complex biomolecules.
- Development of new radiation quantities that incorporate a biological weighting of the radiation. The realisation of such quantities will probably consist in a dual approach: On the one hand, based on measurable parameters of charged particle track structure and numerical simulations building on a verified empirical correlation between track structure characteristics and biological effects. On the other hand, based on standard systems of biological cells and standard metrology-supported protocols for their biological assays [16].

- ❖ Developing a measurands for individual radiation sensitivity

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- Extension of the range of applicability of biological dosimetry toward lower doses by enhancing the through-put and reliability of biological assays through better control of experimental conditions by application of metrology.
- Metrology support for new or redefined radiation protection quantities. Improved standards for occupational radiation protection. Better data base for decision makers and regulatory bodies in the field of radiation protection. Reduction of radiation risk to occupationally exposed personnel and the general public.

- ❖ Improved radiation protection quantities

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## ❖ Radiation resistant nanoelectronics

- Facilitation the development of radiation-resistant nano-electronics and other nano-structured devices as well reliable biological-cell based production techniques. Augmenting the safety of space missions and the reliability and dependability of satellite-based infrastructure like GPS, global communication, etc.

## Deliverables

- Experimental and theoretical tools for the multi-scale characterisation of particle track structure in terms of the functional dependence of characteristic quantities (such as ionisation cluster size distributions or energy deposition distributions) on target size and spatial distance from the track.
- Direct investigation of radiation damage on isolated complex biological nanostructures such as short segments of DNA with a hydration layer or longer segments of DNA wound around histone proteins.
- Quantitative and comprehensive characterisation of the correlation between microscopic particle track structure with the radiation damage to microscopic structures like biological cells, sub-cellular entities or micro- and nano-electronics.
- A novel unified concept of radiation quality based on measurable properties of the particle track structure; its experimental realisation and implementation with 'primary standards' and traceable easy-to-use end-user measurement devices.
- Measurand(s) quantifying radiation hardness of advanced (nano-)electronics and of new materials in nano-technology.
- Development of high-throughput and high-yield biological assays for measurement of biological outcome of single-cell exposure experiments.
- Validated biological models relating microscopic properties (obtained from a comprehensive multi scale characterisation of charged particle track structure) and macroscopic effects as to be used e.g. in treatment planning.

Conception of measurement quantities reflecting the biological effectiveness of ionising radiation for use in radiation therapy and for radiation protection purposes. This deliverable encompasses on the one hand the development of a procedure for their realisation from a comprehensive multi-scale measurement of particle track structure. On the other hand, it also includes the development of biological standards in form of standard cell systems and in form of metrology-supported biological protocols for the realisation of standardised ('traceable') dose-response curves for biological effects at the cellular and tissue level.

## Technologies

- Measurement of ionisation clusters formed by single particle tracks (nanodosimetry) at different equivalent target size from the nanometer level to the micrometer level, i.e. from the size of a nucleotide in the DNA to the size of the nucleus in biological cells.
- Simulation techniques for charged particle tracks in biological matter that
  - include the specific properties of DNA and other complex biomolecular entities such as their interaction cross sections,

- full characterise the track structure in terms of stochastic distributions of characteristic quantities (e.g. ionisation cluster size, energy deposition, production yield of reactive species) for all relevant target dimensions (i.e. from nanometer to micrometer level) and including their spatial and temporal correlations.
- Metrology-assisted radiobiological assays for DNA damage and biological consequences at the cellular level in single cell exposure experiments, where individual cells are targeted by the radiation with full control of the relative arrangement of track and cell geometry and of the environmental conditions affecting cellular reactions to the radiation.

Development of tissue model assays that can be combined with microbeams and allow the comprehensive investigation of the radiation-induced reaction of each cell in the tissue model.

## Enabling Science

- Experimental techniques for measurement of charged particle tracks in gases, including time-of-flight and single particle counting techniques, as well as in solids and liquids.
- Quantum chemistry together with advanced measurement techniques such as reaction microscopy employed for determining comprehensive cross section data for the interaction of charged particles with all relevant biomolecular entities, i.e. from individual biomolecules to complex biomolecular aggregates like proteins.
- Advances in the theoretical description of radiation-matter interactions and the formation of charged particle tracks which properly consider quantum mechanical and multiple scattering effects the nanometer level.
- Improved single-particle micro-beams that
  - allow the dedicated irradiation of sub-cellular entities (e.g. individual chromosome territories) by delivering a sub-micrometer focus size and sub-micrometer targeting capability;
  - are combined with real-time imaging techniques and molecular imaging techniques.
- Advances in radiation biology through
  - development of improved single cell-based assays for radiation effects at the cellular and sub-cellular level (e.g. DNA) based on adequate biomolecular probes such as damage sensing proteins;
  - further development of 2D and 3D tissue models and related biological assays that allow studying the effect of the microenvironment on biological responses to radiation.

## Stakeholders

- EFOMP            European Federation of Organisations in Medical Physics
- ESTRO           European Society for Therapeutic Radiology and Oncology
- EURADOS       European Radiation Dosimetry Group
- HERCA           Association of the Heads of European Radiological protection Competent Authorities
- IAEA              International Atomic Energy Agency
- ICRP              International Commission on Radiological Protection

- ICRU International Commission on Radiation Units and Measurements
- MELODI Multidisciplinary European Low-Dose initiative,

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