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Disclaimer

This deliverable has been prepared by Work Package 5 (MediNet – Network: Nuclear Physics for Medicine) of the Project in accordance with the Consortium Agreement and the Grant Agreement n°654002. It solely reflects the opinion of the parties to such agreements on a collective basis in the context of the Project and to the extent foreseen in such agreements.

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LIST OF ACRONYMS AND ABBREVIATIONS

BNC	Boron Neutron Capture
CATANA	Centro di Adroterapia ed Applicazioni Nucleari Avanzate
CERN	Centre Européen de Recherche Nucléaire
CNAO	Centro Nazionale di Adroterapia Oncologica (Pavia/Italy)
CT	Computed Tomography is a medical imaging technique using a large series of two-dimensional X-ray images.
D	Absorbed dose is a measure of the energy deposited per unit mass of medium by ionising radiation, and so has the unit Gy.
DKFZ	'Deutsches Krebsforschungszentrum' is the biomedical research institute in Heidelberg
DNA	Deoxyribonucleic acid: molecule that carries the genetic instructions used in the growth, development, functioning and reproduction of all known living organisms
ENSAR2	European Nuclear Science And Applications: EU-funded Integrating Initiative with the 'Horizon 2020' funding framework of the EU
eV	Practical unit for energy used in atomic and nuclear physics (e.g. for particle beam energy): 1 eV = 1.6×10^{-19} J
FLUKA	'FLUktuierende KAskade' Monte Carlo code for the simulation code for applications in nuclear science
GATE	GEANT4 Application for Tomographic Emission: (open source) simulation toolkit dedicated to numerical simulations in medical imaging and radiotherapy (maintained by the international OpenGate collaboration)
GFN	Grupo Fisica Nuclear: nuclear physics group at Madrid/Spain
GEANT4	'GEometry ANd Tracking' Monte Carlo code for the simulation of the passage of particles through matter. Its areas of application include high energy, nuclear and accelerator physics, as well as studies in medical and space science.
GEANT4-DNA	GEANT4 code to simulate biological damages induced by ionising radiation at the cellular and sub-cellular scale
GSI	Gesellschaft für SchwerIonenforschung – Centre for Heavy Ion Research located at Darmstadt, Germany
Gy	Gray is the name of the special unit of absorbed dose of ionising radiation, i.e. the absorption of one joule of ionising radiation by one kilogram of matter. 1Gy = 1 J/kg = 1 m^2/s^2
HIT	Heidelberg Ion Therapy facility
HSG	Human salivary gland tumour cells
IBA	Ion Beam Applications: Market leading provider of proton therapy facilities and auxiliary systems (headquarter located in Louvain-la-Neuve, Belgium)
IFJ PAN	Instytut Fizyki Jądrowej, Polish Academy of Sciences (Krakow/Poland)
INFN	Istituto Nazionale di Fisica Nucleare, Italy
FLUKA	'FLUktuierende KAskade' Monte Carlo simulation code
L-Q	Linear-Quadratic
LEM	Local Effect Model
LEM IV	Forth and most recent version of Local Effect Model

LET	Linear Energy Transfer is a measure of the energy transferred to material as an ionising particle travels through it.
L_D	Dose-averaged LET
L_T	Track-averaged LET
LUT	Look Up Tables
LINAC	contraction of the two words *linear* and *accelerator*
LMU	Ludwig-Maximilians-Universität München
LNL	Laboratori Nazionali di Legnaro, (INFN Laboratories)
LNS	Laboratori Nazionali del Sud, (INFN Laboratories)
LPC	Laboratoire de Physique Corpusculaire (Clermont-Ferrand/France)
MediNet	Networking Initiative on Medical Physics within the EU-funded ENSAR2 Integrating Initiative
MedAustron	MedAustron Ion Therapy Centre, Wiener Neustadt, Austria
MKM	Microdosimetric Kinetic Model
microdosimetry	Measurements of the distribution of energy imparted at micrometric sizes, comparable to the sizes of a mammalian cell nucleus
MC	'Monte Carlo' simulation method based on random sampling
MRI	Magnetic Resonance Imaging is a medical imaging technique using a powerful magnetic field and radiowaves RF pulse of around 40 in the 1-100 MHz range.
nanodosimetry	Measurements of ionisation distributions in nanometric sizes, comparable to the DNA molecule sizes
NIRS	National Institute of Radiological Sciences located at Chiba, Japan
NTCP	Normal tissue complication probabilities
PBC	Proton Boron Capture
PET	Positron Emission Tomography is a medical imaging technique using pairs of gamma rays emitted indirectly by a positron-emitting radionuclide.
PSI	Paul Scherrer Institute: largest research institute for natural and engineering sciences in Switzerland, located in Villigen.
RBE	Relative Biological Effectiveness is defined as the ratio of a dose of a reference radiation quality to the dose of the test radiation quality required to cause the same biological level of effect, all other conditions being the same.
RT	Radiotherapy
SF	Survival Fraction
SOBP	Spread-Out Bragg peak is an overlap of several pristine Bragg peaks at staggered depths.
TEPC	Tissue-equivalent proportional counter
TPS	Treatment Planning System used in radiation therapy for planning the doses in the tumour and the surrounding healthy tissue (critical organs).
TRiP	Treatment planning system for ions used in therapy developed at GSI
VINS-UB	Vinca Institute of Nuclear Sciences, University of Belgrade
keV, MeV, TeV	Prefix letters together with a unit denote an abbreviated order of magnitude: keV(kilo-eV): 10^3 eV, MeV (Mega eV): 10^6 eV, TeV (Tera eV): 10^{12} eV

EXECUTIVE SUMMARY

Cancer is a critical societal issue. Worldwide, in 2018 alone, 18.1 million cases were diagnosed, 9.6 million people died and 43.8 million people were living with cancer. These numbers are projected to rise by 2030 and reach to 24.6 million newly diagnosed patients and projects deaths to 13 million.

Cancer imposes an enormous economic burden worldwide—around 2 trillion dollars in 2010 and these costs are rising and putting a major burden on public healthcare budgets. In the EU where over 3.7 million new cases per year are diagnosed and total costs over 120 billion EUR were reported for the EU in 2013 [1]. According to Bray [2] almost two million deaths each year are due to cancer the Europe, see Fig. 1.

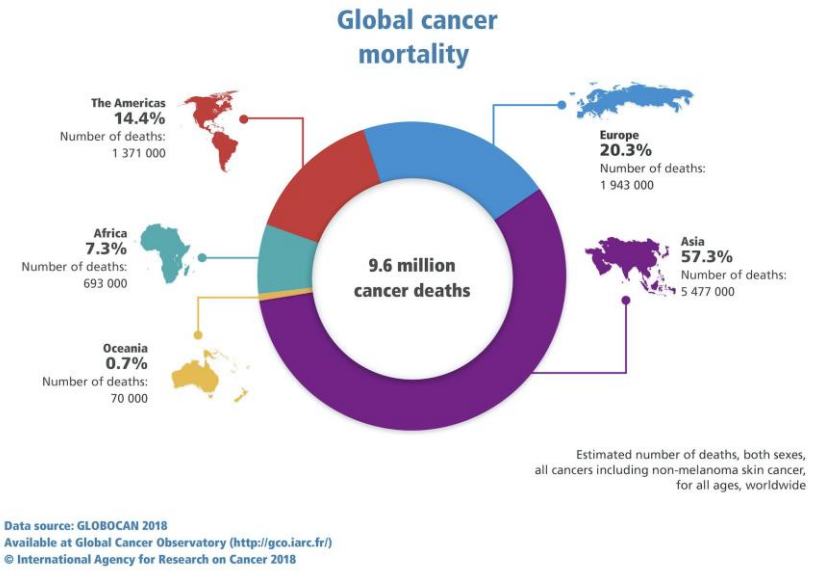

Figure 1. Estimated number of deaths in the world. Source GLOBOCAN [3].

Surgery, chemotherapy, and radiotherapy as well as combinations of these options represent the major pillars in the treatment of cancer. The constant call to the specialists and professionals, who are involved in the research and the development of radiation-therapy technologies, is to provide the most reliable, performant, and cost-effective medical tools. Radiation therapy based on X-rays and ion beams is the specific focus of the groups of joining forces in the MediNet Networking Activity within the H2020 ENSAR2 Integrating Initiative. More than thirty European institutes from thirteen countries collaborate in the common goal of developing, from the nuclear physics area, the tools that could have the most beneficial impact to the medical applications. Translation of basic concepts into practical medical applications also means commercialisation, based on a cross-fertilising interplay between academia and industry.

This deliverable is the fourth and conclusive document produced by MediNet network and it follows:

- MediNet Deliverable 5.1, 'Specific needs and proposed solutions of nuclear tools for medicine', completed on 30 November 2016

- MediNet Deliverable 5.2, 'Clarifying and adapting nuclear concepts to the medical field', completed on 30 November 2017, and
- MediNet Deliverable 5.3, 'Nuclear Physics Instrumentation for Medicine (presentation of Task 1 activities)', completed on 28 February 2019

Deliverable 5.4 collects the original contributions of the groups of the Task 2 of MediNet network, focusing on the tools that originated in the framework of *physics* research that relate to the assessment of the *biological* effectiveness of radiation. These tools include experimental and computational instruments, which are described in specific sections of the document: Microdosimetric detectors, Monte-Carlo simulations, and Computations and Models for treatment planning.

The style of the previous deliverables is maintained here considering that the potential reader may be also non-specialist in the field and hoping that this choice will facilitate the circulation beyond the scientific community. The potential reader is assumed to be a person who has completed high-school studies and has a general scientific knowledge of physics, biology, and information technology.

The structure of the document is the following:

An introductory section presents the rationale behind particle therapy in comparison to conventional X-ray based radiotherapy and gives the motivation for the need of continuing studies and developments of tools for the most accurate characterisation of the ion beams used in ion-beam therapy.

