Nanodosimetric Track Structure Studies for Applications in Particle Therapy

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presented by
Margherita Casiraghi
M.Sc in Physics, Università degli Studi di Milano - Bicocca
born on 01.12.1981
citizen of Italy

accepted on the recommendation of
Prof. Dr. Antony John Lomax
Prof. Dr. Klaus Kirch
Prof. Dr. Reinhard Schulte
Dr. Volker Dangendorf

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Abstract

Compared to the conventional photon therapy, the irradiation with charged particles allows achieving a superior dose conformity to the tumor, a lower integral dose to the patient, and an enhanced biological effectiveness (for heavy ions). These attractive features have encouraged a rapid diffusion of particle therapy centers over the last decade. However, due to the lack of extensive clinical data and epidemiological studies, the assessment of the biological outcome of this relatively new technique is subject to large uncertainties. Moreover, the standard dosimetric quantities are unable to resolve the differences in the radiation biological effects caused by the features of the track structure produced by particles of different types and energies. On the other hand, the capability of nanodosimetry to describe the radiation track structure produced in biological tissue – or in water as a surrogate of biological tissue – through measurements in low pressure gas, has the potential to overcome the limitations of the standard dosimetric approach.

In this thesis, the use of nanodosimetry to address the radiobiological challenges of particle therapy has been proposed. Monte Carlo simulations have been performed to study the introduction of the nanodosimetric approach for the characterization of the track structure of the mixed radiation fields produced in the patient inside and outside the treatment fields. The radiation tracks simulated in a water phantom irradiated with either protons or carbon ions have been analyzed to obtain quantities related to the radiation-induced damage to DNA. Such quantities have been used to quantify the damage caused by secondary radiation of proton beams relatively to the damage caused by photon irradiation. Moreover, biologically weighted treatments have been obtained by optimizing the fluences of the particle beams in order to create a mixed radiation field with given nanodosimetric parameters within the target volume. The second step of the work has been the development of an experimental device for nanodosimetric measurements in the clinical environment. Experimental measurements have been performed to study the working principle of a novel track imaging detector (TIDe) and to characterize the detector performance. Ions produced by low energy alpha particles in low pressure gas have been successfully detected with a TIDe prototype. However, a low ion detection efficiency – of the order of few percent – has been observed. Further work has been performed to enhance the detector performance by varying the detector geometry and building materials.

This work has demonstrated that the nanodosimetric approach allows the characterization of the complex radiation fields produced in particle therapy with measurable quantities, directly related to the induction of biological damage. Furthermore, the first stages of the development of a detector for the measurements of such quantities have been performed. Finally, the next steps, both theoretical and experimental, necessary for the implementation of the approach in the clinical practice of particle therapy have been identified.
Riassunto

L’adroterapia offre alcuni vantaggi fisici rispetto all’ordinaria terapia con fotoni ad alta energia. Questa tecnica permette infatti di ottenere una distribuzione di dose molto conformata al tumore, la conseguente riduzione della dose integrale erogata al paziente ed un maggiore effetto biologico (nel caso dell’irradiazione con ioni pesanti). Questi vantaggi hanno incoraggiato un rapido aumento, negli ultimi anni, del numero di centri per l’adroterapia. L’effettivo vantaggio clinico dell’adroterapia è però messo in discussione dalle incertezze radiobiologiche legate a questa tecnica. Queste incertezze sono in primo luogo dovute alla scarsità di dati clinici ed epidemiologici sulle conseguenze mediche, sia sul tumore che sui tessuti sani, dell’irradiazione con adroni. In secondo luogo, le quantità dosimetriche normalmente usate in nella terapia con fotoni non descrivono le variazioni statistiche dell’energia depositata in tessuto a livello microscopico che determinano la differenza dell’effetto biologico dei diversi tipi di radiazione. Quest’ultimo problema potrebbe essere risolto con la nanodosimetria. Con questa tecnica è possibile infatti descrivere la distribuzione spaziale dei punti di interazione della radiazione in acqua (utilizzata come surrogato del tessuto biologico) tramite misure in gas a bassa pressione.

In questa tesi viene proposto l’uso della nanodosimetria per ridurre le incertezze radiobiologiche in adroterapia. Utilizzando simulazioni Monte Carlo, è stato studiato come utilizzare la nanodosimetria per caratterizzare la struttura di traccia dei campi di radiazione prodotti nel paziente dall’irradiazione con adroni. Le traccie simulate in un fantoccio di acqua, irradiato con protoni e ioni carbonio, sono state analizzate ottenendo delle quantità nanodosimetriche legate all’induzione del danno primario al DNA. Queste quantità sono state usate per quantificare il danno prodotto dalla radiazione secondaria di un trattamento con protoni, rispetto al danno causato dall’irradiazione con fotoni. Inoltre, è stato possibile ottenere dei trattamenti contenenti l’informazione radiobiologica oltre che l’informazione dosimetrica. Questi trattamenti sono stati creati ottimizzando le fluenze dei fasci di particelle con l’obiettivo di produrre nel target un campo di radiazione con determinate caratteristiche nanodosimetiche. Il secondo passo di questo lavoro è stato lo sviluppo di uno strumento per effettuare misure di nanodosimetria nella pratica clinica. Attraverso misure sperimentali è stato studiato il funzionamento di un rivelatore ideato per misurare la distribuzione spaziale delle ionizzazioni prodotte dalla radiazione in gas a bassa pressione. Le misure effettuate hanno permesso di rivelare gli ioni prodotti da particelle alfa a bassa energia. Allo stesso tempo però è stata riscontrata una bassa efficienza del rivelatore. Le cause della bassa efficienza sono state investigate sperimentalmente variando la geometria e i materiali di costruzione del rivelatore con l’obiettivo di migliorarne la prestazione.

Questo lavoro ha dimostrato che la nanodosimetria permette di caratterizzare i campi di radiazione prodotti in adroterapia con quantità
misurabili che sono direttamente legate al danno biologico causato dalla radiazione. Inoltre, sono stati effettuati i primi passi per lo sviluppo di un rivelatore che possa misurare queste quantità in campo clinico. Infine, sono stati individuati i passi successivi, sia teorici che sperimentali, necessari per l’implementazione dell’approccio nanodosimetrico in adroterapia.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>cDSB</td>
<td>complex Double Strand Break.</td>
</tr>
<tr>
<td>DAQ</td>
<td>Data Acquisition system.</td>
</tr>
<tr>
<td>DSB</td>
<td>Double Strand Break.</td>
</tr>
<tr>
<td>FPGA</td>
<td>Field-Programmable Gate Array.</td>
</tr>
<tr>
<td>G-GEM</td>
<td>Glass-Gas Electron Multiplier.</td>
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<tr>
<td>GEM</td>
<td>Gas Electron Multiplier.</td>
</tr>
<tr>
<td>HV</td>
<td>High Voltage.</td>
</tr>
<tr>
<td>ICS</td>
<td>Ionozation Cluster Size.</td>
</tr>
<tr>
<td>ICSD</td>
<td>Ionization Cluster Size Distribution.</td>
</tr>
<tr>
<td>LEM</td>
<td>Local Effect Model.</td>
</tr>
<tr>
<td>LET</td>
<td>Linear Energy Transfer.</td>
</tr>
<tr>
<td>MC</td>
<td>Monte Carlo.</td>
</tr>
<tr>
<td>MKM</td>
<td>Microdosimetric Kinetic Model.</td>
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<tr>
<td>MPGD</td>
<td>Micro Pattern Gaseous Detector.</td>
</tr>
<tr>
<td>MSAC</td>
<td>Multi Step Avalanche Chamber.</td>
</tr>
<tr>
<td>PB</td>
<td>Pencil Beam.</td>
</tr>
<tr>
<td>PCB</td>
<td>Printed Circuit Board.</td>
</tr>
<tr>
<td>PWBA</td>
<td>Plane Wave Born Approximation.</td>
</tr>
<tr>
<td>RBE</td>
<td>Relative Biological Effectiveness.</td>
</tr>
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<td>RPC</td>
<td>Resistive Plate Chamber.</td>
</tr>
<tr>
<td>RPWELL</td>
<td>Resistive Plate Well.</td>
</tr>
<tr>
<td>SOBP</td>
<td>Spread Out Bragg Peak.</td>
</tr>
<tr>
<td>SSB</td>
<td>Single Strand Break.</td>
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<tr>
<td>THGEM</td>
<td>Thick Gas Electron Multiplier.</td>
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<td>TIDe</td>
<td>Track Imaging Detector.</td>
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Chapter 1

Research background and motivation

1.1 Introduction

Ionizing radiation is extensively used in medicine both for diagnostic and therapeutic applications, delivering the largest contribution to population exposure from artificial sources. According to a recent estimate [9], more than 3.600 million X-ray examinations, 37 million nuclear medicine, and 7.5 million radiotherapy procedures are performed annually worldwide. With these numbers rapidly increased over the last years. The rapid development of new irradiation technologies has the potential to improve the risk to benefit ratio and increase the diffusion of radiation medicine procedures. This calls for a parallel development of increasingly accurate models for the assessment of the radiation effects on the human body.

The effects of radiation interaction with biological tissue have been documented in several radiobiological and epidemiological studies relating macroscopic parameters of the radiation exposure to biological and medical effects. Such studies focus on the exposure to sparsely ionizing radiation such as photons and electrons, which are the most common radiation qualities used in medicine. However, a complete understanding of the radiation effects on biological tissue starting from the initial energy deposition of radiation at the microscopic level to the macroscopic biological outcome is still lacking. Achieving such an understanding is a complex and multidisciplinary task involving studies in radiation physics, radiation biology, radiation chemistry, and medicine. Therefore, despite the centenarian use of radiation in clinical applications, therapeutic medical prescriptions and exposure risk assessments are still based on the macroscopic absorbed dose\(^1\). However, this integrated quantity can not describe the distribution of the

\(^1\)The absorbed dose is defined as the ratio of the energy absorbed in a volume to the volume mass.
energy deposition in microscopic volumes, which depends on the radiation quality\textsuperscript{2} and determines the initial radiation damage. The development of new irradiation techniques using alternative radiation qualities – e.g. high energy ions – calls for the definition of new dosimetric quantities directly related to the initial radiobiological damage. Such quantities should be able to describe the features of the interaction at the microscopic level for different radiation qualities, in order to predict – or at least compare – their biological effect. Nanodosimetric quantities are good candidates to meet this demand.

Nanodosimetry is an experimental technique aiming to characterize the radiation quality with measurable properties of the radiation track structure\textsuperscript{3}. The first attempts to devise nanodosimetric measurements date back to the early 1970s \cite{147}. Few authors have developed this niche discipline, resulting in the realization of only four nanodosimeters worldwide. Nevertheless, the potential of nanodosimetry for biologically weighted dosimetry in particle therapy has recently been stressed (e.g. in \cite{168}, \cite{39}, and \cite{140}) fostering the interest in this technique.

The aim of this thesis is indeed to study the applicability of nanodosimetry to particle therapy. In this chapter, the aforementioned concepts are outlined in more details to provide a background for the motivation of this work. A brief overview of particle therapy is given in section 1.2. In particular, the critical points of this technique that nanodosimetry could address are highlighted. In section 1.3, the relation between the physical description of radiation and the radiation biological effect is described in two steps. First, the radiation biological target and the characteristics of radiation induced damage are briefly described. Secondly, a review of the classical dosimetric quantities is presented and nanodosimetric quantities are introduced. The analytical derivation of nanodosimetric quantities is then given in section 1.4. Finally, in section 1.5, the purposes of this work are presented and the structure of this thesis is outlined.

\section{1.2 Particle therapy}

Radiation therapy is a medical application of ionizing radiation – usually, high energy photons or electrons – for the treatment of cancer. The aim of the therapy is to kill the tumor cells whilst sparing the surrounding normal tissues. In practice, normal tissues are inevitably irradiated causing toxicity and a reduction of the quality of life. The technology developments of the

\textsuperscript{2}The radiation quality is defined as a given particle with a given energy. 

\textsuperscript{3}The track structure of radiation is defined as the spatial distribution of energy transfer points in radiation-matter interaction
recent years focus on improving the dose delivering techniques in order to reduce the normal tissue damage and enhance the tumor control rate. The introduction of high energy ions – mainly, protons and carbon ions – into clinical applications has been a step forward in this direction. The use of particle beams rather than standard photon beams allows to deliver a dose distribution more conformal to the tumor with a consequent larger sparing of the normal tissues [162].

About the 50% of cancer patients are treated with radiations. Of these, over the 80% is irradiated with megavoltage X-rays, the 19% is treated with radioisotpes and only the 1% receives particle therapy [62]. However, the clinical interest in particle therapy has been rapidly growing for the last decade. The number of patients treated with high energy protons and carbon ions has increased from roughly 3000 patients in 2005 to more than 150000 in 2015 [148]. At the time of the writing, 61 proton and 10 carbon ion therapy facilities are in operation worldwide [149].

The superior dose distribution of particle therapy over photon therapy is based on the advantageous depth dose distribution in tissue of charged particles. While photon dose is larger at few centimeters form the patient entrance surface and exponentially decreases with depth in tissue, charged particle dose deposition is localized in a narrow region at the distal end of their range i.e., the Bragg peak. The depth of the Bragg peak can be tuned changing the beam energy in order to hit the tumor location with the dose peak whilst sparing the tissue behind the tumor. In order to cover the entire tumor volume, two different delivery techniques are used: the passive scattering and the active scanning delivery. In the passive scattering delivery, the range of a mono-energetic beam is modulated with a modulator wheel in order to create a uniform dose region in the longitudinal direction called spread out Bragg peak (SOBP). In the transversal direction, the narrow beam is broadened with either a single or dual scattering system. Patient specific collimators and compensators are then inserted into the beam in order to conform the beam to the tumor volume. In the active scanning delivery, the tumor volume is scanned in 3D with a narrow pencil beam. The depth of the Bragg peak is adjusted by tuning the beam energy either at the accelerator or introducing range shifters into the pencil beam. Instead, the lateral position of the pencil beam is controlled by deflecting the beam using modulated magnetic fields [162].

The high dose conformity achieved with particle therapy causes a reduction of the integral dose delivered to the patient compared to photon therapy. This leads to a potential decrease of the late effects – such as secondary cancer induction – caused by the exposure of large volumes to intermediate and low doses. This advantage is however challenged by the contribution of secondary neutron fields created in the interaction of high energy par-
1. Research background and motivation

Particles with the beam shaping elements and the patient body [63]. Due to the complexity of the neutron measurements and the uncertainties on the biological effect of neutron, the contribution of such fields to the long term effects of particle therapy is controversial [163]. Nanodosimetry could play a role in this debate due to its capability to characterize the track structure of arbitrary radiation fields, which determines the initial biological damage. This topic is further discussed in chapter 4.

Another important issue in the use of charged particles is the larger biological effectiveness produced at a given value of absorbed dose compared to photons. In the case of protons, a constant difference of 10% in the biological effect is assumed in the clinical practice. However, the effect may change with increasing penetration depth in the tissue. In fact, due to the decreasing proton energy, more frequent energy deposition events are produced at the distal end of the particle range [138]. For carbon ions the increased biological effect is substantial [162]. The dense tracks produced in the interaction of heavy ions with tissue lead to clustered damages, which are difficult to repair (see section 1.3.1). This aspect could be of advantage for the treatment of radio-resistant tumors. On the other hand, due to the lack of radiobiological and epidemiological studies, the actual biological effect on the tumor and on the normal tissue of such radiation is subject to large uncertainties. These uncertainties need to be addressed urgently, in order to evaluate the actual radiobiological advantage of the therapy with carbon ions or heavier ions [24]. Again, nanodosimetry, along with the development of radiobiological models and clinical studies, could be a tool to reduce those uncertainties. This topic is further discussed in chapter 5.

1.3 Radiation biological effect and track structure

1.3.1 Radiation biological damage

The damage to the deoxyribonucleic acid (DNA) is believed the primary mechanism leading to radiation-induced effects in cells. DNA is a macromolecule contained in the cell nucleus that carries the genetic information for cell functioning and reproduction. The most common DNA structure consists of two polynucleotide strands coiled in a double helix with a diameter of 2.3 nm and a helix turn distance of 3.4 nm. Nucleotides making the DNA backbone are composed of one nucleobase (either cytosine, guanine, adenine, or thymine), a deoxyribose, and a phosphate group. Those entities are bound to each other with covalent bonds. Bases of two opposite strands are bound with hydrogen bonds forming the DNA double-strand structure. The sequence of the nucleobases encodes the genetic information [15].
Radiation directly affects the DNA in the target tissue by ionizing and exciting the molecules along its path, causing breaks of the DNA chemical bonds. Indirect DNA damage is also possible. In this case, charged particles interact with the water molecules surrounding DNA producing hydroxyl radicals, which diffuse away from the track and eventually react with DNA components causing damages. The diffusion length of free radicals is of the order of few tens of nanometers and depends on the cellular environment. For sparsely ionizing radiation, indirect damages cause up to 70% of the total DNA lesions. Conversely, densely ionizing radiation produces a larger proportion of direct damages [96].

Damages to the DNA structure affect the macromolecule replication and transcription leading to cell mutation, malfunction or death. There is a wide range of damages that may be caused either by direct ionization or by radicals. Isolated DNA damages such as single-strand breaks (SSB) have little biological consequences because they are efficiently repaired by the enzymatic repair mechanisms. On the other hand, repair of double-strand breaks (DSB) – consisting in two SSB on opposite DNA strands created within a distance of 10 base pairs (3.4 nm) – is more prone to errors and may lead to cell mutation or cell killing. However, the DSB yield is not directly correlated with the cell radiosensitivity. Complex DSBs – defined as a DSB with at least one additional break within 10 base pairs – and other clustered DNA damages are considered the critical lesions for radiobiological effect. Clustered damages may include combinations of strand breaks and base damages or one of the two damage types exclusively. Increasing of the damage complexity reduces the damage repairability resulting in less frequent but more severe effect to cells [80].

1.3.2 Assessment of radiation biological effect

The conventional dosimetric quantity used in radiation therapy and radiation protection is the absorbed dose. This quantity is measurable with high accuracy and precision. For a given radiation quality, the absorbed dose can be related to biological effects and medical outcomes. Conversely, the same absorbed dose produces different effects for different radiation qualities.

The conventional approach to assess the radiation biological effect is to weight the absorbed dose with factors based on the relative biological effectiveness (RBE). The RBE is defined as the ratio of the absorbed doses required by two radiation qualities to cause the same level of biological effect. RBE values are generally obtained from in vitro experiments and depend on several parameters, both physical and biological, such as particle type and energy, dose, dose rate, cell or tissue type, and cell endpoint. Therefore, the use of this approach in practical applications like radiation therapy
and radiation protection is not trivial. Different methods for obtaining dose weighting factors are used in different disciplines and in different centers for particle therapy. This leads to large uncertainties in therapy dose prescription and radiation risk assessment. The limits of the RBE approach have been pointed out by many authors (see for example [136], [183], [5] and [135]). The increasing diffusion of particle therapy, calls for the definition of new standardized operational quantities for the assessment of the radiation biological effect, that are consistent for all treatment modalities. Given the complexity of the processes initiating the biological damage, different quantities describing the physical and biological dependencies should be defined. Moreover, these quantities should be suitable for routine measurements at the treatment site [140].

The physical component of RBE is related to the radiation track structure and is conventionally characterized with the linear energy transfer (LET) [105]. LET represents the energy transferred to electrons of a medium by charged particles per unit of path length. For a wide variety of effects in mammalian cells, RBE plotted as a function of LET shows an increase to a maximum in the LET region of 100–200 keV µm$^{-1}$ and a fall off for higher LET values. This is a first indication that few dense tracks cause an increase in the biological effectiveness per unit of absorbed dose. The RBE decreasing for higher LET values is then caused by the excessive reduction in the number of tracks delivering the same dose. However, LET, like the absorbed dose, is a macroscopic averaged quantity. Therefore, this quantity cannot describe the stochastic nature of the energy deposition in matter and the difference in the track structure of different radiation qualities. Such differences become important for small target volumes, like cells of micrometric dimensions, for low dose levels, and for densely ionizing radiation. Furthermore, LET does not describe the lateral spread of the track due to delta rays. Despite these limitations, LET is still widely used in many applications as an approximate radiation quality parameter.

Microdosimetric quantities, initially introduced by Rossi in the 1960s [153], fulfill the aim of describing the stochastic nature of radiation interaction at the microscopical level. Several studies have been performed to obtain a correlation of microdosimetric quantities, such as lineal energy and specific energy, with RBE (see for example [114] and [115]). A widely used model is for example the microdosimetric kinetic model, which assumes a linear quadratic correlation between the average number of lethal lesions in a sub-cellular structure and the specific energy imparted to the structure [93], [109]. Microdosimetric quantities have the additional advantage to be directly measurable with microdosimeters (e.g. tissue equivalent proportional counters filled with low density gas [153], [54] or silicon detectors [134], [186]). However, such microdosimeters measure the energy deposition in volumes which are still of the order of few micrometers. On
the other hand, track structure simulations and in vitro experiments suggest that the biologically relevant target for radiation induced damage has dimensions of the order of nanometers rather than micrometers. First results in this direction were obtained by Goodhead et al. already in 1977, observing that ultra soft x-rays producing electron tracks of the orders of few nanometers are highly effective for inactivation and mutation of mammalian cells [79], [53].

After the development of Monte Carlo track structure simulations, it became clear that the critical target for radiation induced damage is the DNA. In particular, the spatial distribution of ionizations produced within the DNA structure is related to the damage complexity and the cell biological outcome. First track analyses showed a correlation between biological effects and energy depositions larger than 100 eV in target dimensions of about 3 nm for low-LET, and depositions larger than 340 eV in targets of 5 nm to 10 nm for high-LET radiation [81]. Furthermore, Brenner and Ward [31] presented evidences of a correlation between the number of ionizations produced in a given target size and DNA damage induction. Comparing experimental data of DNA DSB yields with simulated frequencies of ionization cluster sizes as a function of LET, the authors concluded that clustered damages are caused by clusters of at least two to five ionizations localized in target sizes of 1 nm to 4 nm. Studies performed with more advanced track structure codes, including DNA geometry information, revealed that all radiation qualities are efficient in producing clustered DNA damages and that the damage yield is linear with dose. These results suggest that each damage is produced by a single track. Other studies showed that both the proportion of clustered damage relative to simple damages and the degree of damage complexity are larger for densely ionizing radiation [129], [130], and [71].

These findings motivated the development of nanodosimetry, an experimental technique aiming to measure the size of ionization clusters produced in nanometer-equivalent volumes of low pressure gas. Nanodosimetric quantities are considered among the new candidates for standardized radiation quality characterization in particle therapy [150], [140]. Properties of measured ionization cluster size distributions at the nanometric level can be related to DNA damages and could be used to assess the relative radiation biological effect of different radiation qualities (see chapter 3). First attempts to devise experimental devices using differential pumping techniques for simulating nanometric volumes date back to the 1970s [147]. However, due to the costs of the equipment and the technical difficulties for achieving single ionization counting resolution, only four nanodosimeters exist to date (see section 2.2.1). Furthermore, given the complexity and the large size, such devices are not suited for mass production and routine use in particle therapy facilities. Therefore, the development of the next-generation-nanodosimeters is needed for clinical applications of nanodosimetric con-
1. Research background and motivation

1.4 Theory of nanodosimetry

The development of nanodosimetry originated from the need to overcome the microdosimetry physical restrictions, which limit the minimum size of simulated volumes. Measurements of the energy imparted are indeed unfeasible for volume dimensions of the order of few hundreds of nanometers or smaller. This is due to the fact that secondary equilibrium cannot be established for such small volumes and the W-value (i.e. the average energy per ion pair production) cannot be used to calculate the energy imparted to the site from the measured number of ionizations.

In nanodosimetry, instead the radiation track structure is characterized by measuring the ionization component of the track. The rationale behind this is that the number of interactions is small in nanometric volumes and energy deposition fluctuations are determined by the amount of energy loss per interaction rather than by the number of interactions. Hence, ionization is assumed to be the most relevant interaction due to the larger cross-section compared to other processes [18].

The quantity measured with the currently available nanodosimeters is the ionization cluster size. This quantity is defined as the number of ionizations produced in a given volume per primary particle. This quantity has a stochastic nature; therefore, it is characterized by a probability distribution: the ionization cluster size distribution (ICSD) $P_{\nu}(Q|d)$. This distribution is defined as the probability that $\nu$ ionizations are produced by a primary radiation of quality $Q$ in a volume at a distance $d$ from the primary track. This distribution includes the contribution of the secondary radiation (such as $\delta$-rays) and depends on the target volume geometry. The fluctuation of the ionization cluster size is caused by two stochastic components and it can be described as a compound Poisson process [55] as shown in equation 1.1.

$$P_{\nu}(Q|d) = \sum_{\kappa=0}^{\infty} p_{\kappa}[\kappa(Q)]f_{\nu}^{\kappa}(Q|d)$$

(1.1)

The first component of the process ($p_{\kappa}[\kappa(Q)]$) is the probability that a primary particle produces a number $\kappa$ of primary ionizations. Since the range of the primary particles is much larger than the diameter of the target volume, the primary ionization events belonging to the same track can be
1.4. Theory of nanodosimery

Considered independent and thus described by a Poisson distribution with mean equal to \( \bar{\kappa}(Q) \). \( \bar{\kappa}(Q) \) is proportional to the ionization cross-section of the primary particle. The second component \( f_\kappa(\nu|d) \) describes the fluctuation of the distribution \( P_\nu(Q|d) \) when \( \kappa \) primary ionizations are produced. \( f_\kappa(\nu|d) \) can be written as the \( \kappa \)-fold convolution of \( f_1(\nu|d) \) that is the probability normalized to unity to measure a total cluster size \( \nu \) (including the contribution of \( \delta \)-rays) when a single primary ionization occurs. Therefore, equation 1.1 becomes:

\[
P_\nu(Q|d) = \sum_{\kappa=0}^{\infty} \frac{e^{-\bar{\kappa}(Q)}[\bar{\kappa}(Q)]^\kappa}{\kappa!} [f_1(\nu|d)]^\kappa
\] (1.2)

From equation 1.2, it is evident that the measured probability of cluster size formation is related to the probability of cluster size formation in the case of a single primary ionization. It can be shown (see De Nardo et al. [55]) that the moments of the single primary ionization distribution are related to the cumulants of the compound process. In particular, the first and the second cumulant are the mean and the variance of the measured ionization cluster size and are related to the moments of the single-ionization distribution according to:

\[
M_1(Q|d) = \bar{\kappa}(Q)m_1(Q|d)
\] (1.3)

\[
M_2(Q|d) - [M_1(Q|d)]^2 = \bar{\kappa}(Q)m_2(Q|d)
\] (1.4)

with

\[
M_\nu(Q|d) = \sum_{\nu=0}^{\infty} \nu^\nu P_\nu(Q|d)
\] (1.5)

\[
m_\nu(Q|d) = \sum_{\nu=0}^{\infty} \nu^\nu f_\nu(\nu|d)
\]

Both expressions include the mean number of primary ionizations along a relevant path segment of a primary particle, which is not directly measurable. As a result, the cumulants derived from the measured distribution cannot be used to separately determine the moments \( m_\nu(Q|d) \) of the single-ionization distribution. However, the ratios of the moments of the single-ionization distribution can be obtained from the ratio of the cumulants of the measured ICSD. For instance, the ratio of the first two moments of the single-ionization distribution can be obtained from:

\[
\frac{M_2(Q|d)}{M_1(Q|d)} - M_1(Q|d) = \frac{m_2(Q|d)}{m_1(Q|d)}
\] (1.6)

This quantity describes the fluctuation of the cluster-size formation due to
1. RESEARCH BACKGROUND AND MOTIVATION

![Figure 1.1: Left panel: simulation of a 10 MeV alpha particle track in water. The target is a cylindrical volume of water of 2.3 nm diameter and 16 nm height and the impact parameter is \( d = 0 \). Right panel: ICSDs simulated in water for different radiation qualities. Simulations were performed with Geant4-DNA track structure code [101].](image)

electron emission and transport in the case of a single primary ionization.

In figure 1.1, examples of ICSDs produced by different radiation qualities in a water cylindrical volume of nanometric dimensions are shown. The different shapes of the distributions characterize the track structure of the different radiation qualities.

1.5 Aim and outline of the thesis

This thesis investigates the use of nanodosimetry to address the radiobiological challenges introduced by the radiation therapy treatment with high energy ions. The work is organized in three major parts:

- the theoretical and experimental state-of-the-art of nanodosimetry was reviewed and groundwork was performed to understand the potential and the limits of this technique and to study the feasibility of the project;
- in silico studies were performed to introduce physical quantities related to radiation track structure in clinical dosimetry;
- a novel detector was characterized and further developed for measurements of nanodosimetric quantities in particle therapy.

The background of this work is presented in chapter 2. First of all, the state of the art of nanodosimetry is reviewed. The characteristics of the existing nanodosimeters are described and the literature studies aiming to relate nanodosimetric quantities with the biological damage of radiation are presented. In the second part of the chapter, a brief overview on Monte Carlo track structure codes is given. More emphasis is given to the codes used in this work, describing the physical processes implemented for the transport
of low energy charged particles in matter. In the last part of the chapter, the background of the experimental part of this work is presented. Basics on the physics of gaseous detectors are provided. The working principles of existing detectors with characteristics similar to the detector developed in this work are also described.

Chapter 3 deals with the groundwork for this thesis. The theoretical challenges for the introduction of nanodosimetry in particle therapy are outlined and discussed. A track sampling approach to obtain nanodosimetric information from simulated and measured radiation tracks is then presented and preliminary applications of the approach are shown.

In chapters 4 and 5, simulated applications of nanodosimetry in particle therapy are presented. Two aspects of the particle therapy treatment were studied. The first aspect concerns the assessment of the biological effect of the integral dose delivered to the patient in a proton therapy treatment. The mixed radiation field\textsuperscript{4} produced out of the primary treatment field was characterized with nanodosimetric parameters directly related to DNA damage induction. By comparing the nanodosimetric description of the different radiation qualities, the effectiveness of the mixed field was assessed with respect to a reference radiation for which the biological effect is known. The second aspect considered is the optimization of the particle therapy treatment. A new optimization approach was proposed in order to include the energy dependence of the charged particle biological effect into the treatment plan. The approach was tested for the irradiation of a water phantom with protons and carbon ions by optimizing the particle fluence in order to create a mixed radiation field with equal nanodosimetric parameters at different depths in the phantom. This work has been published in Casiraghi M et al. Comput. Math. Methods. Med. 2015 [42].

In chapters 6 and 7, the experimental part of this work is presented. A novel track imaging detector was studied in order to develop an instrument for nanodosimetric measurements in particle therapy. The detector was originally designed by Bashkirov et al. [23] to register arbitrary long segments of radiation tracks produced in low pressure gas. The small size and the versatility of this instrument make it potentially suitable for routine measurements in clinical dosimetry. A prototype of the detector was built and characterized. The detector working parameters were optimized and the prototype performance was assessed by comparing measurements with the simulated detector response. The development of the detector was carried on in order to improve the ion detection efficiency of the device. Part of this work has been published in Casiraghi M et al. Eur. Phys. J. D. 2014 [41], Casiraghi M et al. Radiat. Prot. Dosim. 2015 [42], and Vasi F, Casiraghi M et al. J. Instrum. 2016 [180].

\textsuperscript{4}A mixed radiation field is intended as a field composed by different radiation qualities.
1. Research background and motivation

The thesis ends with a summary of the goals achieved and a discussion on the open challenges for a successful implementation of nanodosimetry in clinical dosimetry for particle therapy. The next steps for the further development of the track imaging detector are also suggested in the outlooks.
Chapter 2

Background and methods

2.1 Introduction

In this chapter, the background of the work presented in this thesis is outlined starting with a description of the state of the art of nanodosimetry. A brief review on the existing nanodosimeters is given in section 2.2.1. Studies present in the literature aiming to relate nanodosimetric quantities measured in gas volumes with the radiation effect in biological tissues – or water as a surrogate of biological tissue – are reviewed in sections 2.2.2 and 2.2.3.

In section 2.3, the track structure codes used for the simulation of the radiation interaction with matter at the nanometric level are described. In particular, the codes used in this thesis work are illustrated in more details.