The following section is dedicated to the topical presentation of the ***Nuclear physics tools to support biological effectiveness assessment in ion-beam therapy*** and it provides information for the scientific and economic community as well as policy makers, and public on the most advanced status of their ongoing research. The heterogeneous scientific outcomes are grouped in three main topics: instrumentation development for microdosimetric analysis of radiation, Monte Carlo simulations, and models for treatment planning. For these three fields of research, particular emphasis is put in describing the constant evolution resulting from the effort of the scientific community to study and improve the instruments, to find fruitful collaboration with commercial partners, and cope with the requests of the clinical users.

The final section of the document proposes examples of collaborative partnerships of some MediNet task 2 Institutes. It collects the original contributions, which focus on the specific research developments of nuclear physics computational and experimental tools funded with resources independent from MediNet budget but in the framework of the network topics. Emphasis is put on the collaborative and common research activities between different Institutes of MediNet Task 2 highlighting the importance of the networking promoted by the network action.

1. INTRODUCTION

One of the most fruitful interactions between physics and medicine involves nuclear physics. The fundamental connection between the two disciplines started in 1895, when the discovery of X-rays and the density-dependent absorption of electromagnetic radiation by W.C. Röntgen, initiated the era of medical imaging. This field became richer and richer during the years, adding more and more imaging techniques as well as a variety of diagnostic applications. Positron-electron annihilations led to PET (positron emission tomography), single photon emission of specific radioisotopes led to scintigraphy and SPECT (single photon emission computed tomography), and magnetic resonance detection led to MRI (magnetic resonance imaging). In-beam dosimetry and prompt gamma detection for real time imaging and particle therapy relate to these techniques. MediNet Deliverable 5.3, **Nuclear Physics Instrumentation for Medicine,** was published 28 February 2019 and provides the most recent updates on the topic with direct insights from the groups of MediNet task 1 (https://medinet.medaustron.at/images/3/37/D5.3-submitted.pdf).

Thanks to the rapid development of particle accelerator technology, also tumour treatment modalities drawing on accelerated charged particles, i.e. electrons and positive ions (like protons and carbon ions) increasingly gained relevance, forming the field of radiotherapy.

Radiotherapy (RT) is now a fundamental component of effective cancer treatment and control. It is estimated that about half of the cancer patients would benefit from radiotherapy for treatment of localised disease, local control, and palliation. The growing burden of cancer is placing increased demand on the already scarce radiotherapy services worldwide. However, RT is by far the most cost-effective modality for cancer treatment with the added advantage of conserving normal tissue function. More than 10,000 electron linear accelerators (linacs) are used currently worldwide to treat patients. The most frequently used modality of RT employs high-energy (6 to 10 MeV) photons produced by bremsstrahlung, and in a small proportion low- to intermediate-energy (3 to 25 MeV) electron beams. Due to the global distribution of facilities using electron linacs for cancer treatment, photon RT is referred often to as the 'conventional' RT.

The photons are produced indirectly by using electron linacs. The electrons bombard a target of tungsten or other material and the electron energy lost in the deceleration is converted to electromagnetic energy of the X-ray photons. These X-rays are collimated and directed toward the tumour. The goal of therapeutic radiotherapy is to control the tumour by optimising the dose (amount of energy per unit mass) in its volume to eliminate cancer cells, while minimising severe side effects and damage to the surrounding healthy tissue. The main limitation of conventional RT is that the dose delivered to the tumour is limited by the dose that can be tolerated by the surrounding normal tissues. Conventional photon RT is characterised by almost exponential attenuation and absorption, and consequently delivers the maximum energy near the beam entrance, but continues to deposit significant energy at distances beyond the cancer target (Fig. 2). The maximum dose for photons beams with an energy of about 8 MeV, is reached at a depth of 2–3cm of soft tissue. Exit doses can be as high as 50% of the dose to the target.

The other form of radiotherapy with external beams is based on the use of proton and carbon ions. Proton therapy and carbon-ion therapy are part of what it is called in general 'hadron therapy', 'ion-

beam therapy' or 'particle therapy'. The physical interactions of the ions with matter are very different from those of the X-rays. The profile of the dose in depth is called 'Bragg curve' and represents the energy imparted to the tissue at different depths. The shape of the Bragg curve is particularly advantageous since the dose increases with the penetration and, at higher doses, the capability of killing the cells increases. At the entrance the heathy tissue is spared while at the end of its path the Bragg peak is formed delivering the maximum dose. Figure 2 shows the depth-dose curves of both, protons and photons in a realistic irradiation scenario. The Bragg peak allows concentrating the dose in the volume of the tumour using beams of different energy but same direction. This allows conformation of the dose to the shape of the tumour using the so-called 'spread-out Bragg peak' (SOBP).

Figure 2 illustrates also the profile of the dose in depth of the X-ray photons. Their behaviour is different to the behaviour of the protons (and of the ions) as the highest dose, maximal at the surface, constantly decreases with the depth. This disadvantage is compensated for by increasing the number of beam directions, which hit the target so to deliver to the tumour the needed dose, diluting, at the same time, the dose to the surrounding healthy tissue.

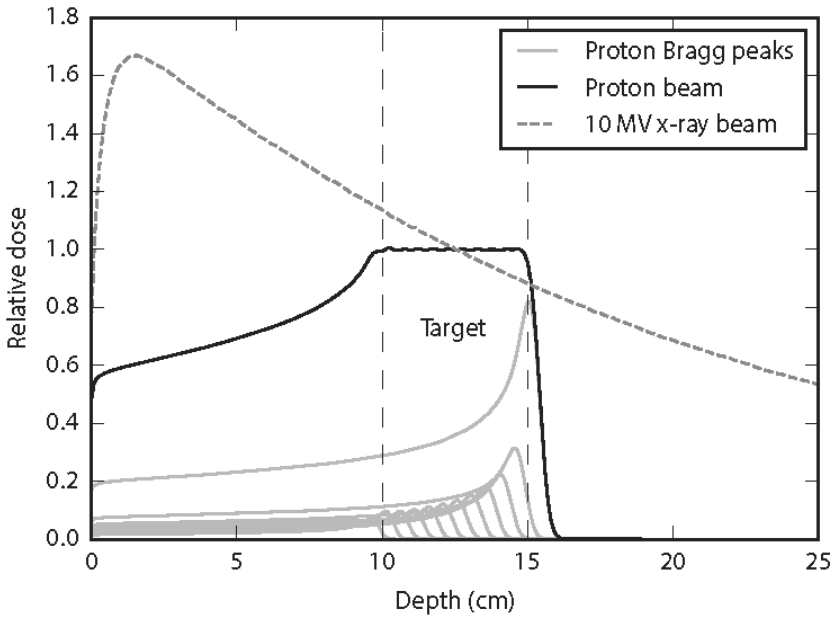

Figure 2. Comparison of the depth-dose distribution of an X-ray photons from a 10 MV linear electron accelerator (dashed curve), and a proton beams modulated in energy (grey curves). Proton beam SOBP (solid curves). The target is a volume at a depth of 10 cm to 15 cm. The dose in the interval from 0 cm to 10 cm is much lower for protons than for photons and the positive effect is a sparing of the superficial tissue. From source Verburg, 2014 [4].

The advantages of the Bragg peak were recognised by Robert Wilson in 1946 [5] and implemented in 1954 when the first patient was treated with protons at Berkeley Laboratory. Hydrogen and carbon are the two species used today in therapy although in the past other particles including helium, silicon, neon, and pions, were employed for treatments. Today helium is considered again as candidate for clinical use.

Treatment modalities based on ion accelerators started in pioneering facilities in the 1950's using proton.

Since the initial years, it was found that the ions heavier than protons show an increase of the biological effectiveness of the radiation when penetrating the tissue. Studies on cell revealed that at different energies the probability of survival are not only linked to the total energy delivered from the radiation but also other radiation characteristic, the so-called radiation quality. These investigations showed that ions at the entrance have lower biological effectiveness than in the Bragg peak and this behaviour is evidently a further advantage of ion-beam therapy, which allows to concentrates the maximum action in the tumour.

The conformation of the dose to the tumour was done, in the initial phase, only using the so-called 'passive methods'. With these methods, the conformation of the transversal radiation field to the shape of the tumour is performed using large irradiation field and metallic collimators produced individually to match the transversal shape of each tumour. Longitudinally, passive modulation of the beam energy was performed to extend the SOBP to cover the thickness of the tumour. For this purpose, plastic absorbers of variable thickness are inserted in the line of the beam to passively move the position of the Bragg peak.

Many years have passed since the first patients, the irradiation techniques have evolved constantly, and today the irradiation can be performed also using active methods of conformation in three dimensions to the tumour target. In 1996 at the Swiss Centre for Proton Therapy at the Paul Scherrer, PSI, the first patient was treated with an active scanning system. One year later at the Gesellschaft für Schwerionenforschung (GSI), Darmstadt, Germany, a similar technique was applied for patients treated with carbon ions. An ion beam, whose cross section is few squared millimetres, is steered transversally using orthogonal scanning magnets and it is modulated in energy to move it longitudinally over the length of the tumour. The active scanning methods allows performing an irradiation precisely conformed to the tumour volume. For what concerns ions heavier than hydrogen, active beam scanning techniques are able to take into consideration the complexity of the biological effects of the radiation and adapt to it.

2. *BIOLOGICAL EFFECTIVENESS AND NUCLEAR PHYSICS TOOLS*

Active scanning techniques resulted in more heterogeneous irradiation fields whose characteristics change every few millimetres. In order to optimise the control of the irradiation for the treatment, different tools must be implemented. These came from the computational and experimental physics of radiation. In particular:

- Microdosimeters can measure the parameters of the radiation linked to the biological effectiveness, a process that is indicated generally as specification of the 'radiation quality'.
- Monte Carlo simulations have the dual role of providing the correlation to the physical experimental data collected with microdosimetric detectors, and with radiobiological information to compare with the biological outcomes on irradiated cell lines.
- The models for the biological optimisation of the Treatment Planning Systems translate the physical parameters estimated in millimetric steps in the target, to the specific biological effectiveness optimised for the treatments.