Finally, a basic overview on the physics of gaseous detectors, useful for the experimental part of this thesis work, is given in section 2.4. Moreover, the working principles of existing detectors with characteristics similar to the Track Imaging Detector developed in this work are described in sections 2.5 and 2.6.

2.2 State of the art of nanodosimetry

2.2.1 Experimental devices

As explained in section 1.4, nanodosimetry aims to characterize the radiation quality by measuring the distribution of the number of ionizations produced in nanometric volumes of biological tissue. As water is the main component of biological cells and integral part of DNA structure [45], this medium is usually taken as a surrogate of biological tissue.
The experimental approach of nanodosimetry is based on the idea that the spatial distribution of the ionization events produced by the radiation interaction with matter linearly scales with the density. As such, microscopic volumes of water can be simulated with macroscopic volumes of low pressure gas. The basic design of a nanodosimeter consists in an interaction region filled with low pressure gas, where the radiation is converted into clusters of electron-ion pairs, and a detection region where single ions or single electrons are accelerated and multiplied in order to be detected. So far, three nanodosimeter models based on this approach have been developed: one based on the detection of single electrons and two detecting single ions.

*The Track-nanodosimetric Counter*

The track-nanodosimetric counter was developed at the Laboratori Nazionali di Lenaro in Italy [55] in collaboration with the Weizmann Institute of Science in Israel [33] and it is based on the detection of single electrons. The device consists in an electron collector corresponding to the detector sensitive volume and a single electron counter comprising a drift column and a multi step avalanche chamber (MSAC). The whole structure is immersed in propane gas at a pressure of about 3 mbar. The sensitive volume is created by a system of electrodes and has a cylindrical shape of both diameter and height equal to 3.7 mm. The electrons created in the sensitive volume by ionizing radiation are transferred into a 17 cm-long drift region in order to separate them in time. At the end of the drift, each single electron is multiplied in the MSAC with a gain of roughly $10^7$. A beam of single primary particles is defined by two collimators positioned in front of a solid-state detector, which triggers the electron signal acquisition. The whole detector structure can be moved with respect to the track main axis – up to a distance of 57 nm at unit density – in order to measure the radial distribution of ionizations within the track. The detector efficiency depends on the collection efficiency of the electrons into the drift and detection regions, and the detection efficiency of the MSAC. An overall detection efficiency of 20% was estimated in [55]. The minimum size of the sensitive volume is limited to roughly 20 nm at unit density due to the ballistic behavior of the electrons, which prevent them to reach the thermal equilibrium within smaller targets.

*The Ion Counting Nanodosimeter*

The the ion counting nanodosimeter was initially developed at the Weizmann Institute [172] and then further developed in collaboration with Loma Linda University in the USA [76]. The collaboration led to the production of two similar nanodosimeters. Due the lower initial kinetic energy and the reduced diffusion of ions compared to electrons, the detection of these particles allows the simulation of smaller sensitive volumes. On the other hand, the detection of ions is more challenging and requires high vacuum conditions. The nanodosieter consists in an interaction volume filled with propane gas at 1.33 mbar and a vacuum detection volume. The two volumes
are connected with a 1 mm diameter circular aperture and the pressure gradient is maintained with a complex double differential pumping system. A system of collimators provides a needle primary particle beam crossing the interaction volume at a given height above the aperture. The ions produced in the low pressure drift towards the aperture under a pulsed drift field and are then extracted into the detection volume by an intense extraction field. Once in the detection volume, the ions are accelerated and individually detected with an ion counter with 90% efficiency. The electric field configuration in the interaction region and the ion transport parameters define the detector sensitive volume. The volume obtained is a candle-flame shaped region extending above the aperture with a transversal dimension of about 3 nm at unit density [166]. The sensitive volume length along the drift direction is varied by collecting the ions within a given arrival time frame. A volume length ranging between 3 nm and 60 nm can be obtained with an extraction efficiency larger than 80%. The nanodosimeter is additionally provided with a silicon tracking telescope for precise localization of the primary beam relative to the aperture axis. As such, ionization cluster size distributions can be measured at different impact parameters in order to characterize the radial extension of the tracks [23]. In recent experiments the nanodosimeter was operated also with nitrogen gas [38].

The Jet Counter
The jet counter was developed at the Soltan Institute for Nuclear Studies in Poland [147]. Similar to the ion counting nanodosimeter, the jet counter is based on the ion counting principle. Conversely, it uses a different strategy for achieving the vacuum conditions for the ion detection; thus, reducing the requirements for the pumping system. In this naodosimeter, the sensitive volume is created by injecting a pulsed jet of gas into a small interaction chamber (IC) with tissue equivalent walls embedded into a larger vacuum region. Within the IC a stable pressure of 1.33 mbar is maintained for a duration of 200 µs. Within this time, the primary beam interacts with the gas (either propane or nitrogen). The ions produced are extracted by an electric field and detected with a single ion detector. The sensitive volume is a cylinder of equal height and diameter and its size depends on the IC dimensions and the density of the gas jet. The latter is determined by measuring the transmission of 100 eV electrons [22]. Sensitive volume sizes between 0.15 nm and 13 nm at unit density were obtained with jets of nitrogen gas. Within such volumes, ions were registered with an efficiency ranging from 50% to 40% depending on the volume size [89]. Similar ion detection efficiency was obtained measuring ionization cluster size distributions in volumes of propane of sizes ranging from 2 nm to 10 nm [22].
2. Background and methods

2.2.2 Equivalence gas-water

The main assumption of nanodosimetry is that nanodosimeters operating at low pressure can simulate ionization yields in biological tissue or at least, in water. The equivalence assumption is valid if the interaction mechanisms of ionizing radiation in gas and in biological material/water are similar. This is already a not trivial assumption as the interaction cross-sections of low energy radiation in biological tissue are in general not known. Some interaction models are available only for liquid water used as a surrogate of biological tissue (see section 2.3). Moreover, it has been shown ([142] and [27]) that even interactions in water vapor are different from those in liquid water. However, larger differences are due to excitation processes that strongly depend on the target species. In the case of ionization cluster formation, differences between media are smaller because the energy distribution of secondary electrons set in motion by impact ionization does not strongly depend on the type of target molecules. For example, in figure 2.1, it is shown that ionization cross-sections in water and propane-based tissue equivalent gas are very similar for alpha particles and for electrons with energies larger than 100 eV. Grosswendt [83] suggests that Monte Carlo (MC) simulations could be used to compare ionization cluster size distributions (ICSD) produced in water and gas media in order to find the correct scaling factor to make the two distributions equivalent. Since the interaction mechanisms in gas are known, measurements can be traced back to primary...

Figure 2.1: Ratio $M_1(Q)/(L \rho) = (N_A/M) \sigma_{ion}(Q)$ of the mean cluster size $M_1(Q)$ and the track length $L$ of primary particles of quality $Q$, within a target volume of density $\rho$, as a function of the initial particle energy. $N_A$ is the Avogadro number, $M$ the molecular mass of the target molecules, and $\sigma_{ion}(Q)$ is the ionization cross-section of the primary particles. The alpha particle energy is expressed as the energy of electrons at the same velocity. Data reproduced from [83].
interaction processes using MC simulations making the proposed approach feasible. Some results of simulations performed by Grosswendt of ICSDs produced in gas and liquid water are shown in figure 2.2. In the left panel of the figure, the mean cluster size distribution $M_1(Q|d)$ produced by 5 MeV alpha particles in water and propane-based tissue-equivalent gas is plotted as a function of the impact parameter $d$. The two plots are in general quite similar. However, for $d$ values smaller than the target radius ($R$) the mean cluster size produced in gas is larger than the mean cluster size produced in water. Conversely, for $d > R$ the mean cluster size in gas is smaller than in water. As explained by Grosswendt [83], this result is due to the different behavior of secondary electrons in the two media more precisely, to the fact that electron ranges are longer in water than in the tissue-equivalent gas. Therefore, in water, the contribution of secondaries to the mean cluster size is greater at large distance from the main track. The opposite happens in gas. In the right panel of figure 2.2, the mean cluster size produced by electrons in tissue-equivalent gas and water is plotted as a function of the electron initial energy. The energy dependence of the mean cluster size produced in the two media is similar. However, the mean cluster size in gas is larger than in water for all energies. Better agreement of the two curves is obtained when mean cluster size values in gas are scaled with the ratio of the ionization mean free path lengths of electrons in water and in gas. The mathematical justification for the scaling factor used to convert ICSDs produced in gas to ICSDs in water is presented in [84] and [86] and is briefly reported here. Following the formalism introduced in section 1.4, the necessary condition for the production of equivalent ICSDs in gas and water

Figure 2.2: Left panel: $M_1(Q|d)$ produced by 5 MeV alpha particles in a cylinder of diameter $R = 0.4 \mu g/cm^2$ made of propane-based tissue-equivalent gas or liquid water as a function of the impact parameter $d$. Right panel: $M_1(Q|0)$ produced by electrons in a propane-based tissue-equivalent gas or liquid water in a cylinder of 0.2 $\mu g/cm^2$ diameter and height as a function of the electron energy. The scaling factor applied to the gas curve is the ratio of the ionization mean free path lengths of electrons in water and in gas. Data reproduced form [83].

produced in gas to ICSDs in water is presented in [84] and [86] and is briefly reported here. Following the formalism introduced in section 1.4, the necessary condition for the production of equivalent ICSDs in gas and water

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2. Background and methods

is the equivalence of the distribution cumulants (eq 1.3 and 1.4). Therefore, the following equivalence should hold:

\[
\kappa^{(\text{gas})}(Q) \cdot m_x^{(\text{gas})}(Q|d) = \kappa^{(\text{water})}(Q) \cdot m_x^{(\text{water})}(Q|d)
\]

\[x = (1, 2, ..)
\]

\[\tag{2.1}
\]

where \(\kappa(Q)\) is the mean number of ionization produced by primary particles, which is equal to the ratio of the mass-per-area path length in the target volume and the mass-per-area ionization mean free path of the particle \((L_\rho/\lambda_{\text{ion}}(Q))\). Using the expression for \(\kappa(Q)\) in equation 2.1, one gets:

\[
(L_\rho)^{(\text{gas})} = (L_\rho)^{(\text{water})} \frac{(\lambda_\text{ion})^{(\text{gas})}(Q)}{(\lambda_\text{ion})^{(\text{water})}(Q)} \cdot \frac{m_x(Q|d)^{(\text{water})}}{m_x(Q|d)^{(\text{gas})}}
\]

\[\tag{2.2}
\]

From equation 2.2 it follows that nanometric volumes of water can be simulated by gas volumes of the same mass per area if the primary particle mass per area ionization mean free path and the spectral distribution and energy degradation of secondary electrons are the same in gas and in liquid water. In order to calculate the exact scaling factor, the moments of the single-ionization distribution in gas and water have to be known. This is non trivial as single distributions can not be measured but can be only obtained with MC simulations. However, in the special case of primary particles traversing the target volume with an impact parameter \(d = 0\) and target dimensions smaller than the range of secondaries, the contribution of secondary electrons is negligible. In this case, the single-ionization distributions \(f_\nu^{(1)}(Q|d)\) is equal to unit for \(\nu = 1\) and zero elsewhere. Therefore, the moments \(m_x(Q|d)\) are equal to unit and equation 2.2 reduces to:

\[
(L_\rho)^{(\text{gas})} = (L_\rho)^{(\text{water})} \frac{(\lambda_\text{ion})^{(\text{gas})}(Q)}{(\lambda_\text{ion})^{(\text{water})}(Q)}
\]

\[\tag{2.3}
\]

which depends only on primary particle parameters.

Examples of the use of the scaling factor defined in equation 2.3 are shown in figure 2.3. In the left panel, simulated distributions produced by 4.6 MeV alpha particles traversing a cylindrical volume of liquid water, propane or nitrogen with impact parameter \(d = 0\) are shown. It can be observed that when scaling the gas volume dimensions using equation 2.3 the distributions in water and gas are similar. In the right panel of figure 2.3, the distributions produced by 5.3 MeV alpha particles in gas and propane volumes are shown. In this case, the primary particles pass the target volume with an impact parameter larger than the volume dimensions. Even though the contribution of secondary electrons is dominant in this case, the distribution obtained in a propane volume with dimensions scaled using the simplified
scaling factor of equation 2.3 is very similar to the distribution produced in water. This indicates that the secondary electron behavior, as regards ionization, is similar in the two media. Other results on the comparison of ICSDs produced in water and gas are reported in [83], [88] and [84]. The scaling procedure was also experimentally validated by Hilgers et al. [95] comparing the ICSDs produced by proton and alpha particles in propane and nitrogen volumes of dimensions scaled according to equation 2.3.

### 2.2.3 Nanodosimetric estimates of biological effectiveness

To date, two main approaches have been proposed to correlate nanodosimetric quantities to initial DNA damage:

1) The first approach was presented by Grosswendt [84]. He suggested that the biological effectiveness of a given radiation quality is directly related to physical nanodosimetric quantities. In particular, Grosswendt made two hypothesis:

- the probability $F_1(Q)$ to measure a single ionization in a volume representing a DNA segment and the surrounding water molecules is expected to be proportional to the probability for a DNA single strand break (SSB) formation;

- the probability $F_2(Q)$ to measure at least two ionizations in a DNA segment of 10 base pairs and the surrounding water molecules is proportional to the probability for a DNA double strand break (DSB) formation.
The cumulative probabilities $F_k(Q)$ for measuring at least $k$ ionizations are given by:

$$F_k(Q) = \sum_{\nu=k}^{\infty} P(\nu|Q)$$

where $P(\nu|Q)$ is the ICSD defined in section 1.4 (the dependence on the impact parameter $d$ has been omitted for ease of notation). The rationale behind the two hypotheses is that in order to have either a direct or indirect damage to the DNA, at least one relevant interaction must occur in the DNA segment or in the surrounding water molecules. Even though the characteristics of the relevant interaction are not known, it is assumed that the probability of this type of interaction is proportional to the probability of a single ionization. Grosswendt’s hypotheses were validated comparing nanodosimetric quantities with radiobiological data in [84], [85], [86], [90], and [150]. A review of a few of these validation studies follows.

In figure 2.4, the energy dependence of $F_1(Q)$ and $F_2(Q)$ is compared with the energy dependence of SSB (left panel) and DSB (right panel) yields for monoenergetic electrons. The cumulative probabilities were calculated from simulated ICSDs produced in a nanometric cylinder of liquid water of 2.3 nm diameter and 3.4 nm height uniformly irradiated with primary electrons. The yields of DNA breaks were calculated from track structure simulations by Friedland et al. [73], including a realistic DNA target model and post-physical stages. Simulated $F_1(Q)$ and $F_2(Q)$ values for different radiation qualities were also compared to experimental data of SSB and DSB cross-section obtained from irradiation of SV40 viral DNA in [176]. As shown in figure 2.5, the measured DSB cross-sections and $F_2(Q)$ have the same dependence on LET, when scaled using one single factor, for all three...
radiation qualities. On the other hand, the LET dependence of the SSB cross-sections and \( F_1(Q) \) did not show a good agreement. This discrepancy might had been caused either by unsuitable experimental technique for accurate detection of single strand breaks or by the inconsistency of Grosswendt hypotheses (as discussed in [150]).

**Figure 2.5**: Comparison of the dependence of the cross-section \( \sigma_{DSB} \) for DSB formation in SV40 viral DNA on the LET (left-hand y axis) and the nanodosimetric track structure quantity \( F_2 \) (right-hand y-axis) for different radiation qualities. The \( F_2 \) values were derived from simulations of ICSDs in a water cylinder of dimensions equivalent to a DNA segment of 10 base pairs (2.3 nm diameter and 3.4 nm height). Plots reproduced from [150].

Other nanodosimetric quantities were found to correlate with radiobiological data. As shown in figure 2.6, the dependence of the ratio of the second to the first moment of the ICSD \( M_2(Q)/M_1(Q) \) on LET is very similar to the dependence on LET of the ratio of DSB to SSB yield in the case of proton primary particles.

More recently, Conte et al. [50] observed that \( F_2(Q|d) \) values obtained from measured ICSDs of carbon ions at different impact parameters \( (d) \) show a saturation effect with decreasing \( d \). Looking at the two plots in figure 2.7, it can be observed that \( F_2 \) saturation occurs at large \( M_1 \) values. This demonstrates an increasing complexity of particle track structure at large \( M_1 \) and small \( d \). Conte et al. believe that the \( F_2 \) behavior is similar to the saturation effect observed for radiobiological cross-sections at large LET values. The similarity was demonstrated by plotting \( F_2(Q|d)/M_1 \) as a function of \( M_1 \). As shown in the left panel of figure 2.8, the plot exhibits a maximum that is followed by a marked decrease. This trend is similar to the dependence of RBE on LET (figure 2.8 right panel).

2) The second approach to relate nanodosimetry and DNA damage was proposed by Schulte and Garty ([74], [167] and [75]). In their approach, a simple combinatorial model was used to convert ICSDs into probability
2. Background and methods

Figure 2.6: Calculated ratio of DSB to SSB yield and $M_2(Q)$ to $M_1(Q)$ due to monoenergetic protons as a function of LET. Data for the DSB and SSB yield are obtained from Friedland et al. [73]. The ratio $M_2(Q)/M_1(Q)$ is obtained from simulations in water. The data are normalized to the DSB/SSB curve for protons at 20 MeV. Plot reproduced from [90].

Figure 2.7: Left panel: mean ionization cluster size $M_1(Q|d)$ due carbon ions as a function of the impact parameter $d$. Right panel: cumulative probability $F_2(Q|d)$ of carbon ions as a function of $d$. The measurements were performed with the Track-nanodosimetric Counter. Plots reproduced from [50].

Figure 2.8: Left panel: ratio of $F_2(Q|d)$ to $M_1(Q|d)$ for carbon ions as a function of $M_1(Q|d)$. Plots reproduced from [50]. Right panel: RBE values at 10% survival from irradiation with ion beams as a function of the dose-averaged LET. Plot from [29].
2.2. State of the art of nanodosimetry

distributions of DNA lesions. The model is based on two assumptions:

- each single ionization has a fixed probability \( p_{SB} \) to be converted into a DNA lesion (e.g. SSB), regardless the number of ionizations in the cluster and the location of the ionization within the target volume;
- a DSB is formed when lesions are present on both DNA strands within 10 base pairs.

The probability distribution of DNA lesions for a given radiation quality is obtained by convolving \( P(\nu|Q) \) with the conditional probability of a cluster size \( \nu \) being converted into a cluster of \( n_{SB} \) lesions:

\[
P(n_{SB}|Q) = \sum_{\nu=0}^{\infty} P(n_{SB}|\nu)P(\nu|Q) \tag{2.5}
\]

where \( P(n_{SB}|\nu) \) is the binomial probability:

\[
P(n_{SB}|\nu) = \binom{\nu}{n_{SB}} p_{SB}^{n_{SB}} (1 - p_{SB})^{\nu-n_{SB}} \tag{2.6}
\]

The model parameter \( p_{SB} \) strongly depends on the biological endpoint and it can be obtained by fitting the model to radiobiological data for each endpoint. Following the second assumption of the model, the probability to form a DSB for a given radiation quality is given by:

\[
P(DSB|Q) = \sum_{\nu=2}^{\infty} \sum_{n_{SB}=2}^{\infty} P(n_{SB}|\nu)p_{DSB}(n_{SB})P(\nu|Q) \tag{2.7}
\]

where \( p_{DSB}(n_{SB}) = (1 - 0.5)^{n_{SB}-1} \) is the probability that not all the lesions are on the same DNA strand. For mathematical details on how to derive the conditional probabilities see [74] and [75]. The yields of SSB and DSB per unit of dose can then be obtained dividing the probabilities obtained in equations 2.5 and 2.7 by:

\[
D = \frac{M_1 W}{m} \tag{2.8}
\]

where \( M_1 \) is the first moment of the ICSDs, \( W \) is the mean energy required to form an electron-ion pair and \( m \) is the mass of the target volume. In Figure 2.9, the SSB and DSB yields of electrons and protons obtained with the combinatorial model are compared with the yields obtained from radiobiological experiments or calculations. The ICSDs obtained from measurements in propane gas and from simulations in water were used as inputs for the combinatorial model. Measured SSB and DSB yields were obtained irradiating plasmid DNA [113]. Calculated yields were obtained with the PARTRAC track structure code [71]. A value of 10% was obtained for the model parameter \( p_{SB} \) by fitting the model to the plasmid irradiation measurements. The
2. Background and methods

Figure 2.9: Predicted and measured yields of SSBs (upper panel) and DSBs (lower panel). The abscissa gives the particle velocity expressed as electron energy (bottom) and proton energy (top). Plots reproduced from from [74]

A combinatorial model was also validated by Schulte et al. [167] by comparing the ICRP 60 [4] radiation quality factors $Q$ and nanodosimetry-based quality factors dependence on LET. Complex DSBs (cDSB) (i.e. DSB associated with additional strand breaks) were considered to be relevant for carcinogenesis and the cDSB yield per unit of energy deposited in the target was calculated for different radiation qualities as:

$$G_{cDSB} = \frac{1}{WM_1} \sum_{n_{SB}=3}^{n_{SB\text{-max}}} \sum_{\nu=n_{SB}}^{\nu_{\text{max}}} P(n_{SB}|\nu)p_{DSB}(n_{SB})P(\nu|Q) \quad (2.9)$$

Simulated ICSDs obtained in a cylindrical volume of water of roughly 2 nm diameter and different lengths were used as inputs for the model. Nanodosimetry-based quality factors were calculated as the ratio of the cDSB yields for a given radiation quality and for electrons of 0.4 keV µm, which were used as reference radiation. In figure 2.10, the result of the comparison of nanodosimetry-
2.3 Track structure simulations

based quality factors with ICRP 60 quality factors is shown. The best agreement of the two curves was obtained for $p_{SB} = 15\%$ and a target volume length of 16 nm.

Figure 2.10: Nanodosimetry-based quality factors as a function of LET derived from ICSDs obtained from simulations. The Q-factors from ICRP Publication 60 are shown for comparison. Plot from [167].

2.3 Track structure simulations

Track structure MC simulations are important for the study of early stage radiation interaction with matter. These codes are the only tool for the calculation of the energy deposit in biological structures with nanometric dimensions. In contrast with condensed history codes, which simulate the average energy loss of primary particles over a certain track length, track structure simulations reproduce the interaction of charged particles with matter event-by-event until complete stop. The interaction location is determined by the total mean-free-path length while relative total cross-sections are used to determine the interaction type. Differential cross-sections are then used to determine the interaction details and the production of secondary particles. The interaction parameters are randomly sampled from cross-section data converted into cumulative probability distributions [57].

The material of the simulated target is usually vapor or liquid water, used as a surrogate of biological tissue. Cross-sections for radiation interaction in liquid water can not be experimentally measured like for the gas phase. Therefore, theoretical or semi-empirical models are used to determine the cross-sections of the interaction processes. Interactions of low energetic particles with molecules are complex and can not be described using the Bethe
theory. Different models are available for different particles and different energy ranges. Most of the theoretical models for inelastic collisions are based on the first order plane wave Born approximation (PWBA). The PWBA approach is valid for point particle projectiles with speed much larger than the bounded atomic electrons. Within this approximation, the target material is described with the generalized oscillation strength, for microscopic atomic description, and with the dielectric response function for macroscopic condensed phase description. The dielectric function is modeled as a superposition of ionization and excitation levels in the optical limit and fitted to experimental data, which are available only for zero momentum transfer. Extension algorithms are then used to model the function for larger transferred momenta. For low energies (e.g. < 300–500 eV for electrons and < 100 keV for protons) corrections to the PWBA have to be calculated using semi-empirical models, alternative theoretical models, such as the distorted wave Born approximation, or higher-order corrections. Alternatives to the PWBA are the Bethe approximation or semi-empirical models like the Rudd model for proton transport [57]. Elastic interactions are only considered for electrons at very low energies while are generally neglected for ions.

Geometrical models of DNA and other biological targets are included in many track structure codes for the study of biological damages. Models with different degree of complexity are available. However, all models use water cross-sections for the radiation transport. Cross-sections for elastic and inelastic scattering of electrons in DNA constituents in the gaseous state have been recently measured in [20] and [19]. Unfortunately, up to now, the models based on these measurements have only been included in private versions of a few codes ([39], [44]). Pre-chemical and chemical stages of water radiolysis can also be simulated with a few track structure codes. The spatial distribution of ionized and excited water molecules is calculated and the chemical parameters are used to obtain the water radical diffusion and interaction at different times after irradiation.

Since the 1960s, many track structure codes have been developed by different authors for specific applications in radiobiology and biophysical modeling. The most used codes are KURBUC, LEPHIST, and LEAHIST ([178] and [177]), which use water vapor cross-sections for transport of electrons, protons, and alpha particles, respectively. PARTRAC [71], which relies on both vapor and liquid water cross-sections for transport of electrons and ions, is also widely used. These codes have also chemical modules for the simulation of water radiolysis. Moreover, PARTRAC can simulate biokinetic processes like the repair of DNA damages [72]. Many of these codes are however not publicly available and not easily accessible to the scientific community [131]. In 2007, Geant4-DNA was released as an extension of the general purpose Geant4 MC simulation toolkit for track structure simulations [98]. Geant4 is open source and is freely available for all
users. PTra is another well-known track structure code that was developed at Physikalisch-Technische Bundesanstalt (PTB) for nanodosmetric applications. This code has the peculiarity to include models for tracking electrons and light ions in gases used in nanodosimeters – such as propane, methane, and nitrogen – beside in water.

In this work, Geant4-DNA (v9.03, v10.00, and v10.02) was used for the simulation of the physical interaction of protons, alpha particles, and carbon ions (from 100s of MeV until stop) with liquid water while PTra code was used for the simulation of the interaction of protons (400 keV – 5 MeV) and alpha particles (4 MeV – 20 MeV) with propane gas.

2.3.1 Geant4-DNA

Geant4-DNA is an extension of the Geant4 toolkit for simulating the interactions of particles down to the eV scale in liquid water. Geant4-DNA includes models for the physical, physiochemical, and chemical stages of radiation interaction. Geometrical models of the DNA double helix, chromatin fibers, and other biological targets are also provided.

Geant4-DNA physical models describe the transport of primary particles and their secondaries step-by-step. Each single interaction is treated individually and the average step length (i.e. the distance between two interactions) is of the order of nanometers. The models describe both the cross-section and the final state of the interaction taking the molecular structure of water into account. Physical models for elastic scattering, electronic excitation, and ionization are available for electrons in the range of 7.4 eV–1 MeV, protons and neutral hydrogen atoms in the range of 100 eV–100 MeV, and helium atoms and their charged state in the range of 1 keV–400 MeV. Additionally, vibrational excitation and molecular attachment models are available for electrons. Electron capture and electron loss models are available for protons, and charge exchange models are available for helium atoms. Finally, ionization models are implemented for Lithium, Beryllium, Boron, Carbon, Nitrogen, Oxygen, Silicon, and Iron ions in the range of 0.5 MeV/u–10⁶ MeV/u.

Geant4-DNA users can choose among different physical models by editing the “PhysicsList” class. In this work, the models included in the default “DNAPhysicsList” were used. These models are briefly summarized in this section. For a detailed description please refer to [101], [68], [25], and [100] and references therein.

The first order Born approximation is used to calculate the ionization and excitation processes for electrons and protons with energy above 500 keV. The target material is described with the dielectric formalism using the
Emfietzoglou and Nikjoo [64] model for electrons and the Dingfelder [59] model for protons. In the case of K-shell ionization from electrons, the ICRU model [104] is used. The semi-empirical Rudd model [156], [157] and the Miller and Green model [121] are used for ionization and excitation, respectively for proton and neutral hydrogen with energies lower than 500 keV. The same models are implemented for light ions, scaling the proton cross-sections by an effective charge factor [60]. For sub-excitation electrons with energies lower than the water molecule last excitation state (8.22 eV), the vibrational excitation Sanche model based on water vapor measurements scaled for the liquid phase [119] is used while a model based on Melton measurements [118] is implemented for the attachment interaction. For calculating the total cross-section and the scattering angle of the elastic interactions, the Champion semi-empirical model – based on the partial wave analysis and taking polarization and exchange effects into account – is implemented for electrons [43]. For proton elastic scattering, the standard Geant4 multi-scattering process based on the Urban model is used for energies above 1 keV. Charge transfer processes for protons, neutral hydrogen, and alpha particles are calculated with the Dingfelder semi-empirical model [61]. The angular distribution of the primary electron scattering after inelastic collisions and the ejected secondary electrons is calculated with the Grosswendt and Waibel model [91]. The angular distribution of secondary electrons from ions is obtained with the Rudd model for electron energies larger than 100 eV and an isotropic distribution between 0 and $2\pi$ is assumed for lower energies.

As regards heavy ions, the ionization process is modeled with the Rudd semi-empirical model with the relativistic extension [144]. The cross-sections are obtained from proton cross-sections using a speed scaling procedure and applying a correction for the ion effective charge. This correction takes into account the screening effect of the electrons of the ion shell depending on the ion speed and the media [69].

Finally, standard Geant4 Livermore models for Photoelectric effect, Compton and Rayleigh scattering, and pair production are implemented for the photon transport. Standard electromagnetic models for multiple scattering, ionization, annihilation and bremsstrahlung are used for positrons. Standard Geant4 atomic de-excitation can also be activated.

### 2.3.2 PTra

With the PTra track structure code physical tracks of protons with energies down to 300 keV and alpha particles with energies down to 1 MeV can be simulated in propane, methane, propane-based tissue-equivalent gas and water [83]. Primary and secondary electrons can also be tracked down to
2.3. Track structure simulations

the ionization energy. Models based on measured cross-sections for electron interactions with tetrahydrofuran, trimethylphosphate, and pyrimidine have been recently included in the code in order to simulate the interaction with DNA segments [39]. This section summarizes the interaction models included in the code for propane gas only. For a detailed description of the physical models implemented in Ptra please refer to [83], [89], and [38] and references therein.

The code tracking mode assumes that the spatial distribution of ionizations produced in the interaction medium depends only on the mean-free-path length of the primary particles and the energy and angular distribution of the secondary electrons and the subsequent electron interactions. Therefore, the processes considered are elastic scattering, electronic excitation, and impact ionization for electrons and ionization and electronic excitation for light ions. Secondary electrons are tracked down to 10 eV, below the ionization threshold (11.1 eV for propane). Models for charge transfer processes for low energy protons and alpha particles have been recently included [38]. Cross-sections for interaction processes in gas have been measured by different groups and the code uses semi-empirical models based on those measurements for the calculation of the total and differential cross-sections.

The electron impact ionization process in propane is described with the Chouki semi-empirical model [48] by combining the first order Born approximation with experimental data for low energy corrections. The energy distribution of the secondary electrons from electron impact ionization is obtained from the Green and Sawada model [82] fitted with methane data.

As experimental data of the directions of the primary electron after the inelastic collision and the ejected secondary electrons are not available, these quantities are calculated with the Grosswendt and Waibel model [91]. Electron excitation processes are also based on Chouki data: cross-sections for discrete excitation with a 9.13 eV threshold, vibrational excitation, molecular dissociation, and electron attachment are available [48]. For electron elastic scattering, the Rutherford model modified to take atomic screening effects into account is used to calculate the differential cross-section with respect to the solid angle and the total cross-section. The model parameters are obtained from fitting experimental data of total cross-section in propane. Correction factors are applied for electrons with energies smaller than 200 eV.

Ionization is the most important process causing energy loss of light ions in gas while the energy lost for gas molecule excitation is a negligible fraction and does not influence the ionization yield. Charge transfer processes are also negligible for protons with energy larger than 100 keV and alpha particles with energy larger than 4 MeV. No measured cross-sections of proton impact ionization in propane are available. For describing this process, the code uses the semi-empirical Rudd model parametrized with experimental
cross-sections for methane scaled by the ratio of the valence electron number of the two molecules, as proposed by Wilson and Toburen [185]. The alpha particle impact ionization is described with the Rudd model taking charge transfer processes into account. Scaled experimental cross-sections of methane are used for ionization and electron capture processes of He$^+$ and He$^{2+}$ while scaled nitrogen data are used for He$^0$. The Barkas empirical model [94] for effective charge correction is also available. To simulate the secondary electron distribution after proton and alpha particle ionization, the single-differential cross-section with respect to the electron energy obtained from the Hansen-Kocbach-Stolterfoht model [104] is used. The same model is used to obtain the double differential cross-section with respect to the energy and emission angle. This quantity is used to sample the polar angle of electron emission with respect to the primary particle flight direction. The azimuthal angle is assumed to be uniformly distributed between 0 and 2$\pi$.