2.1 **MICRODOSIMETRIC DETECTORS IN ION-BEAM THERAPY**

2.1.1 The physical base of the radiation action

When high-energy photons are used in clinic to treat tumours, there is a unique relationship between the absorbed dose, which is proportional to the photon fluence, and the observed biological effect. Therefore, the radiation biological effect in a given point inside the patient body can be deduced by measuring, or calculating, the absorbed dose in that point. When light ions are used, this unique relationship does not hold anymore: the observed biological effect in different points of the patient body can be different even if the absorbed dose in those points is the same. This fact points out that the biological effect depends also on the modality the energy is imparted. In fact, the same energy is differently imparted in different points of the body. Generally, the ionising radiations do not impart the energy uniformly to the target, but in small, discrete events, i.e. in a granular way. Similarly to the shot of the hunting gun, large areas, where the tissue does not experience any damage, are marked by few points of energy absorption. Moreover, the imparted-energy in those points can be more or less dense. This heterogeneity is larger for charged particles and in general it increases with the depth in tissue.

Photons impart small quantities of energy in plenty of points in tissue, while charged particles impart larger quantities of energy in fewer number of points. This difference in imparting energy plays a role in the biological effect, since a larger quantity of energy absorbed in small biological sites gives rise to more complex biological damage that is more difficult to be repaired, causing deadly effects to all the living system.

In order to quantify such a biological action difference, radiobiologists compare the absorbed dose necessary to obtain a given biological effect with conventional photon radiation with the absorbed dose of a charged particle that gives the same effect. The ratio of the photon dose to the particle dose is called the relative biological effectiveness (*RBE*) of the particle. The *RBE* value changes with kind and energy of

the charge particle. However, it has been observed that a clear relationship exists between the *RBE* and the energy that the particle imparts per unit of length. This physical quantity is called linear energy transfer (*LET*) of the charged particles.

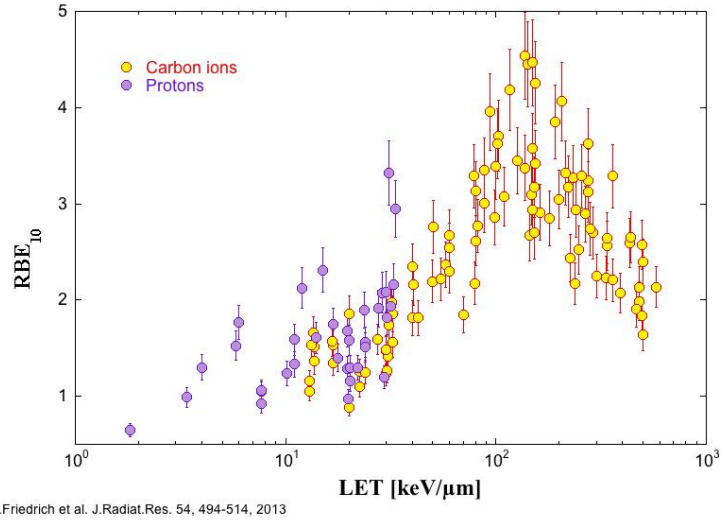

Figure 3. RBE for asynchronous radio-resistant human-cell surviving after irradiation with protons and carbon ions are plotted against the particle LET in tissue. The RBE subscript 10 means that the RBE values have been taken at 10% of cell surviving fraction [6].

In Fig. 3, *RBE* data are plotted against *LET* values of protons and carbon ions. In order to produce these radiobiological data, a mono-layer of human cells has been irradiated with mono-energetic protons and carbon ions. The *LET* value of the mono-energetic beams has been calculated; see Subsection 2.2.2. Different *LET* values have been obtained by changing the ion energy. Radiobiological measurements have a precision of about 10%, when performed by the same research group. However, data in Fig. 3 show higher *RBE* fluctuations, since apart from the physical characteristics of the ion beam, RBE also depends on the biological system, i.e. on the cell line used to determine the RBE, and the data shown in Fig. 3 are obtained with different cell lines. In spite of that, Fig. 3 shows clearly that *RBE* increases with the *LET* value up to about 150 keV/µm, then it decreases. However, the rise of RBE appears at lower LET values for protons as compared to carbon ions, for which no low LET data are available..

The decrease of *RBE* towards very high *LET* likely due to the so called “overkill” effect, which can occur when *LET* overcomes the value that assures the biological destruction of the site, hence the cell death. This effect is indicated as damage saturation at high *LET* values.

There is indeed a general awareness that the biological effect depends on the size of energy imparted by a single particle to a biological structure, which is of fundamental importance for the cell surviving. That biological structure can occupy a volume *V* as large as the cell itself (approximately 10 µm of thickness), or smaller than a chromosome (about 1 µm of thickness) or as small as the DNA strand (2 nm of thickness). The *imparted energy* is called ε_1, where the subscript 1 points out that the energy is imparted by a single particle. The physical quantity ε_1 has a stochastic nature because its value changes from particle to particle, even if the particle kind and energy is always the same. That because the particle cross-

ing path through the biological structure may have different lengths, being the particle trajectory casually distributed in the space. However, the stochastic nature of ε_1 rises also from more fundamental physical reasons. In fact, the ε_1 value changes casually also for the same path, because the interaction particle-target is not deterministic when only one or few collisions occur in the target.

Since ε_1 is a stochastic variable, repeated measurements give rise to a spectrum of values, which is called microdosimetric spectrum. The microdosimetric spectrum of a particle depends, of course, on the *V* size of the biological structure. Therefore, the same mono-energetic ion beam gives rise to different microdosimetric spectra in volumes of different size. If the destruction of a given biological structure causes a higher probability of cell death, the microdosimetric spectrum in the volume occupancy *V* of this biological structure is likely the correct description of the physical events that will cause eventually the biological effect.

2.1.2 The microdosimetry model

The microdosimetric model assumes that the quality of the radiation action, namely the biological effect per unit of absorbed dose, depends only on the single-event imparted-energy ε_1 to the critical biological site. Moreover, the model claims that ε_1 measured by a microdosimeter is equal to ε_1 in the biological site if the microdosimeter sensitive volume is tissue-equivalent and the product of its geometrical thickness by its density is equal to the critical biological-site thickness (the tissue density is assumed to be 1 g/cm^3), see Fig. 4. The ε_1/m ratio, where *m* is the mass of the biological site is called *specific energy of single event* and it is written z_1. Repeated measurements of z_1 give rise to a spectrum of values, the average of which is called frequency-mean of z_1 and it is written $\bar{z}_{1F}$. This average has the same physical dimensions of the absorbed dose *D*, but not its value, since the latter does not depend on the *V* size, unlike $\bar{z}_{1F}$.

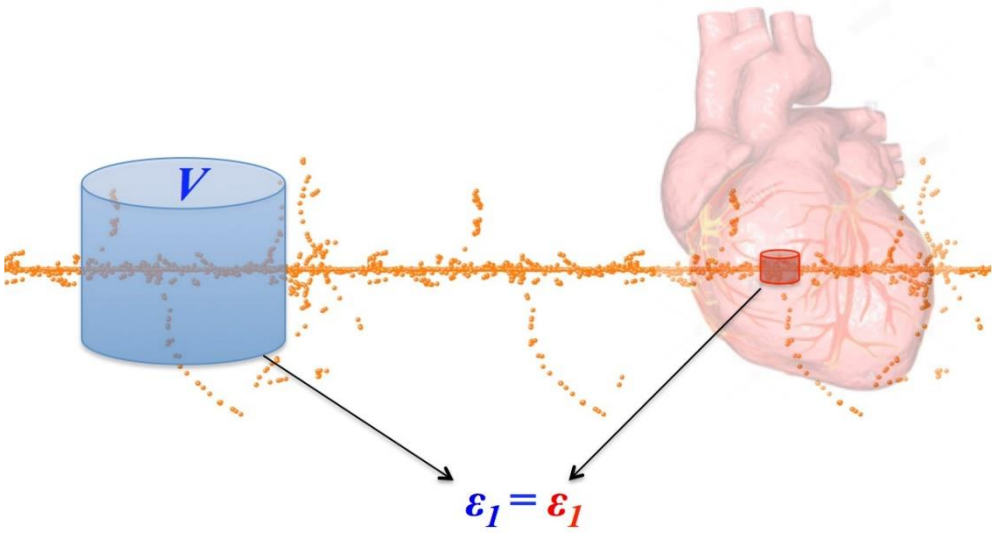

Figure 4. The microdosimetric model claims that the imparted energy of a single particle to the detector sensitive volume (left side of the figure) is equal to the imparted energy to a tissue volume of the same mass-thickness (right side of the figure). The two volumes in the figure are not in scale. In a gas detector

for instance, the detector sensitive volume is about 1,000 times larger than the tissue volume, since the tissue-equivalent gas that fills the detector is about 1,000 times less dense that the tissue density.

The ratio $\varepsilon_1/\bar{l}$, where $\bar{l}$ is the biological site mean-chord length, is called lineal energy, y. Similarly to z_1, repeated measurements of *y* give rise to a spectrum of values, the average of which is called frequency-mean of *y* and it is written as $\bar{y}_F$. The frequency-mean lineal energy has the same physical dimensions of *LET*, but not necessarily the same value. In fact, the *LET* value does not depend on *V*, since it is defined in a point, unlike $\bar{y}_F$.

Since the mean effect (for a given biological end-point) of an ion impinging a living cell is expected to be always the same, while both $\bar{z}_{1F}$ and $\bar{y}_F$ depend on *V*, it is legitimate to ask whether the value of *V* has a radiobiological meaning (e.g., if the size of *V* can be interpreted as the size of the "critical" living-cell structure, like the heart for a human being). If such a critical site really exists then the microdosimetric spectrum in its volume *V* would be more correlated to radiobiological data than microdosimetric spectra in volumes of different size.