The PTra code has been benchmarked for interactions in propane with experimental data of protons and alpha particles obtained with the ion counting nanodosimeter showing a good agreement between simulated and measured ICSDs [76],[23], and [38].

2.4 Basics of gaseous detector physics

2.4.1 Charge diffusion and drift in gas

The radiation detection process begins with the formation of electron-ion pairs produced in gas. These are produced in either primary or secondary ionizations of gas atoms or molecules. The electrons and ions created in the process lose energy in collisions with the gas molecules and diffuse with thermal energy. The spatial distribution of charges diffusing in gas after a time $t$ is described with a Gaussian function with standard deviation in each direction given by:

$$\sigma_x = \sqrt{2Dt}$$ (2.10)

where $D$ is the diffusion coefficient. The application of an electric field – generally, of the order of few V/cm – is necessary to avoid the recombination of the electron-ion pairs in the gas. Under the influence of such field, electrons and ions drift towards the detector anode and cathode, respectively. The average velocity of the charges is called drift velocity ($w$).

In the case of ions, the drift velocity is linearly proportional to the electric field up to very high electric field values. The proportionality constant is
defined as mobility ($\mu$) and is measured in cm$^2$ V$^{-1}$ s$^{-1}$:

$$\mu = \frac{w^+}{E}$$

(2.11)

The mobility value is specific of a given ion in a given gas and scales with pressure ($P$) and temperature ($T$) as:

$$\mu = \frac{T}{T_0} \frac{P_0}{P} \mu_0$$

(2.12)

Moreover, the ion mobility is related to the diffusion coefficient ($D$) by the Nernst–Townsend formula:

$$\frac{D}{\mu} = \frac{kT}{e}$$

(2.13)

where $k$ is the Boltzmann constant and $e$ is the electron charge. From this relation and equation 2.10 it follows that the RMS transverse displacement of drifting ions does not depend on the ion type and on the gas pressure but depends on the electric field strength and the gas temperature according to:

$$\sigma_x = \sqrt{\frac{2kT}{e}} \frac{x}{E}$$

(2.14)

Experimental values of ion mobility in various gases are available in the literature. For multi-atomic gases like propane, several ion species are present in the gas due to ionization and charge transfer processes occurring during the drift. Therefore, the experimental ion transport data are averaged values over the different ion species [160]. Some parameters for the transport of propane ions in low pressure propane gas have been measured by Shchemelinin et al. [171]. The measured data were used in this thesis work (see chapter 6) and are shown in figure 2.11. The ratio $D/\mu$ (expressed in mV) and the reduced ion mobility $\mu_0$ (defined in equation 2.12) as a function of the reduced field $E/P$ (V cm$^{-1}$ Pa$^{-1}$) are plotted in the left and right panel of the figure, respectively. The measured data are averaged values over all species produced by radiation ($^{241}$Am alpha particles) in propane. In [171], the data were fitted with the following analytical functions:

$$\frac{D}{\mu} = 27 + 65.3 \frac{E}{P}$$

(2.15)

$$\mu_0 = 0.618 - 0.0664 \frac{E}{P}$$

(2.16)

The thermal velocity of electrons is several orders of magnitude larger than the ion velocity at the same electric field strength. As a consequence, electrons have a larger mobility than ions. Moreover, due to their smaller mass,
2. **Background and methods**

![Figure 2.11](image)

**Figure 2.11**: Points represent the measured ion transport parameters and lines the analytical fit (equations 2.15 and 2.16). Left panel: transverse diffusion to mobility ratio. Right panel: reduced mobility. Plots from [171].

electrons are accelerated more between collisions with gas molecules when an external electric field is applied. Therefore, the electron mobility is not constant but strongly depends on the field strength and the gas type. In a classical formulation, the electron drift velocity can be defined as:

$$w^- = \kappa \frac{eE}{m} \tau$$ \hspace{1cm} (2.17)

where $m$ is the electron mass and $\tau$ is the mean time between collisions, which depends on the gas and electric field. The parameter $\kappa$ assumes values between 0.75 and 1 depending on the assumptions on the electron energy distribution [160]. Electron RMS is obtained from equation 2.18 where the dependency on the energy distribution is represented by the characteristic energy parameter ($\epsilon_k$).

$$\sigma_x = \sqrt{\frac{2\epsilon_k \chi}{e\epsilon}}$$ \hspace{1cm} (2.18)

A wide collection of experimental measurements of electron drift and diffusion properties is present in the literature along with studies on rigorous electron transport theories (for representative examples see [160]). Dedicated electron transport simulation programs, e.g. MAGBOLTZ [26], have also been developed for the computation of drift properties of electrons in most gases and mixtures commonly used in detectors.

### 2.4.2 Charge amplification

As the electric field strength increases, electrons are accelerated above the ionization threshold of the gas molecules and produce additional electron-ion pairs initiating the charge multiplication process. This process, called Townsend avalanche, is at the basis of signal amplification in the gas detectors.
2.4. Basics of gaseous detector physics

The inverse of the ionization mean free path is defined as the first Townsend coefficient \( \alpha \) and describes the number of ion-electron pairs created by an electron per unit drift length. The Townsend coefficient depends on the gas pressure \( P \) and the electric field strength \( E \). In equilibrium conditions the ratio \( \alpha / P \) is a unique function of the reduced field \( E / P \), independently from the gas type and pressure. An empirical approximation obtained by Korff [111] for \( \alpha \) is given by:

\[
\frac{\alpha}{P} = Ae^{-\frac{EP}{A}}
\]

(2.19)

where where \( A \) and \( B \) are phenomenological constants.

Under the assumption that the mean free path of electrons is much smaller than the size of the avalanche, the increase in the number of electrons \( n \) along a distance \( \Delta x \) is given by:

\[
n = n_0 e^{-\int_{x_1}^{x_2} \alpha(x) dx}
\]

(2.20)

The quantity \( n / n_0 \) is defined as multiplication factor or gas gain. In the particular case of a parallel plate geometry with plate distance \( d \) and a constant Townsend coefficient, the multiplication factor is \( M = e^{\alpha d} \).

The Townsend avalanche generation is a stochastic process therefore, fluctuations of the multiplication factor at a given \( E / P \) have to be considered. The avalanche size distribution is the probability that an avalanche of \( n \) electrons is formed along a path \( x \). In the case of a uniform field and for an avalanche generated by a single electron, the avalanche size distribution can be written as:

\[
P(n, x) = \frac{1}{\bar{n}} \left( 1 - \frac{1}{\bar{n}} \right)^{n-1} e^{-\frac{n}{\bar{n}}}
\]

(2.21)

where \( \bar{n} \) equals the average number of electrons of the avalanche. This approximation, valid for \( \bar{n} \gg 1 \), is referred as the Furry distribution. For a large number of primary electrons \( n_0 \), the avalanche size distribution tends to a Gaussian distribution with average \( \bar{n}n_0 \) and variance \( \sqrt{\bar{n}_0} \) [160].

The Furry distribution describes well the avalanche statistics only for \( \bar{n} < 10^5 \), whereas for larger \( \bar{n} \) (or high \( E / P \) values) the avalanche statistics is better represented by a Polya distribution:

\[
P(n, d) = \frac{b}{\bar{n} (b - 1)!} \left( \frac{bn}{\bar{n}} \right)^{b-1} e^{-\frac{bn}{\bar{n}}}
\]

(2.22)

where \( b = (1 + \theta) \) and \( \theta \) is a parameter depending on the gas conditions. This change of behavior of the avalanche statistics is explained by the fact that at high \( E / P \) values the electron energy gain per mean free path is greater...
than the average electron energy. Therefore, the average electron energy increases over a number of collisions [51].

During the avalanche evolution, photons are created due to de-excitation of the gas molecules. These photons can further ionize the gas molecules or undergo to photoelectric interaction with the metal surfaces, introducing non-linear effects in the avalanche development. This process is known as photon-feedback. Additional non-linear effects can be introduced by ion impacts causing the extraction of electrons from the cathode. Such electrons are accelerated in the electric field causing secondary avalanches.

2.4.3 Breakdown in gases

The electric breakdown in gases occurs when an electron avalanche proceeding from cathode to anode develops into a self-propagating current, which forms a conducting plasma between the electrodes. There are two main discharge mechanisms relevant for gaseous detectors: the Townsend discharge and the streamer.

The Townsend discharge is a delocalized breakdown caused by the multiplication of electrons extracted from the cathode by ion impact or photoelectric processes. A self-sustained discharge is formed when the number of secondary electrons extracted from the cathode equals the number of initial electrons. In the case of a parallel plane geometry with gap length $d$, the breakdown condition is given by:

$$\gamma (e^{ad} - 1) = 1$$

(2.23)

where $\gamma$ is the average number of secondary electrons produced at the cathode per ionizing collision in the gap and is known as Townsend’s second coefficient. The Townsend breakdown develops over relatively long periods of time, typically larger than 1 µs [70].

The Townsend theory describes a diffused form of discharge. However, in practice, many discharges are found to be filamentary. The streamer theory predicts the development of a spark discharge directly from a single critical avalanche. The transition from avalanche to streamer occurs at high gains due to the distortion of the external electric field caused by the large space-charge. Such distortion causes the formation of regions with an increased Townsend coefficient. The streamer evolution is due to the avalanche photon-feedback which creates secondary electrons outside the primary avalanche. Such photoelectrons start to move towards the primary avalanche causing the growth of the avalanche in all directions and the formation of a thin plasma filament. If not damped by the detector geometry
or by a reduction of the electric field, the streamer can propagate through the whole gas gap, leading to a spark breakdown.

The transition from avalanche to streamer occurs when the space-charge field becomes comparable to the external electric field. For parallel-plate geometry at atmospheric pressure, the empirical threshold for the transition—known as Raether limit—is $ax < 20$ or a total avalanche size $(n_0 m)$, of roughly $10^8$. In general, for any geometry and pressure, streamers occur when external fields larger than a critical value are applied. For micro-pattern gaseous detectors (MPGD), the critical charge value is smaller than the Raether limit and depends on the micro-pattern detector geometry and $n_0$. As a consequence of the $n_0$ dependence, the gain value at which the sparking appears decreases with increasing primary radiation rate.

The signal obtained from the transition from avalanche to streamer consists in a precursor, corresponding to the primary avalanche, followed by a fast current pulse, corresponding to the propagation of the streamer, and finally a spark signal [66]. The streamer regime is observable through the behavior of the induced charge as a function of the applied voltage with deviates from the exponential shape and becomes almost linear [65].

Steamers limit the maximum gain of proportional gaseous detectors. On the other hand, the large and fast signal produced is exploited to obtain high gains and high time resolution in resistive plate chambers (see section 2.5).

## 2.5 Resistive plate chambers

The Resistive Plate Chamber (RPC) is a gaseous detector developed in 1981 by Santonico and Cardarelli [158] widely used in experimental high energy physics for timing and trigger purposes.

Standard RPCs consist in two parallel plate electrodes creating a constant and uniform electric field in a gap filled with gas. Either one or both electrodes are made of high volume resistivity material. Typical materials are glass ($\rho \approx 10^{12} \, \Omega \text{cm}$) and Bakelite ($\rho \approx 10^{11} - 10^{10} \, \Omega \text{cm}$) [116].

RPCs can run either in avalanche or streamer mode. In avalanche mode, the initial charge multiplication occurs as a Townsend avalanche. In streamer mode, strong electric fields are applied to generate confined discharges. The discharge propagation in the gas gap is prevented due to the high resistivity of the electrodes causing a drop of the electric field in a limited area around the discharge point. The spatial limitation of the avalanche is provided using gas mixtures with high absorption coefficient for ultraviolet light and high electron affinity. The fast avalanche to streamer transition and the large signal produced allow to achieve time resolutions smaller than nanosec-
onds [40]. The large difference between the duration of the discharge (≈ 10 ns) and the relaxation time (1 – 10⁻² s) insures that during the discharge the electrode plates behave like insulators. Therefore, only a limited area around the discharge point remains inactive for a given time.

A limitation of RPCs is given by the high resistivity of the electrodes, which is responsible for a drop of the effective electric field in the gap at large particle rates or large gas gains. In turn, this voltage drop affects the detector efficiency and the counting rate capability. A simple model to describe this effect has been proposed by Abbrescia [11]. In this model, the static description of the voltage drop in the resistive electrodes – valid for low particle rates – is extended including the dynamics of the fluctuation of the field in the gas gap. According to Abbrescia’s model, the initial charge \( q_p \) accumulated in the resistive plate capacitance \( (C_p) \) is given by:

\[
q_p = \varepsilon_0 \frac{A}{g} V_{ext}
\]

where \( A \) is the area of the discharged region in the plate, \( g \) is the gap width, and \( V_{ext} \) is the voltage applied across the gap. The total charge \( q_a \) of the avalanche, developed in the gap as a consequence of the particle interaction in gas, causes a partial discharge of \( C_p \). Therefore, the actual voltage across the gap is:

\[
V_{gap} = \frac{g}{\varepsilon_0} \frac{q_p - q_a}{A}
\]

The charge provided by the external power supply for recharging the plate increases exponentially as a function of time with a time constant given by:

\[
\tau = 2R_p(2C_p + C_g) = 2\rho\varepsilon_0 \left( 2\varepsilon_r + \frac{t}{g} \right)
\]

where \( \rho \) and \( \varepsilon_r \) are the plate volume resistivity and relative dielectric constant, respectively, \( t \) is the plate thickness, \( C_g \) is the gap capacitance, and \( R_p \) is the plate resistance. Alternative and more complete models for the description of the dynamics of the gap voltage are described in [117] and [78].

As shown in equation 2.26, the time needed for restoring the nominal voltage in the gap after the avalanche development is inversely proportional to the electrode resistivity. For example, a relaxation time of the order of tens of milliseconds is obtained for a resistivity value of the order of \( 10^{10} \Omega \) cm. Therefore, with standard RPCs operating in streamer mode, the counting rate is limited to few hundreds of Hz cm⁻². Due to the smaller total charge produced in the avalanche compared to the charge produced in a streamer, RPCs operating in avalanche mode can achieve counting rates of the order of few kHz cm⁻². The recent development of new materials with relatively
2.6 Gas electron multipliers

Gas Electron Multiplier (GEM) detectors were invented by Sauli in 1997 for applications in high energy physics. GEMs consist in a thin polymer foil, metal-coated on both sides and perforated with a large number of holes, typically 100 per mm². Such structure is placed in a drift chamber filled with gas. Electrons produced by the ionization of the gas, drift into the GEM holes. Here, multiplication occurs due to the large difference of potential applied between the two sides of the foil which creates a strong dipole electric field within the holes. In this way, each hole works as an independent proportional counter. After the multiplication, electrons enter a transition region leading to either the readout anode or a second GEM. The confinement of the avalanche in the hole allows the reduction of the photon-feedback. In addition, the hole structure provides the localization of the primary ionization with high resolution.

GEM foils can be manufactured with printed circuit technology. Standard GEMs are made of copper-clad Kapton foils with a thickness of 50 µm and have holes of 50 µm to 70 µm diameter and 140 µm pitch. The performance and the long-term stability of the detector depends on the hole diameter and shape, and on the manufacturing quality. In optimal conditions, an effective gain above $10^3$ can be obtained for a single stage GEM. Larger gains are not achievable due to the spark ignition occurring at high applied fields. However, multi-GEM strictures allow to obtain higher proportional gains (larger than $10^6$) without occurrence of discharges [161].

The thick-GEM (THGEM) is a variation of the standard GEM with about 10 to 50-fold expanded dimensions, leading to improved robustness and simpler manufacture [32]. THGEMs are made of standard double-face copper-clad printed circuit boards of glass epoxy, which are mechanically drilled with sub-millimeter diameter holes. The operation mechanism and the role of the different electric fields involved in the operation, are similar to that of standard GEMs. However, values of the operation parameters (e.g., operation voltage, electric fields, and electron diffusion) do not scale with dimensions. Therefore, a specific optimization for THGEMs is needed. In
particular, the maximum voltage difference across the THGEM for spark ignition does not scale with dimensions.

The electric field produced in the THGEM holes is smaller than in a GEM. However, due to the larger THGEM thickness, higher gains can be obtained with this device. Furthermore, electron focusing into the holes is more efficient than in standard GEMs due to the larger hole size. A down side of the large hole size is that part of the avalanche could develop outside the hole at large gains. This effect is undesired as it can create operation instability. The best geometry for obtaining both large electric field strength and avalanche confinement is a hole size comparable to the board thickness. Compared to standard GEMs, coarser localization and slower pulses are obtained with THGEMs [169].

It was observed that the etching of the copper layer around the holes (hole rim) allows the operation at larger potential differences due to a reduction of the spark occurrence. On the other hand, the dielectric rim enhance the charging-up effect producing a gain decreasing with irradiation time [32]. The latter effect, arises due to small currents generated in the dielectric material by electrons migrating towards the ions hitting the dielectric surface. These currents create a potential gradient in the THGEM holes affecting the applied field and thus the detector gain [161].

THGEMs were tested for operation at low pressure in various gases. For example, Shalem et al. [170] tested the THGEM operation in isobutane and Ar/CO₂ gases at low pressure. They observed a spark-free operation in a pressure range from 1.3 mbar to 66.5 mbar. The maximum gain achievable was in a range from 10⁵ to 10⁷ and the value decreased with decreasing pressure in a range of 1.3 mbar to 13 mbar. Moreover, larger gains were obtained for isobutane than for Ar/CO₂. In the same work, a deviation from proportionality of the multiplication process was observed for applied electric fields larger than 1.8 kV cm⁻¹ and 2.5 kV cm⁻¹ at a pressure of 0.6 mbar and 1.3 mbar, respectively.

The main limitation of GEMs and MPGDs in general, is the occurrence of occasional discharges at high gains and high particle rates. Similar to RPCs, the use of resistive electrodes for damping the discharges in MPGDs has been investigated by several authors. Some examples of such devices are resistive MICROMEGAS [17], resistive GEM [133], and resistive MicroDot [65] detectors. THGEM-based detectors with resistive electrodes have also been developed. Among various configuration of resistive THGEMs, the Resistive-Plate Well (RPWELL) proposed by Rubin et al. [155] is particularly promising. This structure consists in a THGEM, copper-clad on one side and in contact with a resistive plate of high bulk resistivity on the other side. Compared to other structures, RPWELLs have the advantage of a superior discharge damping and of allowing the transport of the accumulated charge
through the resistive layer rather than transversely. This leads to a lower avalanche-induced charge-spread. RPWELLs have shown discharge-free operation at high gas-avalanche gains and high ionization background in 1 atm of Ne/5%CH\textsubscript{4} \cite{34} and Argon gas mixtures \cite{125}. On the other hand, such structures are affected by gain saturation with increasing counting rates, with gain loss dependent on the bulk resistivity of the resistive plate. Rubin \textit{et al.} \cite{155} showed that plates made of Semitron polymer – with a bulk resistivity of $2 \cdot 10^9 \Omega \text{cm}$ – produce larger counting rate capability than other resistive materials leading to a gain stability up to values of $10^4$ under counting rates of the order of 1 kHz mm\textsuperscript{-2}.

### 2.7 Summary

In this chapter, the background of this thesis work was presented. In section 2.2, the characteristics of the existing nanodosimeters were described and the literature studies aiming to relate nanodosimetric quantities with the biological damage of radiation were presented.

In section 2.3, a brief overview on MC track structure codes was given. The codes used for the simulations performed in this thesis work were described in more details. In particular, Geant4-DNA (v9.03, v10.00, and v10.02) was used for simulations of physical radiation track structure of protons, alpha particles, and carbon ions in liquid water while PTra code was used for simulations of protons and alpha particles in propane gas.

In the last part of the chapter, theoretical information useful for the experimental part of this work was presented. In section 2.4, a basic overview on the physics of gaseous detectors was given. In sections 2.5 and 2.6, the working principles of RPC and GEM detectors were briefly described. Such detectors have characteristics similar to the detector developed in this work.
Chapter 3

Nanodosimetry for the estimation of radiation biological effectiveness in particle therapy

3.1 Introduction

For the purpose of introducing nanodosimetry in particle therapy, several crucial points have to be addressed, both experimental and theoretical. First of all, a new nanodosimeter suitable for routine measurements in the treatment room should be developed. This point is addressed in chapter 6 of this thesis where the development of a track imaging detector (TIDe) is presented. Secondly, the experimental data obtained with the nanodosimeter should be analyzed in order to extract information that is relevant for the estimation of the radiation biological damage. Finally, an approach should be proposed to integrate nanodosimetry information into the treatment plan framework. In this chapter, some preliminary studies and discussions to address the last two points are presented.

In section 3.2.1, a radiation track analysis approach is proposed for the post-processing of the data recorded with the TIDe and obtained from MC simulations. In section 3.2.2, the equivalence of nanodosimetric quantities obtained in water and propane gas with the track analysis approach was tested using simulated proton tracks as an example.

In section 3.3, the idea to create customized mixed radiation fields in order to obtain given ionization cluster size distributions in nanoscopic volumes of water is presented. As it will be shown in chapter 5, this idea could be introduced in particle therapy for producing treatment plans with a given distribution of nanodosimetric quantities and thus, a given biological effect in the target volume. In the same section, a preliminary work to test the
3. Nanodosimetry for the estimation of radiation biological effectiveness in particle therapy

feasibility of this idea in a microscopic volume, before the more demanding application to the macroscopic geometry of a treatment plan, is presented.

In section 3.4, the steps necessary to link the nanodosimetric quantities measured in gas to the radiation biological damage are summarized and discussed. In the discussion, studies present in the literature are complemented with the results of the work performed.

3.2 Analysis of registered radiation tracks

3.2.1 Track sampling approach

In the state-of-the-art nanodosimeters, the radiation target is represented by a cylindrical volume filled with low pressure gas simulating targets of nanometric dimensions. Such devices have a limited freedom for the irradiation geometry of the target. Usually, this geometry consists in a collimated needle beam traversing the cylindrical target volume perpendicularly to the cylinder main axis. The only degrees of freedom are given by the height of the beam incidence and the lateral distance of the beam with respect to the cylinder center. With these devices ICSDs are obtained by scoring the number of ionizations produced in the fixed target volume with dimensions defined by the detector sensitive volume (see section 2.2.1).

In this thesis work, a dedicated TIDE was developed to overcome the geometrical limitations of the state-of-the-art nanodosimeters. The TIDE allows, indeed, more freedom in the irradiation geometry and sensitive volume dimensions. The detector can collect long radiation track segments produced in a gas sensitive volume of dimensions adjustable in a wide range (see section 6.2.1). The information obtained with this detector is – in the ideal case – the raw spatial distribution of the ionization events. Therefore, a track post-processing is needed to obtain ICSDs produced in biological meaningful targets and relate measurements in gas with damage to DNA.

The track post-processing adopted in this work consists in sampling measured or simulated radiation tracks with cylindrical target volumes placed at random position and orientation in a larger cylindrical volume. The latter volume represents the experimental gas sensitive volume where the tracks are produced and its dimensions can vary according to the each specific application. The dimensions of the cylindrical target were scaled using equation 2.3 in order to be equivalent to the dimensions of a water cylinder of 2.3 nm diameter and 16 nm height. This represents a DNA strand of approximately 50 base pairs. The cylinder centers and axes directions were randomly sampled. Different random number generators were used in or-
3.2. Analysis of registered radiation tracks

Figure 3.1: Left panel: simulation of an alpha particle track produced in a cylindrical sensitive volume of propane gas. Red dots represent ionization interactions obtained with the PTra track structure code (see section 2.3). Right panel: visualization of the track sampling. Blue cylinders are the sampling volumes simulating a DNA strand of approximately 50 base pairs.

In order to minimize the autocorrelation between independent variables, no constraint was applied for avoiding the overlap of the target cylinders.

In figure 3.1, the sampling procedure applied to a simulated alpha track is shown. Sampling cylinders are superimposed to the track and the number of ionizations obtained within each cylinder is scored. By analyzing a series of tracks, ICSDs produced in the target volumes are obtained. In figure 3.2, the ICSDs obtained with the described approach for protons in 1.33 mbar propane gas are shown. The distributions were normalized to the total number of events producing at least one ionization in one target cylinder (conditional distributions). The plots show that larger clusters are produced with larger frequency as the proton energy decreases. This behavior is expected as it reflects the LET increasing with decreasing primary particle energy.

3.2.2 Validation of the random cylinder sampling approach concerning gas-water equivalence

The nanodosimetry formalism introduced in sections 1.4 and 2.2.2 was specifically developed to model the data obtained with the experimental setup of the state-of-the-art nanodosimeters. Namely, a radiation beam penetrating diametrically a cylindrical sensitive volume with a certain impact parameter. However, all the listed mathematical relations are valid in general and do not depend on the setup geometry. Therefore, those relations can be used to describe ICSDs obtained with the random cylinder sampling approach. An exception is given by equation 2.3 that is used to scale macroscopic dimensions in gas to nanometric dimensions in water. From a mathematical point
Nanodosimetry for the estimation of radiation biological effectiveness in particle therapy

Figure 3.2: Conditional ICSDs produced by protons at different energies in randomly oriented cylinders of 2.3 nm diameter and 16 nm height water equivalent placed within the gas sensitive volume (propane gas at 1.33 mbar). Error bars are omitted as within the symbols.

of view, equation 2.3 is valid only in the special case of a needle primary beam penetrating a cylindrical target volume at half of its normal height with an impact parameter $d = 0$ and target dimensions smaller than the range of secondaries. This condition is not satisfied in the random cylinder sampling approach as the target cylinders have random position and orientation with respect to the primary track. In this case, the contribution of secondary electrons to the ICSDs can not be neglected. On the other hand, the simplified scaling factor can still be used in the case the secondary electron behavior as regards ionization is similar in water and gas as discussed in section 2.2.2.

MC simulations were performed to test the equivalence of the ICSDs produced in water and in gas obtained with the random cylinder sampling approach. Proton tracks produced in water and gas were simulated using Geant4-DNA and PTra track structure codes, respectively. The two codes are described in section 2.3. For the simulations in water, physics model included in the default “G4EmDNAPhysics” constructor of Geant4 version 9.06 were used. In the left panel of figure 3.1, the simulation geometry is shown. A proton needle beam traversing a water or gas cylindrical sensitive volume was simulated and the coordinates of the ionization events produced in the volume were recorded. For the simulations in water the sensitive volume was 50 nm in diameter and height while the volume dimensions in gas were scaled in order to be equivalent to the dimensions in water using the simplified scaling factor of equation 2.3. Propane was used as gas medium in order to simulate the TIDe sensitive volume (see section 6.2.1). Protons energies ranged from 400 keV to 5 MeV. $10^4$ events were simulated for each proton energy. The tracks obtained in the simulations were analyzed using the random cylinder sampling approach. The scoring cylinders had a diameter of 2.3 nm diameter and a height of 16 nm in water. The cylinder
3.2. Analysis of registered radiation tracks

dimensions in gas were scaled using equation 2.3. Each track was sampled with $10^4$ random cylinders.

Conditional ICSDs obtained in gas and water for protons of 5 MeV, 800 keV, and 400 keV are compared in figure 3.3. From the plots, it can be observed that for the same probability value the cluster size produced in gas is in general larger than the cluster size produced in water. However, the differences are small and the distributions in water and propane are almost equivalent for the first two proton energies. Starting from 400 keV the difference between the distributions gets more pronounced. For a more quantitative comparison, the mean ionization cluster size ($M_1$) was calculated from the distributions and plotted as a function of the proton energy (figure 3.4). It can be observed that the $M_1$ value is identical in water and gas for 5 MeV and 3 MeV protons. The difference between $M_1$ in water and gas increases with decreasing energy and it reaches a value of 17% at 400 keV.

It should be mentioned that a component of the differences between ICSDs obtained in water and gas could be related to the inaccuracy of the interaction models used in the track structure codes. Results of simulations in water are more critical as they rely on the accuracy of the theoretical and semi-empirical models used to calculate the interaction cross-sections. As explained in section 2.3, the different models available produce different results in particular in the low energy region ($< 500$ MeV for protons) where the PWBA is no longer valid and higher order perturbation effects have to be taken into account. Larger accuracy is expected for results in propane as experimental data are available for interaction cross-sections. Moreover, PTra code is experimentally benchmarked with nanodosimetric measurements. On the other hand, slightly different results can be obtained using different models to fit experimental cross-section data as shown in [87] and [38].

Nanodosimetric estimates of radiation biological effectiveness were calculated from the ICSDs produced in water and gas. Using the Schulte and Garty model (see section 2.2.3), the probability distribution of additional strand breaks per DSB (i.e. complex DSBs) was calculated from the ICSD produced in water and gas using equation 3.1 with $\nu_{max} = 15$ and $p_{SB} = 15\%$.

$$P(adSB) = \sum_{n_{SB}=adSB+2}^{v_{max}} \sum_{2v=n_{SB}}^{v_{max}} P(n_{SB}|v)p_{DSB}(n_{SB})P(v|Q)$$  (3.1)

In figure 3.5, the complex DSB distributions produced in water and propane are compared for different proton energies. The plots show that the distributions produced in water and gas are similar.

The yield of complex DSB per unit of dose was calculated from the ICSDs in gas and water using equation 2.9 multiplied by the target volume mass. In figure 3.6, it can be observed that the yield of complex DSB in the two media
3. Nanodosimetry for the estimation of radiation biological effectiveness in particle therapy

**Figure 3.3:** Comparison of the conditional ICSDs produced in cylindrical volumes of water and propane gas by protons at different energies. Error bars represent statistical uncertainties.

**Figure 3.4:** Comparison of the mean cluster size values $M_1(Q/d)$ obtained in cylindrical volumes of water and propane gas as a function of the proton energy.
3.2. Analysis of registered radiation tracks

Figure 3.5: Comparison of the probability distribution of additional strand breaks associated with a DSB obtained in gas and water for different proton energies.

increases with increasing LET as expected. The relative difference between the yields in water and gas is within 11% for all the proton energies. The yield in water is larger than the yield in gas for all the proton energies. This is due to the fact that the W-value used in equation 2.9 is smaller for water than for propane (23 eV for water [21] and 27 eV for propane [145]).

An upper threshold to the biologically relevant cluster size was set for the calculation of the DNA damage yield. Very large clusters were assumed to be less effective in producing complex damage due to recombination of radiation-induced radicals. This hypothesis is based on evidences that radicals recombine more efficiently with high LET particles favoring the formation of molecular species [108]. In particular, a maximum cluster size of fifteen ionizations was used for the SB and DSB frequency computation. This choice may be controversial as it is not known at which value of ioniza-
3. Nanodosimetry for the estimation of radiation biological effectiveness in particle therapy

Figure 3.6: Comparison of the complex DSB yield per unit of dose produced in water and in propane gas as a function of the proton energy.

...tion cluster size radical saturation effects may intervene. Anyway, when no threshold to the biologically relevant ionization cluster size is set, differences between the complex DSB yield in water and gas increase only of 1%.

3.3 Optimization of mixed field ICSDs

The experimental characterization of the track structure with nanodosimetric quantities related to the biological damage is useful for benchmarking track structure codes and for the estimation of the biological effectiveness of mixed or unknown radiation fields. Conversely, different radiation qualities could be combined in order to produce given values of the nanodosimetric quantities and thus, a given biological effect that can be experimentally assessed. In this section, a preliminary work is presented to test the possibility of combining protons and alpha particles of various energies in order to obtain a given ICSD. Results of this test are useful to study the feasibility of the optimization of a nanodosimetry based treatment plan in particle therapy (see chapter 5).

ICSDs of protons and alpha particles were obtained simulating radiation tracks in water with Geant4-DNA and analyzing them with the random cylinder sampling approach using the same geometry and procedure explained in section 3.2.2. The obtained ICSDs were then used as input for an optimization problem aiming to optimize the fluence of the different primary particles in order to obtain a given ICSD.

The Matlab function `lsqnonneg` was used to solve the nonnegative least-squares problem:

$$\min_x \| C \cdot x - d \|_2^2 \quad \text{with} \quad x \geq 0$$
3.3. Optimization of mixed field ICSDs

where $C$ is a matrix containing the ionization cluster size frequency produced by particles of different qualities, $d$ the vector of the goal ionization cluster size frequency and $x$ is the solution vector containing the optimized weights for the particle fluence. This procedure was applied to solve three optimization problems.