2.1.3 Microdosimetric detectors

Microdosimetric detectors can be based on gas counters or on solid-state counters. First microdosimeters were gas proportional counters made with tissue-equivalent plastic and filled with tissue-equivalent gas mixtures. Because of that, they were called TEPC (tissue-equivalent proportional-counter). Afterwards, microdosimetric detectors made of silicon and artificial diamond were developed. TEPCs have high detection efficiency, since they can detect also few ionisation events thanks to the electron multiplication in the filling gas. However, they need high voltage to work, accurate gas pressure control, energy calibration and they cannot operate in very high-intensity radiation fields, since their geometrical size is hardly less than 1 mm. Although this geometrical size is much larger than the relevant biological structures mentioned in section 1.1.1, appropriate rescaling according to the different densities of gas and tissue-equivalent material leads to an effective size of these counters in the order of micrometres. Solid-state microdosimeters have instead lower detection efficiency (they can detect ε_1 only when the imparted energy produces several thousands of ionisation events in the detector) and are poorly or not at all tissue-equivalent. However, they need only low voltage to work and their geometrical size can be as small as 1 µm, making them fit to operate also in very intense radiation fields.

2.1.4 Microdosimetric spectra to monitor significant clinical parameters

The microdosimetric spectrum can be mathematically processed to obtain the dose-distribution of *y* and then its average, which is called dose-mean of *y* ant it is written $\bar{y}_D$. Differently from $\bar{y}_F$, which gives the mean value of all measured *y* values, the $\bar{y}_D$ is the dose weighted lineal energy.

Recent advances in TEPC technology has allowed to perform measurements with the proton beam of CATANA (62 MeV protons used to treat ocular melanoma treatments) with high spatial precision. $\bar{y}_D$ values measured in different points were compared with *LET* values calculated in the same points. The difference between the two sets of values has been resulted to be less than 5%. It is also possible to process the same microdosimetric spectra to calculate the *RBE* for crypt cell regeneration after 8 Gy of

dose on living rats. This possibility arose from the findings of a previous European project, which had compared radiobiological end-point data (which have only 3% uncertainty) with the microdosimetric spectra measured in the same radiation fields, namely gamma, proton and fast neutron. The result of that project was an analytical function, which can be used "to weight" microdosimetric spectra to assess the *RBE* of the radiation field. This assessment is called RBE_{micros} to distinguish it from *RBE*, which is the result of a real radiobiological measurement.

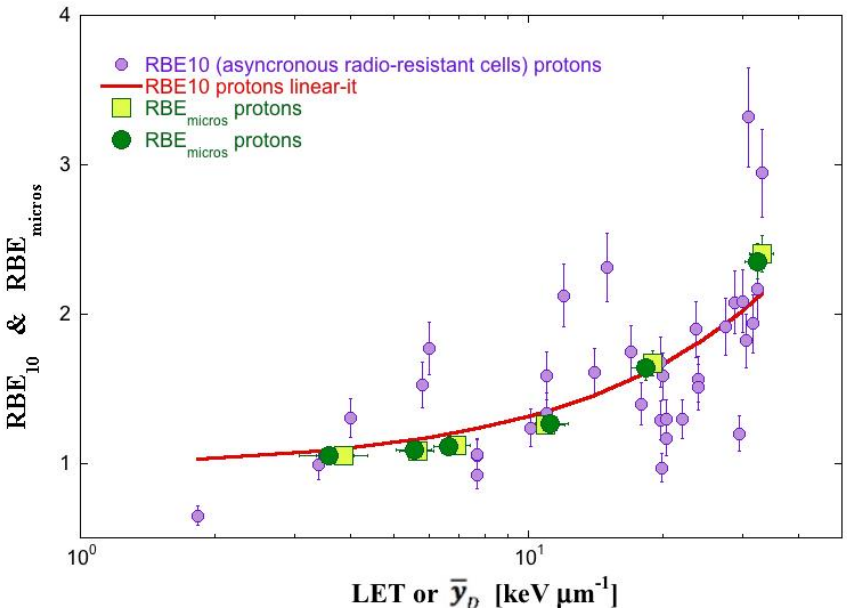

Figure 5. RBE_{micros} (squares and circles) versus measured $\bar{y}_D$ (TEPC measurements in 1µm site) and biological RBE_{10} (violet circles) against calculated LET values. The red line is the linear best fit of RBE_{10} data. The green squares and circles point out two different shifts of measurements 4 months apart. Source [7].

In figure 5, the RBE_{10} of protons of figure 1 and the RBE_{micros} measured at CATANA are plotted against the calculated *LET* values and against the measured $\bar{y}_D$ values respectively. Microdosimetric values almost superimpose the linear best fit of radiobiological data (red line). This finding suggest that microdosimetric spectra in a volume *V* of 1 µm of tissue-equivalent thickness are able to monitor the biological quality of therapeutic proton beams with about 5% of accuracy. However, as indicated by the shift of the *RBE*(*LET*) dependence between protons and carbon ions shown in Fig. 3, the transfer of the microdosimetric method to characterise the RBE of carbon ions would require another weighting function, which is not yet available.

Nowadays, the dose correction factor is kept constant at any depth in the patient tissue, because of the difficulty to monitor with accuracy its variation. Gas proportional counters, constructed with tissue-equivalent materials, have proven to be capable to monitor the biological efficiency of protons of different LET values with about 5% of accuracy. This new technological possibility could significantly improve the therapeutic gain of proton beams.

2.1.5 Microdosimetry and new acceleration modalities: An outlook

The paragraphs above focus is on the existing therapeutic proton and carbon-ion beams based on synchrotron and cyclotron acceleration. However, there are new challenges linked to upcoming novel acceleration systems that will be available in the field of ion-beam therapy [8]. There are several studies which investigate unconventional modalities which potentially could change the scenario of future treatment modalities. These include the use of ions different from hydrogen and carbon, the development of laser-driven ion beams, the use of high-dose-rate and high-intensity beams enabling the "Flash" irradiation scheme, biologically-enhanced treatment modalities, radioactive beams, and collimated microbeams. Also, Boron Neutron Capture (BNC) and recently Proton Boron Capture (PBC) modalities are the focus of radiobiological, dosimetric, and microdosimetric studies for therapeutic application.

Unconventional and innovative ways of accelerating particles and using them for therapy, require also re-thinking of the characteristics of the detectors used for dosimetry and for radiation quality assessments. For some of the novel radiation modalities, the delivery may foresee very high dose-rates. This means that the dose necessary to kill the tumour cell is imparted in very short time intervals: one thousandth of a second is the case of linear ion accelerators, less than one billionth of a second is the case of laser-driven ion accelerators. For other modalities, the radiation fields show exceptionally high gradients, as in the case of micro-beam radiation therapy, where regions of high-dose and low-dose are alternated in sub-millimetric patterns. Finally, for other modalities, ionisation characteristics show additional complexities in generated particle types and energies, as in the case of antiproton beam therapy, resulting from the collision of matter and antimatter.

The assessment of radiation quality for unconventional therapeutic ion beams is a topic of increasing interest. In the framework of microdosimetry, as it is described in section 2.1.2, the radiation quality is described using the spectra of lineal energy, which require collecting the individual energy imparted by a single particle in the detector. For the very high dose rates, this is possible only by reducing the physical size of the microdosimeter. Detectors with physical sizes of the order of one micrometre have been produced and this could provide a partial solution for moderately high dose rates as the linear ion accelerators and the micro-beam irradiation. At the highest particle fluences of the laser-driven accelerators, the collection of single events distributions is not possible and other methods should be considered. One solution could be obtaining an indirect, non-spectrometric characterisation of $\bar{y}_D$, using the method of the variance-covariance technique. Through complex mathematical equations, it is possible to estimate the moment $\bar{y}_D$, also when several particles reach the detector simultaneously. The method of variance-covariance was elaborated more than thirty years ago and, although it provides an information less complete than the conventional microdosimetric test, it has the advantage of having a simple experimental implementation. This is proven by the fact that detectors based on variance-covariance method were carried on airplanes to estimate the radiation quality during transatlantic flight and they were contained in the size of a small suitcases [9,10].

2.2 MONTE CARLO IN ION-BEAM THERAPY

2.2.1 The background

Application of ion beams for tumour therapy requires the precise knowledge of energy deposition and dissipation in tissue on different scales. On the largest, macroscopic scale, general properties like the depth dose distribution, including effects of scattering and fragmentation, are required in order to determine the irradiation parameters for an optimal conformation of the dose to the target volume. On the microscopic scale, the energy deposition distribution of secondary electrons released from interaction of primary ions with the target material is of utmost importance for the characterisation of the increased biological effectiveness of ion beam radiation.

The optimisation of the treatment parameters for optimal dose conformation in general is achieved using analytical and/or semi-empirical physics models, allowing high calculation speed and thus sufficient number of iterations within the optimisation process.

However, application of these codes is based on certain idealisations and simplifications, leading to limitations e.g. in cases determined by a high grade of heterogeneity of the tissue composition. In these cases, Monte Carlo, MC, approaches that are based on detailed simulations of the penetration of individual ions through tissue material, are expected to achieve a higher accuracy, although at the price of substantially higher calculation times, preventing their application in optimisation for treatment planning. MC codes are thus frequently used in combination with analytical/empirical models, i.e. the latter are used for the optimisation, and MC codes are then used for a more detailed recalculation of the optimised plan.

Monte-Carlo programmes used for medical applications are typically based on codes that are originally developed for pure physics applications, like e.g. simulation of detector setups in the framework of nuclear physics experiments, as they are performed at large accelerator facilities. Examples of these codes are GEANT4, FLUKA or PHITS; they all represent general purpose programmes able to tackle the issues relevant for ion beam therapy, as for example the characterisation of the scattering and fragmentation processes resulting from nuclear interactions when ions penetrate tissue. They may differ, however, in the details of the physics models used for the description of these processes, and therefore, the choice of the optimal MC programme depends on the specific scientific aspect that is to be modelled. Resulting from the rising interest of the medical physics community in these approaches, specifically designed modules / toolboxes for medical applications are available for these MC programmes.

As for the macroscopic level, also the description of the physics processes on the microscopic level that govern the biological radiation effects can be modelled using analytical, empirical or detailed Monte-Carlo models. For Monte Carlo models, the description of the release of secondary electrons by the primary ions is an important first step in the chain of processes leading to biological damage like e.g. DNA double strand breaks. However, additional processes like the production of chemically reactive radicals and their diffusion in the cellular medium have to be taken into account in order to realistically model the biological damage induction.

An example of a Monte Carlo code specifically designed for modelling ion beam radiation effects is PARTRAC that is used to model a broad variety of biological effects from DNA DSB induction up to the formation of chromosome aberrations. More recently, attempts are made to also extend the above mentioned general purpose physics Monte-Carlo programmes like GEANT4 towards applications in the field of radiation biology; for example, the GEANT4-DNA toolkit includes modules for modelling of biological damage induced by ionising radiation at the DNA scale.

2.2.1.1 The Monte Carlo approach

'Event-by-event track structure' simulations can be very helpful in understanding the action of radiation in biological targets because they can represent a starting point for the development of models based on the energy deposited at the nanometre scale. Unfortunately, this simulation approach cannot be used for the treatment planning in radiotherapy, due to the enormous number of interactions involved and the consequent high computational time required. A 'condensed story' approach can be applied as alternative. This approach is very efficient but an obvious consequence is a loss of information. A good compromise between 'condensed story' and event-by-event track structure code is the integration in condensed-history Monte-Carlo codes of calculation results carried out using event-by-event track structure code.

The potentialities of GEANT4 in this procedure are presented here to calculate the cell Survival Fraction, *SF*, of in-vitro cells exposed to a proton-beams radiation and the *RBE*. The Linear-Quadratic (L-Q) model provides the fraction of cell surviving the radiation as a function of the linear value (*D*) and the quadratic value (D^2) of the dose. It is out of the scope of this document to examine the details of this function, which is widely discussed in literature [11]. The analytical expression of the SF based on the L-Q model is the following:

$$SF = e^{-(\alpha D + \beta D^2)}$$

which shows how the number of cells surviving the irradiation decreases exponentially depending of the dose. The parameters α and β depend on the cell type and the type of radiation.

The potentialities of Monte Carlo codes for the estimation of the radiobiological damage are presented as an alternative method to evaluate the biological effect considering the physical characteristics of a beam (i.e. particles species and energy spectra) and to be applied to the proton therapy treatments. The flowchart of the algorithm implemented is reported in Fig. 6.

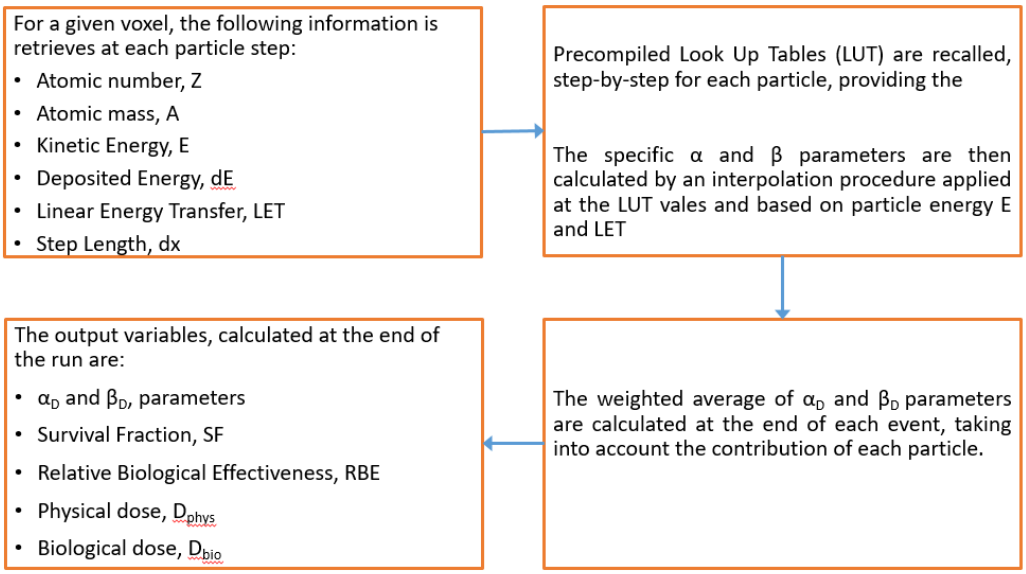

Figure 6. Outline of the main steps to compute the RBE coupled to GEANT4.

The α_D and β_D parameters are calculated in a geometry subdivided in small volumes of water simulating a phantom placed at the end of each beamline. The LET value of any primary ion and of the secondary particles, generated in each slice of the phantom is retrieved at each simulation step. The corresponding values of α_{Di} and β_{Di}, for each specific radiation type *i* with a released dose D_i, are calculated by linear interpolation of α_D and β_D values inserted in specific Look-Up Tables (*LUT*). All interpolated α_{Di} and β_{Di} are then weighted to derive the average values $\langle\alpha_D\rangle$ and $\langle\beta_D\rangle$ in each slice. This approach allows taking into account, at run time, the complexity due to the presence of a mixed radiation field. The final value Survival Fraction curves are then calculated according to the Linear-Quadratic model:

$$SF = e^{-(\langle\alpha_D\rangle D + \langle\beta_D\rangle D^2)}$$

An international collaboration was established to validate the code with different cell lines irradiated in the same facility: the CATANA (Centro di Adroterapia ed Applicazioni Nucleari Avanzate) proton therapy facility of INFN-LNS (Catania, I). The comparison with the experimental data obtained by irradiating a sample of cells U87 was in different positions along with the 62 MeV proton SOBP Bragg peak.

2.2.2 Algorithms to compute the Linear Energy Transfer

As it is described in the following section 2.3, the biological outcomes of ion-beam radiotherapy are not only derived from the macroscopic measure of physical dose but are related also to the microscopic pattern of energy deposition. Different radiations produce different energy patterns and these characteristics are known as the radiation quality. In general, the physical quantity used to describe the radiation quality at cellular level is the *LET*. The experimental descriptions of the radiation quality is established the field of microdosimetry, discussed in section 2.1. Since the 1950's many strategies to estimate this quantity with the highest possible precision were adopted. Microdosimeters and nanodosimeters, as well as dedicated algorithms, were developed to this scope. In this framework, Monte Carlo simula-

tions have revealed to be a valuable method to simulate the components of a clinical beam and to estimate, according the LET, also in a biological effectiveness. Nowadays, more than one Monte Carlo based algorithms are known.

2.2.2.1 A practical approach for LET calculation

Monte Carlo simulations offer a very powerful solution to obtain local energy spectra in a given geometry making use of the information retrieved step-by-step along particle tracks. GEANT4 hence permits a precise calculation of the ratio between the total energy deposited and the total track lengths from all primary charged particles interacting with a given material, this information is necessary for a precise and reliable estimation of the LET of the radiation in a medium. Dedicated applications calculate the LET by using the GEANT4 Monte Carlo code and compute the dose-averaged LET, L_D, and track-averaged LET, L_T. Specifically developed algorithms produce results independent from the simulation transport parameters such as voxel size, secondary particle threshold, and step length. The values of dose- and average track-averaged LET, L_D and L_T, are estimated using these algorithms. A validation process is ongoing to verify the accuracy in a clinical environment.

2.2.2.2 An international collaboration to validate the code

An international collaboration was established to perform the experimental measure of the LET along a clinical SOBP for eye proton therapy. The microdosimetric spectra will be assessed at the same depths thus providing a physical characterisation of the radiation field at several irradiation points. Four different microdosimeters were employed, a tissue-equivalent proportional counter with geometrical size lower that 1 millimetre called 'mini-TEPC' developed at INFN laboratories in Legnaro [12], a silicon detectors SOI MicroPlus developed at the University of Wollongong [13], a monolithic silicon telescope developed at the Politecnico di Milano [14], and an avalanche confinement TEPC also developed at the Politecnico di Milano [15].

The mini-TEPC (see Fig. 7) and the SOI MicroPlus probe of CMRP (see Fig. 8 and 9) allows microdosimetry measurements with high sensitivity (full LET range) in high beam intensity.

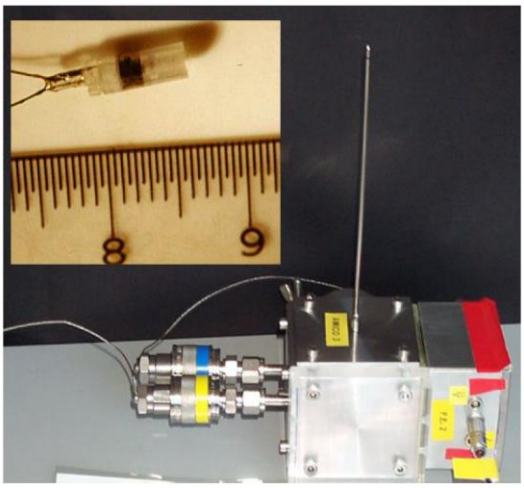

Figure 7: The mini-TEPC; the bare detector (left insert) and the whole set-up, inclusive of the case for front-end electronics and connectors for the gas flowing.

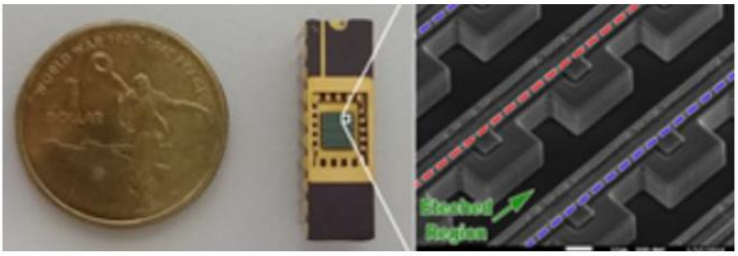

Figure 8: MicroPlus probe; the sensitive area (left insert) and the whole set-up, inclusive of the board (right insert)

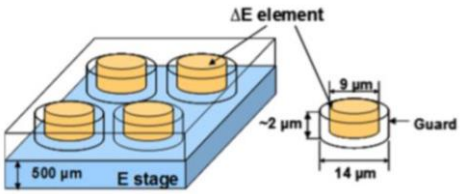

Figure 9: Sketch of the segmented silicon telescope.