In the first problem, the ICSD produced by protons of 1 MeV was chosen as goal distribution while the other distributions shown in the left panel of figure 3.7 were used as input for the optimization. The ICSD resulting from the optimization is compared with the goal distribution in the right panel of figure 3.7. The black curve represents the ICSDs produced by a mixed field of 39% 2 MeV protons and 61% 800 keV protons. This curve is very similar to the 1 MeV distribution and the mean ionization cluster size calculated from the two distributions is the same and equal to 1.95.

![Figure 3.7](image1.png)

**Figure 3.7:** Left: ICSDs of protons in water used in the first optimization problem. The red curve represents the goal distribution. Right: comparison of ICSDs produced by a mixed field of protons and the goal distribution.

As a second example, the ICSD produced by protons of 200 keV was chosen as goal distribution while the other distributions shown in the left hand side of figure 3.8 were used as input for the optimization. In this case, a mixed field composed by 44% 400 keV protons and 56% 100 keV protons produces an ICSD equivalent to the goal distribution. This is shown in the right hand side plot of figure 3.8. The mean cluster size is equal to 2.9 for both the distributions.

![Figure 3.8](image2.png)

In the last problem, the 200 keV proton distribution was kept as a goal, but the ICSDs produced by alpha particles – shown in figure 3.9 – were included in the optimization. In this case, the least-squares solution is a mixture of 88% 5 Mev alpha particles, 4% MeV alpha particles and 8% 100 keV protons. As shown the right panel of figure 3.9, the distribution produced by mixing different particles has an even better agreement with the goal distribution than the distribution obtained by mixing protons exclusively.
3. Nanodosimetry for the estimation of radiation biological effectiveness in particle therapy

Figure 3.8: Left: ICSDs of protons in water used in the second and third optimization problem. The red curve represents the goal distribution. Right: comparison of ICSDs produced by a mixed field of protons and the goal distribution.

Figure 3.9: Left: ICSDs of alpha particles in water used in the third optimization problem. Right: comparison of ICSDs produced by a mixed field of protons and alpha particles and the goal distribution.

3.4 Discussion and summary

As explained in the previous chapters, nanodosimetry allows the experimental characterization of radiation track structure by measuring ionization clusters produced in nanometric equivalent gas volumes. This technique is promising for obtaining quantities that can be used for the estimation of the biological damage caused by the mixed radiation fields produced in particle therapy. However, several critical points have to be addressed before the clinical application of the nanodosimetric approach.

The first issue to address is the correlation between the physical information on the spatial distribution of the ionization events within a biologically relevant target and the biological damage. Unfortunately, only few studies have been performed in this direction. Moreover, the two models for relating ICSDs to DNA damage yield, presented in the literature review of section 2.2.3, have some limitations, as discussed in [167], [75], and [150]. In particular, Grosswendt’s approach of correlating track structure parameters directly to the biological effect has the advantage to be independent...
on biological parameters. However, the model proposed may be too simple. In fact, the hypothesis that a ionizing interaction within a DNA segment would always cause a strand break is unrealistic. In this regard, Schulte and Garty model may be more realistic as introduces a parameter representing the probability that an ionization is converted into a DNA strand break. On the other hand, the use of such parameter makes the model dependent on biological factors that may vary with biological tissue and biological endpoint [39]. Both approaches have the important advantage to predict DNA DSBs without assuming a detailed model of the DNA structure and taking into account the chemistry of DNA damage production. Even more important, the two approaches are based on quantities that can be experimentally measured using gas detectors simulating condensed matter. In order to define standardized dosimetric quantities describing the radiation track structure and its relation with the initial biological damage, additional studies to validate the existing models or to develop more advanced biophysical models are still needed. For this purpose, dedicated radiobiological experiments where the radiation quality of irradiated cells is characterized with nanodosimetric quantities should be performed [150].

An important parameter of the relation between nanodosimetric quantities and the radiation biological effect is the size of the biologically relevant target. On one hand, nanodosimetric quantities strongly depend on the dimension of the volumes where the ICSDs are produced. On the other hand, the biological relevant target for radiation damage induction is still unknown. Although the clustered damage to DNA is considered the initial damage leading to the different cell endpoints, it is not known which spatial extension this damage should have in order to be relevant. The relevant size may also be different for different biological effects (see section 1.3.2). The TIDE detector developed in this work goes beyond the target issue as arbitrary long segments of radiation tracks can be registered with such instrument. Different track post-processing can then be applied in order to extract biological relevant information from the data collected with the detector. For the studies performed in this thesis work, the track analysis approach presented in section 3.1 was used. The whole scoring volume geometry comprising the cylindrical sensitive volume and the target cylinders is not intended to represent a biological entity (at variance, for example, with the cell model used by Incerti et al. [99]). Instead, the aim is to random sample the track with biologically meaningful volumes in a similar way as presented by Nikjoo et al. [128]. The target volume dimensions were chosen to represent a DNA segment of 16 nm of length. Other authors have used a shorter length of 3.4 nm corresponding to the maximum interaction length of individual breaks forming a DSB [85], [75]. However, such short volume could prevent the scoring of biologically relevant large clusters extending beyond 3.4 nm. This is supported by Schulte et al. results [167] where a
volume length of 16 nm was found to lead to more realistic results than a short segment of 3.4 nm.

The second critical point of nanodosimetry applications consists in the possibility of estimating nanodosimetric quantities produced in nanometric volumes of biological tissue – or at least of water – from measurements in macroscopic volumes of low pressure gas. In the literature review presented in section 2.2.2, it was shown that the nanodosimetric quantities produced in volumes of water and in volumes of gas with the same mass per area are equivalent up to a scaling factor. This scaling factor depends only on the ratio of the primary particle mean free path in the two media and on the different behavior of secondary electrons in gas and water. Moreover, the scaling factor dependence on secondary electrons can be neglected for the particular irradiation geometry commonly used in the nanodosimetry studies. This makes the scaling procedure straightforward.

The simplified scaling procedure was used in this work to convert the ICSD obtained in gas with the random cylinder sampling approach to distributions in water (see section 3.2.2). Despite the procedure is not formally correct for the particular geometry proposed, nanodosimetric quantities obtained in gas and water were found to be very similar. This indicates that the secondary electron ionization mean free path, spectral distribution and energy degradation are similar in propane gas and in liquid water. The small differences observed between the ICSD produced in the two media are likely to be related to the slightly different behavior of secondary electrons in water and gas. As shown in figure 2.1 of chapter 2, the electron ionization cross-section is slightly larger for propane gas than for liquid water. This is consistent with the larger mean ionization cluster size observed in propane for all the proton energies investigated. Differences between the mean cluster sizes obtained in the two media increase with decreasing particle energy. This could be explained by the larger number of secondary electrons produced with increasing LET. The difference between gas and water is further reduced when comparing nanodosimetric quantities obtained from ICSDs in the two media. As shown in section 3.2.2, the distributions of additional SB – in particular in the large cluster region– is more sensitive to differences in the ICSDs, differences between the yields in the two media are within 11%. In light of these results, it is reasonable to state that by analyzing radiation tracks measured in gas with the random cylinder sampling approach the value of biologically relevant nanodosimetric quantities that would be produced in nanometric water volumes can be predicted.

Under the assumption that different mixed radiation fields producing similar ICSDs – and irradiating the same biological tissue – are biologically equivalent, it would be of great interest for particle therapy to combine dif-
3.4. Discussion and summary

Different radiation qualities in order to obtain a given biological effect. In section 3.3, it was shown that by optimizing the fluence of different radiation qualities a mixed radiation field producing an ICSD equivalent to a reference radiation distribution can be obtained. This result could be used to produce biologically weighted particle therapy plans as will be shown in chapter 5. Before the clinical application of these results, radiobiological experiments assessing the equivalence of the biological outcome of cells irradiated with mixed particle radiation fields characterized with nanodosimetric quantities should however, be performed.
Chapter 4

Nanodosimetric characterization of out-of-field radiation in proton therapy

4.1 Introduction

The increasing diffusion of radiation therapy for cancer treatment calls for an accurate estimate of long term radiation effects, in particular of secondary cancer induction due to out-of-field radiation. Because of the long lifetime expectation and larger sensitivity to radiation compared to adult patients, the main concern is on the treatment of young patients. Epidemiological data from the Childhood Cancer Survivor Study show a correlation between x-ray radiation treatment and secondary tumor occurrence.

In proton therapy, highly conformal dose distributions can be delivered due to the sharp distal dose fall-off characteristic of ion interaction with matter. Therefore, the integral dose to healthy tissue is reduced compared to photon irradiation causing a significant reduction of the secondary cancer risk. However, the contribution of neutron fields produced in nuclear interactions of high energy protons is not included in the standard integral dose calculation [63]. Although the absorbed dose from secondary neutrons is small compared to the primary proton dose, such neutron fields could give an important contribution to long term effects due to the large neutron biological effect [2].

The intensity and energy spectra of neutron fields created in proton therapy depend on the delivery technique. In the passive scattering delivery, the most part of neutrons are produced due to proton interactions with high-Z materials of the multiple beam-shaping components present in the beamline. On the other hand, in the active scanning delivery, neutrons are essentially produced only in the patient. Several studies have been performed to simulate and measure the neutron out-of-field radiation and compare the
dose equivalent delivered to the patient by the different irradiation techniques [187]. The general finding is that treatments with protons deliver higher neutron dose equivalent than x-ray treatments, in particular for the passive scattering delivery. However, dose levels were found to be still comparable – or even lower in the case of active scanning – to stray radiation in photon therapy [137], [92]. Risk models based on simulated and measured dose equivalent have been developed to assess the risk for secondary malignancy induction of the treated patients. Applications of those models showed that considering both primary dose and secondary dose contributions, as much as 50% secondary cancer incidence reduction is obtained with the active scanning delivery compared to 3D conformal photon therapy. Moreover, Schneider et al. [165] showed that the secondary cancer risk for the passive scattering delivery is larger than active scanning risk but still comparable with the risk for IMRT photon therapy. Results of the aforementioned studies are still controversial [163]. Neutron measurements are indeed difficult to perform and prone to errors. Moreover, the biological effect of neutrons for the cancer induction endpoint is not well known. According to the ICRP recommendations [4], neutron equivalent doses are calculated using weighting factors based on RBE for the induction of stochastic effects. This approach supersedes the previous use of LET dependent quality factors for dose equivalent calculation [3]. The ICRP approach is subject to several limitations and the obtained weighting factors could be underestimated for very low neutron doses [110]. Additionally, neutron weighting factors strongly depend on the particle energy. Therefore, time-consuming spectra measurements have to be performed along with dose measurements for the assessment of the biological effectiveness of neutron fields in proton therapy. Finally, risk models are subject to large uncertainties due to the lack of information on cancer induction processes. Epidemiological studies which could be used to benchmark the risk models are scarce due to the long follow-up time necessary for the evaluation of radiation induced malignancies.

Nanodosimetry could become a convenient alternative method for the experimental characterization of out-of-field radiation in particle therapy. Indeed, the track structure of the mixed field radiation could be directly characterized and compared for different treatment modalities. Thus, the overall biological effect of the out-of-field radiation could be assessed without the need of measuring the different radiation components. This allows to avoid the critical use of weighing factors or RBE models for equivalent dose conversion.

The work presented in this chapter aims to test the applicability of nanodosimetry for characterizing out-of-field radiation in proton therapy with Monte Carlo (MC) simulations. A combination of condensed history and track structure simulations was used to obtain values of the nanodosimet-
ric quantities produced in a macroscopic water phantom irradiated with a monoenergetic proton field. Values of nanodosimetric quantities produced by neutrons were compared to those produced by the rest of out-of-field radiation in order to assess the relative biological effectiveness of the different components. Furthermore, nanodosimetry-based radiation quality factors were calculated for comparing the biological effectiveness of out-of-field radiation relative to reference low-LET radiation.

4.2 Materials and Methods

4.2.1 Simulation set-up

MC simulations were performed with Geant4 version 10.02, including the Geant4-DNA extension. Due to the large computation time needed for track structure simulations, condensed history and step-by-step approaches were combined for the particle transportation in macroscopic volumes. The simulation set-up consisted in two stages.

1) A first Geant4 simulation was performed to obtain the out-of-field radiation phase-space within a water phantom irradiated with protons. In figure 4.1, the simulation geometry is shown. A cube of 40 cm side made of water was irradiated with a proton circular field of 5 cm diameter. The field comprised $10^9$ protons with an energy of 200 MeV. The out-of-field radiation phase-space was collected at five positions in the phantom. In order to improve the statistics, the following scoring approach was adopted. Rings of different radius made of 1 cm side voxels were placed at three depths along the beam axis. Namely, three rings of 10 cm radius were set at 15 cm, 24 cm, and 35 cm depth in order to get information on out-of-field radiation at 10 cm off-axis before, at, and after the Bragg peak. Furthermore, two rings of 5 cm and 14 cm radius were added at 24 cm depth in the phantom to obtain additional information at the Bragg peak depth at 5 cm and 14 cm off-axis. Information on type, location, energy, and momentum of particles entering the voxels of the five scoring rings were collected for the five scoring locations. The neutron field component was distinguished from the rest of the out-of-field radiation. The energy deposited in the scoring volumes was also collected. Standard Geant4 physics including the recommended physics models for hadrontherapy simulations was used at this simulation stage. Namely, standard electromagnetic (EM) physics (G4EmStandardPhysics_option3), hadron physics (G4HadronPhysics_QGSP_BIC_HP), hadron elastic scattering physics, stopping physics, ion physics and decay models were activated. A range cut of 100 μm was set for the tracking of all particles. Information obtained at this stage was used for the
4. Nanodosimetric characterization of out-of-field radiation in proton therapy

Figure 4.1: Macroscopic simulation geometry. A 5 cm diameter circular proton beam impinges on a cubic water phantom of 40 cm side. The five voxelized rings surrounding the beam represent the scoring volumes.

Macroscopic characterization of the different field components and as input for the second simulation stage.

Figure 4.2: Sketch, not in scale, of the microscopic simulation geometry. A voxel of 1 cm is subdivided in regions comprising an outer-shell and an inner-shell. At the center of the inner-shell region, $10^4 \times 10^4$ cylindrical sensitive volumes are set.

2) The particles collected at the surface of the five scoring rings were used as source for a second simulation. In order increase the statistics without increasing the computation time, the voxels composing the five scoring rings were condensed by shooting all particles from the entrance surface of one single voxel for each scoring location. As shown in figure 4.2, the voxel was subdivided in regions in order to use different tracking models and parameters within the volume. A slab of 3µm thickness was set in the middle of the voxel (inner-shell region). Within this region, Geant4-DNA EM models based on step-by-step transportation were activated and a kill threshold of 11 eV was set for electrons. A two-dimensional array of $10^4 \times 10^4$ cylindrical volumes of 1µm diameter and height was created at the center of the inner-shell region and set as sensitive volume for the collection of radiation tracks. The inner-shell region was embedded in the outer-shell region consisting in a slab of 11µm thickness. The Livermore EM models with a
production cut of 1 µm were used in the latter region while the Livermore EM models with a production cut of 10 µm were used in the rest of the voxel volume. The same nuclear physics models used in the first simulation were also activated in all the voxel regions. The output of the second simulation stage consisted in the coordinates of ionization events produced within the cylindrical sensitive volumes.

4.2.2 Macroscopic characterization

The phase-space obtained at the first simulation stage was analyzed for obtaining information on the composition of the mixed radiation field produced outside the primary irradiation field. For analysis purpose, the out-of-field radiation was divided in two subfields. The neutron component \((n)\) comprised neutrons and all particles created by neutron interactions. The second subfield \((n^c)\) comprised all the rest of out-of-field radiation. The composition of the \(n\) and \(n^c\) subfields was compared computing the fluence per primary proton of the different particles composing the two mixed fields. Furthermore, the particle kinetic energy spectra were obtained for each scoring location. The physical absorbed dose delivered by the two components was also compared.

4.2.3 Nanoscopic characterization

The radiation tracks obtained at the second simulation stage were analyzed with the track sampling approach presented in section 3.2.1 of chapter 3. For each sensitive volume, \(10^5\) random cylinders of 2.3 nm diameter and 16 nm height were used for sampling the collected tracks. From this procedure, the ICSDs produced by the out-of-field radiation at different locations in the target were obtained.