The avalanche confinement TEPC is capable of measuring fluctuations of the imparted energy in sites from 300 down to 25 nm. Monte Carlo simulations of the whole experimental set-up, including the physical characteristics of the proton beam, were implemented using the GEANT4 toolkit.

2.3 TREATMENT PLANNING MODELS

Besides the different **macroscopic** physical properties of ion beams as compared to conventional photon beams, they also substantially differ in their **microscopic** pattern of energy deposition. Whereas photons deposit their energy homogenously distributed throughout the irradiated volume in numerous small energy events, ions deposit their energy preferentially in a narrow region along the trajectory of the ions (Fig. 10).

This concentrated energy deposition pattern is the major cause of the increased RBE of ions, as it leads to a high density and corresponding clusters of DNA damage, which are more difficult to tackle by the cellular repair system as the more sparsely distributed damages as induced by photon irradiation.

Since the pattern of energy deposition depends on the ion species as well as the ion energy, also the RBE varies with these physical parameters of the ion beam. Furthermore, physical parameters like the dose level as well as biological parameters characterising the particular cell or tissue system affect the increase of RBE. Because of these complex dependencies, it is not feasible to determine experimentally the RBE values for all potentially relevant combinations of the above-mentioned parameters. Instead, biophysical models are required to allow for the corresponding interpolation / extrapolation and prediction of RBE in treatment planning.

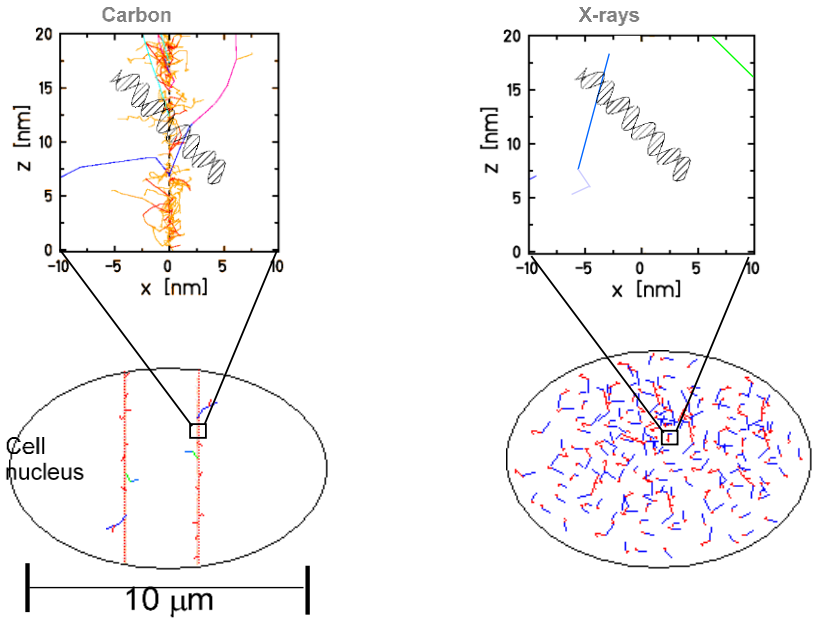

Figure 10: Schematic representation of the microscopic energy deposition of ions (left) and photons (right) as compared to the dimensions of the DNA double helix (top) and the cell nucleus (bottom). Ion radiation is characterised by a localised energy deposition distribution along the particle trajectory, concentrated on a scale corresponding to the dimension of the DNA double helix, whereas for photon radiation the energy depositions are randomly distributed throughout the cell nucleus.

The transition from the initial energy deposition to the final observable biological effect after a radiation insult includes numerous complex biological processes and pathways, from which many are still unknown or at least not yet accurately quantified, and any model thus can represent an approximation to reality only. One of the major challenges of modelling in the framework of treatment planning therefore is to find the right balance between accuracy and model complexity, i.e. number of different processes and mechanisms to be taken into account. A higher level of detail corresponds to an increasing number of degrees of freedom by introduction of additional parameters. If, however, the number of degrees of freedom is too high, no significant parameter values can be expected any more from fitting the model to experimental data. In contrast, if a model has too few degrees of freedom, the model is incomplete, resulting in a reduced predictive power of the model. One has to keep in mind that because of the required approximations different ways of approximation might be feasible, which may lead to similar predictions, even if assumptions about the underlying mechanisms are different.

Different approaches are therefore proposed for modelling in the framework of proton and ion beam therapy, respectively. They differ with respect to the level on which the complexity of RBE dependencies is reflected. For protons, the RBE is only slightly enhanced towards the distal edge of the treatment field, and the dependence on the above mentioned parameters is much less pronounced as compared e.g. to carbon ion beams. Therefore, for modelling proton RBE typically simplified approaches are proposed, which in a good approximation characterise the increased RBE solely as a function of the linear energy transfer (LET) of the particles [16,17]. However, comparing these approaches it has been demonstrated, that predicted RBE values significantly depend on the data sets that are used to calibrate the models, so that the uncertainties are in a similar order of magnitude as the increase in RBE itself [18]. The debate

is therefore ongoing in how far integration of such RBE models in treatment planning for proton therapy will help to improve patient treatments.

In contrast, for carbon ion beam therapy RBE values in general are substantially higher; typical values are in the order of 3, but vary with the physical and biological parameters described above. Therefore, much more detailed models are required in order to take into account the increased RBE in treatment planning as accurate as possible.

At present, different models are used in the Japanese and European facilities. In Japan, the Microdosimetric-Kinetic Model (MKM) is used. The MKM is based on the knowledge of energy deposition in micrometre-sized sub compartments of the cell nucleus and is thus strongly linked to the experimental and theoretical work in microdosimetry, which is described in the following sections. Its original version has been developed by Hawkins [19], and subsequent further developments have been implemented in the framework of the Japanese heavy ion therapy projects and implemented in a treatment planning environment [20,21]. In the meantime, it serves as a replacement for the former experimentally based approach used to optimise the shape of SOBPs in the Japanese treatment planning approach [22].

In the European ion therapy facilities, biological optimisation in treatment planning is based on the Local Effect Model (LEM). Since the establishment of the pilot project for carbon ion beam tumour therapy that had been performed at GSI, the LEM in its original version LEM I [23] had actually been used for planning. However, substantial improvements of the model have been implemented in the meantime, and the model in its recent version, LEM IV [24, 25], has been demonstrated to accurately predict the increased effectiveness of ion beams over a wide range of different ions, energies and biological effects. A key feature of the LEM and its underlying concepts is the characterisation of DNA damage on three different length scales:

- the nanometre scale, related to the induction of double strand breaks in the DNA helix;
- the micrometre scale, related to the interaction of DSB in specific DNA/chromatin substructures;
- the 10 micrometre scale, related to the size of the cell nucleus, representing the critical target for radiation damage to a cell.

Figure 11 shows a comparison of model predictions and experimental data for the RBE of He and C ions at different survival levels. Both the shift of the RBE(LET) curves between He and C as well as the decrease of RBE with decreasing survival level are accurately predicted based on a single set of model input parameters.

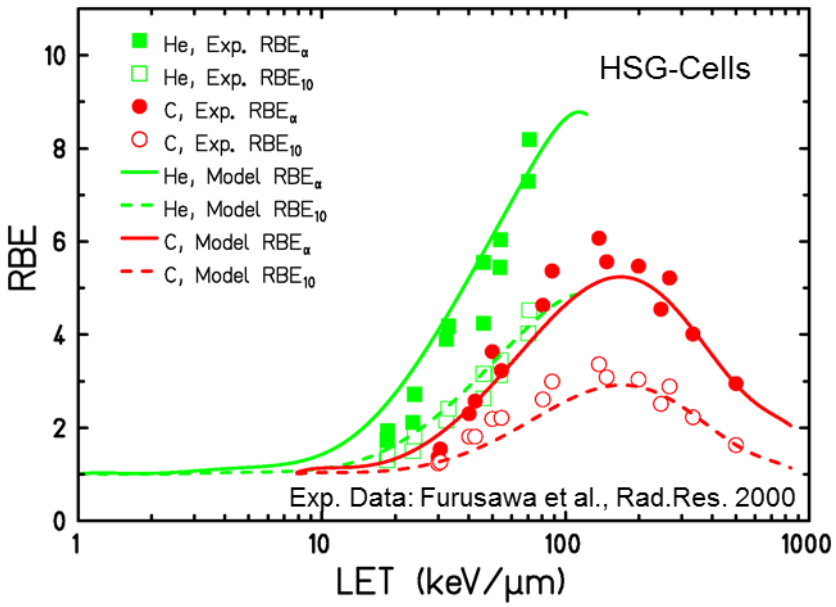

Figure 11: Comparison of LEM prediction and experimental data for the RBE of human salivary gland (HSG) tumour cells after He and C ion irradiation at two different survival levels.

Both the MKM as well as the LEM represent semi-empirical approaches and do not fully simulate the detailed biological processes leading from initial energy deposition to the final observable biological effect. As a key feature, they rather exploit the knowledge of the response to conventional photon radiation, in which all these processes are contained as in a “black box”.

Other models have been also proposed like e.g. the RMF [26], but a comparison with the LEM and MKM indicates that although many general trends predicted by the models appear similar, there are also substantial differences in the quantitative values [27]. Therefore, more detailed comparison and validation by means of experimental data are desirable to allow better assessment of the potential pros and cons of the different models for application in treatment planning.

This also applies to approaches based on Monte-Carlo programmes originally developed for nuclear physics applications, like e.g. GEANT4, aiming at a more detailed mechanistic modelling of the individual steps of the radiation response (e.g. [28,29]). As discussed above, the predictive power of these models is not necessarily higher compared to the semi-empirical models because of the higher number of degrees of freedom and the corresponding parameter uncertainties.

With increasing number of models, systematic comparisons with and validations of t experimental data are of increasing importance in order to allow the choice of an appropriate model for treatment planning. It would be extremely helpful here to agree on a common set of experimental data, which are most relevant for model testing. As a minimum requirement for a general-purpose model, simultaneous prediction of RBE values *in-vitro* for p, He and C ions for different cell lines covering a broad range of sensitivities might be a starting point. Furthermore, applicability to predict RBE values *in-vivo* can be considered as prerequisite for clinical application. However, the choice of the relevant biological effects will largely depend on the specific clinical application, and therefore guidance from a clinical perspective

would be highly desirable here. This also includes the definition of potential gaps in the modelling approaches as well as definition of accuracy requirements, which are needed in order to determine the strategy for potential model improvements.

3. SPECIFIC RESEARCH ACTIVITIES OF MEDINET TASK 2 PARTICIPANTS

The following section is dedicated to an overview of the activities in the member institutions of the MediNet task2 emphasising the specific research developments of nuclear physics computational and experimental tools and are performed in the single home institute and supported by internal resources. The focus is on the research activities on tools promoting the biological effectiveness assessment. The collaborative research activities between different Institutes of MediNet task 2 are highlighted to stress the importance of the networking action promoted by MediNet.

Universidad Complutense de Madrid, Grupo de Física Nuclear

Short description of the activities of the institute (GFN-UCM)

In Madrid there are two facilities for proton therapy under construction, expected to deliver their first proton beams in late 2019-early 2020. They are equipped with IBA and HITACHI accelerators, gantry and delivery rooms. The nuclear physics group (GFN) has established collaborations with both facilities in order to put into play all the knowledge in nuclear instrumentation and simulation available at the group. In fact, Universidad Complutense has joined efforts with Quironsalud and CUN to promote the organisation of the international PTCOG meeting in 2022, which will indeed be held in Madrid after our proposal was selected.

The contribution of GFN-UCM to the topic of interest (nuclear physics tools to support biological effectiveness assessment) is two-fold. Firstly, with the development of an ultrafast, GPU-based hybrid Monte Carlo (MC) code for proton transport (HMC) which is able to calculate proton LET distributions in arbitrary geometries with an execution time about two orders of magnitude lower than currently available, CPU-based general-purpose MC codes. And secondly, with the design, implementation and initial test of a treatment planning scheme (MultiRBE) which would facilitate an inclusion of variable-RBE models in proton treatment planning while preventing loss of physical-dose coverage of the target with respect to uniform-RBE schemes.

Contributing to Excellence in Monte Carlo simulation: GPU accelerated MC calculations from GEANT4

At the GFN-UCM, we have developed a MC accelerated package which runs in the GPU. It is based on a few precomputed tables in different energies and materials. This way it can incorporate physics models of any standard MC simulation package, such as GEANT4, FLUKA or penH-nuclear. The programme performs a complete MC simulation, with no approximations, and can track any particle considered in the original package. The tables are computed from MC simulations setups designed to obtain the LET of primary particles in different materials at proton energies from 5 a 250 MeV. Besides LET, stopping powers, proton absorption due to nuclear processes and secondary particles (energy and angle) are also stored in tables. Calculation of these tables requires a computer cluster and tables for a new material require about 2 days of calculation in our medium-size 500 cores cluster.

Once the tables are precomputed, these can be used in the GPU code, which then can compute the full MC within seconds. For instance, a simulation of a 1-cm radius pencil beam of 10 million protons of 150 MeV in water takes 30 seconds (0.5x0.5x0.5 mm3 voxels). Furthermore, the code can also fold the proton fluxes on the different materials and compute activation in no additional time. The speed of the code is the same in homogenous or heterogeneous materials, and it is independent from voxel size. As an example, tables with GEANT4 via TOPAS, FLUKA and penH (nuclear and non-nuclear) were derived. The LET tables obtained from the simulations were compared to NIST (National Institute of Standards and Technology) and other reference values, and the results of the GPU MC were benchmarked with the original full MC, with no remarkable differences observed.

Contributing to excellence in Treatment Planning:

Clinical treatment planning protocols for protons recommend a uniform value RBE of protons of 1.1 throughout the treatment field, despite evidence from in-vitro and animal studies that proton RBE increases with LET, causing tissues placed distally to the target location to receive a presumably higher biological dose than estimated. The researchers at GFN-UCM have investigated on a mixed RBE model (MultiRBE), where a uniform RBE is used in the target contours to ensure an adequate tumour coverage in terms of physical dose, but a variable RBE is used elsewhere. This model was implemented in the open-source treatment planning system matRad and several example cases were planned and subsequently evaluated in terms of physical dose coverage (V95%) and variable RBE-weighted dose in organs at risk and normal tissue complication probabilities (NTCP), where prediction models were available. The planning algorithm showed potential for reducing the biological dose in organs surrounding the planning target and thus decreasing the probability for complications in normal tissue (by up to 62%), without compromising the target coverage or homogeneity in terms of physical dose, as a result of a smarter redistribution of dose among the surrounding tissues with regard to the optimisation constraints.

GSI Helmholtzzentrum für Schwerionenforschung

GSI Biophysics department has been involved in the pilot project for carbon ion tumour therapy, that has been performed at GSI in cooperation with the University Clinics Heidelberg, DKFZ Heidelberg and FZ Rossendorf from 1997 – 2008. After finalisation of the pilot project and translation of the patient treatment activities to the Heidelberg Ion Therapy (HIT) facility, GSI Biophysics is still very active in many research and development activities related to ion beam tumour therapy, comprising – among others – biophysical modelling and treatment planning.

Biophysical Modelling

One of the major activities is the development and validation of models applicable for biological optimisation in ion beam treatment planning. The Local Effect Model (LEM) in its most recent version (LEM IV) has been extensively used for tests, planning studies and comparison with experimental data in-vitro [30,31,32] and in-vivo [33,34,35].

A major focus of the modelling activities was to validate the general concept of the LEM, which is based on the classification of DNA damages according to the clustering properties in specific chromatin structures, so called “chromatin loops”. The same concept has been shown to be applicable to photon radiation, allowing to correctly reproduce e.g. dose rate effects [36,37], DNA damage re-joining kinetics

[38,39], cell cycle and repair pathway dependencies [40], the increased effect of ultra-soft X-rays [41] and mixed photon-ion radiation [42], giving further support for the LEM concept.

A major breakthrough was achieved in cooperation with groups from Hochschule der Bundeswehr in Munich, Ludwig-Maximilians Universität LMU and Technische Universität München TUM, where the role of the micrometre-size clustering of DSB could be explicitly demonstrated by comparing broad beam irradiation and focused irradiation with low-LET proton beams [43].

Current activities focus on further extension of applications e.g. to predict the induction of cell transformation in-vitro and in-vivo, aiming at the estimation and comparison of secondary cancer induction risks resulting from proton and heavier ion beam radiotherapy.

Comparison to other models like the MKM and RMF have been performed in order to highlight potential differences that might be relevant for therapeutic applications [44].

Biologically Optimised Treatment Planning

A major topic in treatment planning studies is to test other ions, for example heavier ions like oxygen which are expected to show advantages in the case of hypoxic tumours [45], or lighter ions like Helium which have advantages for cases where better conformation as for protons is required, but increased biological effectiveness does not further contribute [46,47].

In order to tackle the problem of hypoxic tumours two different approaches have been investigated: the "kill-painting" approach and the multiple-ion approach. In the kill painting approach, the aim of treatment planning is to achieve homogenous cell killing throughout the target volume even under circumstances of heterogeneous distribution of sensitivity. Higher doses are thus put e.g. into hypoxic regions of the tumour, and the feasibility has been demonstrated by means of in-vitro experiments [48]. Similarly, by using multiple ions, the outer, oxygenated rim of a tumour can be treated with lighter ions like e.g. helium, whereas for the irradiation of the hypoxic core heavier ions like e.g. oxygen can be used, which show a less pronounced oxygen effect. An extension of the TRiP treatment planning system now allows handling simultaneous multi-ion biological optimisation [49]

LNL-INFN. National Laboratories of Legnaro of the Italian Nuclear Physics Institute

The LNL-INFN group is a nuclear research group, which studies the radiation physics application in medicine, namely the interaction of nuclear particles with the biological matter. Two are the research lines: microdosimetry and nanodosimetry.

Microdosimetry

Microdosimetry measures the energy imparted distributions in microscopic tissue-equivalent samples of the size of a living cell or of cell sub-structure. Mixture of organic gases can be used to simulate the human tissue. The LNL-INFN group designs and manufactures tissue-equivalent gas-proportional detectors (TEPC) since the eighties of the last century [50]. Thanks to the pioneering experimental work (performed in collaboration with the University Paul Sabatier of Toulouse) about the electronic avalanche occurring in central electric fields [51,52], the group was able to miniaturise the TEPC with the aim to use it with the intense particle fields of ion beam therapy [53]. These mini-TEPC have been used to study

the imparted energy distributions in a chromosome (1 μm thick sample) in therapeutic proton beams [54,55], showing that these measurements can assess with accuracy the RBE variation with the depth. Mini-TEPCs have been used also to similarly characterise carbon-ion therapeutic beams [56]. The group has developed also gas counters to measure the imparted energy distribution in a chromatin fibre (25 nm) [57]

Nanodosimetry

Nanodosimetry measures ionisation cluster distributions in nanoscopic tissue-equivalent samples of the size of the DNA molecule. The LNL-INFN has designed and constructed detection system to measure the number of ionisation occurring in a nanometric tissue-equivalent site when a charged particle crosses it or it passes nearby [58]. The experimental and theoretical studies [59], performed in collaboration with the PTB Institute in Braunschweig, aim to describe the biological action of radiations at the most fundamental biological level, since the fate of a human irradiated cell likely depends on the primary DNA damage [60].

Vinča Institute of Nuclear Sciences, University of Belgrade

The Vinča Institute of Nuclear Sciences, University of Belgrade (VINS-UB) (http://www.vin.bg.ac.rs/index.php/en/) was founded in 1948 having for aim the basic and applied research for peaceful use of nuclear energy. It is the largest and multidisciplinary national research institution in Serbia. In due course, research gradually also turned to classical aspects of physics, chemistry, biology, power engineering and technology, radiation and environmental protection, materials science, etc. Owing to the multidisciplinary approach, the Institute is capable of responding to the major strategic lines of research defined at the national level: advanced materials and nanoscience, energy engineering and technology, biomedicine and environmental protection. Currently the total number of employees fluctuates around 800, out of which about 300 hold a PhD degree while 200 are PhD students.

The biophysics group of VINS-UB was founded in 1996 and its activities are focused on two separate and complementary activities. Investigation of molecular mechanisms in normal and malignant cells triggered after irradiations with ϒ-rays, protons and carbon ions, as well as with helium and oxygen ions, is one of these activities. The other one is characterised by developments and numerical simulations of GEANT4 toolkit for experimental setup design, evaluation of DNA single and double strand brakes (SSB and DSB) and their comparison with experimental data. The common aim of these activities is to improve treatment protocols for hadron therapy.

Radiobiological studies [61,62,63,64,65,66,67,68,69,70,71,72]

For radiobiological studies performed by biophysics group of VINS-UB, the Monte Carlo simulation toolkit GEANT4 plays an important role at several stages and is extensively used. This approach contributes to the improvement and validation of the toolkit itself. The design of experimental setup for cell irradiations with protons, carbon and oxygen ions as well as alpha particles is done using data of simulations of particle dose, fluence and LET. Obtained distributions as function of depth are indispensable for the precise positioning of targets. In simulations, effects of secondary particles are being distinguished from those that are primary, thus following in a more precise way the events along particle

tracks. Experimentally obtained radiobiological data, survival curves and RBE are compared to the newly developed simulation models that use GEANT4 toolkit to estimate these parameters. In addition, to check and improve GEANT4-DNA, extension of GEANT4 toolkit, experimentally obtained DNA damage (single and double-strand breaks) induced by various radiation species are compared to those obtained by simulations. All these activities are being achieved in close collaboration between VINS-UB, INFN LNS and CNRS IN2P3 CENBG Bordeaux.

Networking and outreach activities

Within the scope of MediNet activities, the biophysics group from VINS-UB together with the team from INFN LNS has organised two international GEANT4 schools at VINS (IV and VIII International GEANT4 School), the first taking place in 2016 while the other in 2019. There were 55 followers (post-docs or researchers) coming from 19 countries, from 5 continents that attended the courses, including 7 experts that gave lectures. Moreover, MediNet midterm meeting was also organised in spring of 2018 at the Vinca Institute of Nuclear Sciences in Belgrade representing the activities of the two MediNet tasks.

EBG MedAustron

The group of MedAustron focuses its activities in two separate and complementary activities: first, the study and development of novel microdosimetric detectors, which are compatible with the stringent requirements of ion-beam therapy, and second, the assessment of methodologies and formalism for an improved characterisation of the microdosimetric outcomes.

Solid-state microdosimeters for ion beam therapy

MedAustron is studying and developing solid-state microdosimeters adapted to the characteristics of the beams used in ion-beam therapy. This is a common project shared with the University Tor Vergata in Rome which develops detector prototypes and it is performed in the framework of scientific collaborations with European research institutes, including other ion-beam therapy facilities, institutes developing silicon microdosimeters, research groups focusing on the development of Monte Carlo simulations, and facilities for micro-beam analysis. An essential process is the IBIC (Ion Beam Induced Charge) analysis performed at the microbeam of the Rudeness Bošković institute in Zagreb. This technique allows investigating the geometrical and electrical characteristics of the sensitive volumes of the solid-state detectors as well to assess the radiation hardness.

The Chemical-Vapour-Deposition single-crystals synthetic diamond microdosimeters are developed in collaboration with University of Rome Tor Vergata [73,74,75]. The process of prototyping of the optimal diamond microdosimeters can be considered completed today: sealed detectors have been tested in dry phantoms and water phantoms in therapeutic proton and carbon-ion beams. A campaign for systematic measurements along and across pristine proton and carbon-ion beams at different energies started in 2019 and it will be completed in two years.

Tests of the silicon telescope developed by Politecnico di Milano were also part of the research activities of MedAustron [76].

The tests performed with solid-state microdosimeters can provide an important link to Monte Carlo simulations. A study was performed in collaboration with Hasselt University and focused on the experimental and Monte Carlo study of the response of diamond microdosimeters exposed to a 241-Am alpha source. The research aimed to assess the feasibility of microdosimetric measurements for the upcoming

proton therapy facility [77]. Other research collaborations foresee the sharing of the raw microdosimetric experimental data provided from MedAustron. The data will be used in the framework of scientific collaborations for computational and simulation purposes.

Methodologies and formalisms for microdosimetry in ion-beam therapy

A research activity performed at MedAustron concerns the elaboration of the methodologies and formalisms to provide univocal and detector-independent outcomes from microdosimeters of different in shape, material, and working characteristics [78,79].

Microdosimetry in the framework of ion-beam therapy is within the group's research. The computational processes used to generate the microdosimetric spectra are not performed in a single way and, the differences between these are, sometimes, incompatible. These processes are -called 'self-calibration' and are based on the recognition of a specific edge on the spectrum, the geometrical assessment of the mean-chord length, the extrapolation of the spectra below the lineal energy values due to the noise cut-off, the transformation of a spectrum collected experimentally with one microdosimeter to the spectrum that would be collected by a microdosimeter of different shape and material. The convergence to a homogeneous reproduction of the microdosimetry outcomes is a prerequisite to be accepted by the ion-beam therapy users. In this framework, the action of MedAustron is to revisit the methodology and the formalisms elaborated in the past for radioprotection purposes which consider the particle crossing the sensitive volume in completely random directions (this condition is named isotropic radiation) and adapt to the peculiar characteristic of the ion therapy beams where the primary ions cross the sensitive volume in parallel trajectories (this condition is named unidirectional radiation). These theoretical studies show that, in general conditions, the microdosimetric spectra collected with slab detectors closely resemble the distributions of LET, for a specific material. Using rather simple analytical tools, it is possible to transform the microdosimetric spectra of solid-state detectors (which have a slab shape) to the LET distributions in different material.

Networking and outreach

The possibility of estimating indirectly and starting from experimental data the LET of a radiation in different material creates a valuable information, which can be compared to the LET distributions provided as output of the Treatment Planning System. This comparison can be performed in simplified experimental conditions for instance collecting microdosimetric spectra at different depth in a (homogeneous) water phantom, as well as in more complex conditions, which mimic the different densities and compositions of the human tissue in anthropomorphic phantoms.

In the framework of the outreach activities and the spreading of good practice, MedAustron together with other members of MediNet Task2, namely University of Hassell, the TU Wien, LNL Legnaro, and non-MediNet partners as the Surrey University and the National Physical Laboratory, NPL in UK promoted the workshop on "Microdosimetry in ion-beam therapy for beginners" (https://medinet.medaustron.at/index.php/Microdosimetry4Beginners). Focusing on five PhD programmes, which start in four European Universities almost simultaneously at the end of the year 2019, the workshop was the first step for coordinating common research activities promoting the complementarity between the research programmes, building on reciprocal experience, and avoiding duplicate. For this, the basic elements are the creation of a 'common language' in microdosimetry in ion-beam therapy and the initiation of collaborations between research groups in the field of microdosimetry applied to ion-beam therapy.

4. CONCLUDING REMARKS

Now, more than 70 years after the initial idea of using proton and heavier ion therapy, ion-beam therapy has eventually reached the critical time of transitioning from a limited number of specialised institutions to many particle-therapy centres worldwide [80,81].

Currently, proton therapy is flourishing with around seventy hadron therapy facilities in the clinical practice. About the same number is under construction or planning [82,83,84] with half of them spread across Europe, thirty-one in the US. Following the pioneering days of Berkeley Lab [85] where carbon and other ions were originally tested, in 1994 the first patient was treated with a carbon-ion beam [86] at dedicated centre at the National Institute of Radiological Sciences (NIRS, Chiba, Japan), which since then has been the pioneer centre for this type of radiotherapy. In Europe carbon ions were employed at first at GSI "Pilot Project" that treated 440 patients with carbon ions resulting in the construction of the HIT facility in Heidelberg, Germany. Since then around 25,000 patients have received the treatment at thirteen centres in Germany, Italy, Austria, Japan, and China. More facilities are under development in South Korea, Taiwan, and France.

This remarkable condition is the result of a well-coordinated effort of all the sectors involved, medical, institutional, private, and technical. In this development, the European scientific community has played, since the pioneering year, an essential role studying the most favourable way of accelerating the ions, conforming the beam to the shapes of the tumours, studying the measuring tools for the control of the treatment parameters, and assessing the effectiveness via computational instruments.

The establishment of ion-beam therapy facility completely developed by private company did not diminished the role of the scientific community, which, at the contrary, created fundamental partnerships with the industrial sectors. After several decades of treatments with accelerated ions, the need of translating the results of physics research into clinical tools remains. The optimisation of the treatments as consequence of the implementation of the scientific results into the therapeutic practice continues to grow.

MediNet task 2 network includes some of the leading European groups in the field, actively contributing to the progress in specific areas of ion-beam therapy. They provide continuous support and optimisation for particle therapy and auxiliary technologies in the specific fields of microdosimetry detectors for the specification of the radiation quality, the modelisation of the radiation action for the accurate planning of the treatment, and the Monte Carlo simulations which link the characterisation of the physical parameters of the beam to the biological effects of the radiation fields. The translation of the scientific results to the clinical routine is still the highest challenges. Nevertheless, there are several successful stories including the implementation in clinical routine of all European ion-beam dual facilities of the modelling for the biological optimisation treatment planning and the growing use of Monte Carlo computations in several steps of the clinical workflow. The networking activities are instrumental for promoting the interdisciplinary discussion and cooperation in these fields. Furthermore, they provides the link between the different communities of nuclear physics of ENSAR2 and the practitioners of the ion-beam centres on the topics of the research on radiations for clinical use

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