Conditional ICSDs \((P^*(v|Q))\) – defined as distributions normalized to the total number of events producing at least one ionization in one target cylinder – were calculated for characterizing the track structure of the mixed radiation field components. From those distributions, the following nanodosimetric quantity was calculated:

- Cumulative probability of biologically effective clusters:

\[
F_{4-15}(Q) = \sum_{v=4}^{15} P^*(v|Q)
\] (4.1)

This quantity was defined for describing the average quality of a given radiation field in terms of clusters of four to fifteen ionizations. Such clusters
were assumed to be relevant for induction of clustered DNA damages leading to the carcinogenesis endpoint (see discussion in section 4.4).

Absolute ICSDs ($P(\nu|Q)$) – defined as distributions normalized to the total number of primary particles – were calculated for deriving the yield of large clusters per primary proton defined as follows:

- Yield of large clusters:

$$Y_{LC} = \sum_{\nu=4}^{15} P(\nu|Q)$$  \hspace{1cm} (4.2)

Large clusters were defined as those clusters comprising four to fifteen ionizations. Such clusters are generally assumed to be responsible for complex DSBs or other clustered damages. Very large clusters with more than fifteen ionizations were assumed to be not biologically relevant (see section 4.4). The ionization cluster yield takes both radiation quality and fluence into account. Therefore, such quantity was used to quantify the biological effectiveness of a given radiation field.

The listed quantities were calculated for the $n$ and $n^c$ subfields separately and for a uniform irradiation of the voxels with $^{60}\text{Co}$ gammas chosen as reference low-LET radiation. Nanodosimetry-based radiation quality factors were then calculated as the ratio of nanodosimetric quantities produced by out-of-field radiation and $^{60}\text{Co}$ gammas according to equation 4.3.

$$Q_{ND}^* = \frac{F_{4-15}}{F_{4-15}^{(\text{ref})}}$$ \hspace{1cm} (4.3)

$Q_{ND}^*$ was used to compare two radiation fields in terms of the relative probability of producing biologically relevant ionization clusters. Furthermore, large cluster yields were converted to $^{60}\text{Co}$-dose using equation 4.4. This quantity represents the amount of gamma dose necessary to produce the same yield of large clusters as a given radiation.

$$D_{(^{60}\text{Co})} = \frac{Y_{LC}}{Y_{LC}^{(\text{ref})}}$$ \hspace{1cm} (4.4)

Finally, comparing the dose per proton delivered by a given radiation field with $D_{(^{60}\text{Co})}$, a dose weighing factor taking both radiation quality and fluence into account was obtained (equation 4.5).

$$Q_{ND} = \frac{D_{(^{60}\text{Co})}}{D}$$ \hspace{1cm} (4.5)

Given the large statistics, the maximum statistical error was less than 1% for all nanodosimetric quantities.
4.3 Results

4.3.1 Macroscopic characterization

In figure 4.3, the fluence composition of the mixed radiation field produced outside the primary proton beam is shown. The composition of the neutron subfield ($n$), is rather similar at all scoring points. Electrons and protons are the most frequent charged secondaries from neutrons. The proportion of those two components with respect to the total number of charged particles varies from 26% to 65% and from 35% to 72% for electrons and protons, respectively. The rest of charged particles from neutrons are hydrogen and helium isotopes, respectively while the ions contribution includes carbon, beryllium, boron, oxygen, nitrogen, lithium and their isotopes.
4. Nanodosimetric characterization of out-of-field radiation in proton therapy

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Figure 4.4: Neutron spectra at 10 cm off-axis and 15 cm, 24 cm, and 35 cm depth in the water phantom. Sampling point coordinates are indicated in the plot titles. Fluence is measured in number of particles per mm^2 per primary proton.

Helium isotopes, and heavy ions. The contribution of those particles is smaller than 2% at all scoring locations. The composition of the n_c subfield varies for the different scoring points. Gamma is the most frequent component at all locations. This radiation component is generated by nuclear interactions of primary protons. The proton fluence reaches its maximum at 5 cm off-axis (52% of the charged particles) and decreases with increasing distance from the primary field. Such protons are mainly primary protons undergoing to elastic Coulomb scattering with the target nuclei or protons produced in nuclear interactions. Helium isotopes and heavier ions are present only in the close proximities of the primary field and their proportion is <1% of the charged particles.

Neutron energy spectra produced at 10 cm off-axis and at three different depths are shown in figure 4.4. The distributions are characterized by two peaks one in the thermal region and one in the fast – ultra-fast region. The relative height of the two peaks changes with depth: the fast neutron component increases between the first and second depth and decreases between 24 and 35 cm depth while the slow neutron component decreases with increasing depth.

In figure 4.5 and 4.6, the energy spectra of protons belonging to the n and n_c subfields are shown for the three depths considered. Protons generated from neutrons (figure 4.5) are mainly low energy particles. This high-LET radiation contributes to the large biological effect of neutron radiation. On
4.3. Results

**Figure 4.5:** Energy spectra of protons generated by neutron interactions. The coordinates of the sampling points are indicated in the plot titles. The fluence is measured in number of particles per mm$^2$ per primary proton.

**Figure 4.6:** Energy spectra of scattered primary protons. The coordinates of the sampling points are indicated in the plot titles. The spectrum at the r10-d35 coordinate is missing because the proton fluence equals zero at that location. The fluence is measured in number of particles per mm$^2$ per primary proton.
the other hand, the most frequent energy of protons composing the $n^c$ sub-field is of the order of few tens of MeV (figure 4.6).

The contribution of the $n$ and $n^c$ subfields to the absorbed dose delivered by the out-of-field radiation is shown in figure 4.7. In the proximities of the primary field, the main dose contribution is given by the scattered primary protons and gammas from proton nuclear interactions. However, such contribution shows a steep decrease both with depth and off-axis distance. On the other hand, neutron dose slightly increases with depth before the Bragg peak and slightly decreases afterwards. Furthermore, the neutron dose decreases with increase in off-axis distance at a slower rate than proton and gamma dose. As result, the neutron dose contribution becomes dominant few centimeters away from the primary field edge.

![Figure 4.7: Plots of out-of-field absorbed dose per primary proton as a function of depth in the phantom (left panel) or off-axis distance (right panel). The dose contribution of $n$ and $n^c$ subfields are shown in black and red, respectively. The total out-of-field dose per proton is represented in green.](image)

### 4.3.2 Nanoscopic characterization

The conditional ICSDs obtained at 10 cm off-axis and three different depths ($d$) in the phantom are shown in the upper panels of figure 4.8. Such distributions are representative of the average quality of the mixed radiation field produced at each scoring location. The ICSDs produced by the $n$ and $n^c$ subfields are compared to the distributions produced by a uniform irradiation with $^{60}$Co gammas. In the legend box, the values of $F_{4-15}(Q)$ per primary proton producing at least one ionization in the target volume are reported. The distributions of the $n$ subfield are remarkably different from the gamma distributions. Secondaries from neutrons produce in general larger clusters with larger frequency than low-LET reference radiation. The ICSDs produced at different depths are similar to each-other. However, the cumulative probability of biologically relevant clusters slightly increases with depth. Conversely, the $n^c$ distributions are different at different depths.
4.3. Results

Figure 4.8: Upper plots: conditional ICSDs obtained at 10 cm off-axis and three different depths ($d$) in the phantom (before, at, and after the Bragg peak). Lower plots: conditional ICSDs obtained at 24 cm depth and three different off-axis distances ($r$). The ICSD produced by uniform irradiation with $^{60}$Co is shown as reference. In the legend box, values of the $F_{4-15}(Q)$ per primary proton producing at least one ionization in the target volume are reported.

Before and at the Bragg peak, the contribution of scattered protons and ions from nuclear interactions is visible. After the Bragg peak, only low-LET radiation is present and the ICSD produced at this location agrees with the reference distribution. In the lower panel of figure 4.8, the same analysis is shown for the out-of-field radiation produced at 24 cm of depth and different off-axis distances ($r$). Also in this case, the neutron ICSDs differ from the reference distribution. The cumulative probability of biologically-relevant clusters slightly decreases with off-axis distance indicating that the composition of the mixed field produced by neutrons varies with distance from the field edge. In the case of the $n^c$ component, the distributions are more similar to the gamma distribution at all the locations. However, the $F_{4-15}(Q)$ values are larger at small off-axis distance due to the contribution of scattered protons.

The nanodosimetry-based quality factors $Q_{ND}$ calculated from the conditional ICSDs are plotted in figure 4.9 as a function of depth and off-axis distance. The neutron quality factor slightly increases with depth - going from 3.6 to 3.9 - and decreases with off-axis distance. In the case of the $n^c$ subfield, the average quality factor increases with depth until the Bragg peak and rapidly decreases down to unit afterwards. A steep decrease of $Q_{ND}$ is also visible at large off-axis distance. The average quality factor of
4. Nanodosimetric characterization of out-of-field radiation in proton therapy

Figure 4.9: Nanodosimetry-based quality factors $Q_{ND}^*$ as a function of depth (left panel) and off-axis distance (right panel).

The total out-of-field radiation increases with increasing distance from the field edge as the neutron component becomes dominant. In figure 4.10, the absolute ICSDs obtained at different depths (upper plots) and different off-axis distances (lower plots) are shown. Those distributions represent the combined probability of a secondary particle producing a ionization given the probability of such secondary particle being produced by a primary proton. As a consequence absolute distributions depend both on radiation quality and particle fluence. The effect of the secondary particle fluence on the distributions is visible, for example, by looking at the $n$ subfield plots in figure 4.10. Due to the fact that both neutron dose and quality factor are rather constant with depth, the absolute ICSDs obtained at different depths are similar. Conversely, the neutron fluence decreases with off-axis distance. As a consequence, the frequency of all cluster sizes is much smaller at 14 cm than 5 cm off-axis. Similar observations are valid for the $n'$ subfield. In the legend box of the plots, the values of $Y_{LC}$ per primary incident proton are reported.

The yields of large clusters per primary proton obtained from the absolute ICSDs were converted to $^{60}$Co-dose per proton using equation 4.4. The results are plotted as a function of depth and off-axis distance in figure 4.11. By comparing the $^{60}$Co-dose plots with the plots of the physical absorbed dose (figure 4.7), it can be observed that, due to the large radiation quality factor of neutrons, the $^{60}$Co-dose is larger than the physical absorbed dose. For a quantitative comparison of the $^{60}$Co-dose and physical dose plots, the ratio of the two values was calculated for each sampling point in the phantom according to equation 4.5. The $Q_{ND}$ values obtained are plotted in figure 4.12. From the plots, it can be observed that the neutron out-of-field dose results in a yield of large clusters that is from 1.6 to 2 times larger than the yield produced by low-LET radiation at the same dose level. The out-of field dose of the $n'$ subfield is also up to 1.3 times more effective in producing large clusters than low-LET radiation in the proximities of the
4.3. Results

Figure 4.10: Upper plots: absolute ICSDs obtained at 10 cm off-axis and three different depths ($d$) in the phantom (before, at, and after the Bragg peak). Lower plots: absolute ICSDs obtained at 24 cm depth and three different off-axis distances ($r$). Distributions include events producing zero ionizations in the target volume. However, due to the large frequency of such events, the zero bin is not shown for a better visualization of the plot. In the legend box, values of $Y_{LC}$ per primary incident proton are reported.

Figure 4.11: Plots of $^{60}$Co-dose that would produce the same yield of large clusters as the out-of-field radiation at different distances from the field edge.
primary field edge. As result, the total out-of-field dose produces a yield of large clusters that is from 1.4 to 1.7 times larger than the yield produced by gamma dose depending on the distance from the primary field edge.

### 4.4 Discussion and summary

In this chapter, results of MC simulations performed to prove the potential of nanodosimetry for the characterization of the biological effectiveness of the out-of-field radiation produced in proton therapy were presented.

The out-of-field radiation consists mainly in primary scattered protons, and gammas and neutrons produced in nuclear interactions of high energy protons with the target nuclei. Among those components, the neutron radiation is of particular concern, due to its large biological effectiveness. Moreover, the assessment of the neutron biological effectiveness is subject to large uncertainties and is complicated by the strong dependence on neutron energy. According to the latest ICRP recommendations [2], the neutron radiation weighting factors vary as a continuous function of energy in a range from 2 to 20 and the largest values are obtained for energies between 0.1 MeV and 10 MeV. The standard approach to characterize the biological effectiveness of out-of-field radiation consists in measuring the dose contributions of the different components of the mixed field and using either quality factors or weighting factors to obtain point equivalent doses or average equivalent doses to organs. Energy spectra measurements are also necessary for the assessment of the quality factor (or weighting factor) of the neutron component (see for example [107], [127], and [49]).

Results of the macroscopic characterization of the out-of-field radiation presented in section 4.3.1 give an idea of the complexity of the mixed field produced out of the primary field even in the simplified case of mono-energetic protons interacting with a water phantom. The neutron spectra obtained at different scoring points in the phantom show that the neutron energy...
distribution varies with depth and lateral distance from the field edge. As consequence, the neutron biological effect is different at each location. The plots of the absorbed dose as a function of depth and off-axis distance show that neutrons deliver dose far away from the primary beam. This is due to the long mean free path of neutron interactions in water. Elastic scattering is the most frequent neutron interaction in water while energy deposition occurs mainly via secondary protons. As shown in the proton spectra obtained from simulations, such protons are mainly low energy protons and thus, particles with large biological effectiveness.

In section 4.3.2, it was shown that the complex characterization of the different out-of-field components could be avoided using nanodosimetry. Important information for assessment of radiation biological effectiveness can indeed be obtained from the direct characterization of the spatial distribution of ionizations produced by the mixed field. From the conditional ICSDs, nanodosimetry based quality factors $Q_{ND}$ were obtained to describe the average quality of the mixed field as a function of the distance from the primary field edge. Those factors may be seen as LET dependent quality factors $Q(L)$ [3] or $Q(y)$ based on microdosimetric measurements of lineal energy distributions [103]. However, $Q_{ND}$ values have the merit of including information on the track structure at the nanometric level. For the simple irradiation geometry simulated in this study, average quality factors ranging from 2.5 to 3.6 were obtained for the total out-of-field radiation. The largest values were found at large distances from the field edge where the neutron component is dominant. The relative low $Q_{ND}$ value indicates that neutrons produced by proton irradiation have energies outside the most effective energy range 0.1 MeV – 10 MeV. This is visible also in the neutron energy spectra obtained in section 4.3.1. The yield of large clusters per primary proton $Y_{LC}$ was proposed as nanodosimetric quantity for the quantification of the biological effect of the out-of-field radiation. This quantity includes both information on the total fluence and average quality of charged particles composing the mixed field. Therefore, $Y_{LC}$ could be considered as a substitute of the conventional dose equivalent, with the advantage of being directly measurable. Furthermore, $Y_{LC}$ was converted into $^{60}$Co-dose per proton. This allows to describe the radiation quality at a given out-of-field location in terms of low-LET radiation for which the biological effect is known. The $^{60}$Co-dose values obtained in this study rapidly decrease with both depth and off-axis distance, reflecting the rapid drop of charged particle fluence. However, the $^{60}$Co-dose decrease is less steep than the physical dose drop due to the increase of the quality factor values with distance from the field edge. The $^{60}$Co-dose per proton is from 1.5 to 1.7 times larger than the physical dose. Such low values indicate that, despite the large neutron quality factor, the large cluster yield produced by the total out-of-field radiation does not drastically increase. This is due to the fact that the neutron
fluence is low.

For the case of study presented in this chapter, the gantry geometry was not included in the simulations. Therefore, the contribution of neutrons produced in the beam line and in the beam modifier components was neglected. This omission affects the results for the PS proton delivery technique but not necessarily for the active scanning delivery as the most part of neutrons is produced within the patient in the latter case [164].

Results of the characterization of the out-of-field radiation obtained here rely on the accuracy of the physical models included in Geant4-DNA, which are subject to large uncertainties (see section 2.3). However, since the characterization is based on measurable quantities, these results could be readily benchmarked with the track imaging detector presented in chapter 6.

Nanodosimetric quantities proposed in this work for the assessment of the radiation biological effectiveness are physical quantities directly related to the radiation track structure. No biophysical models were used to convert ionization clusters into DNA damage. The rationale behind this choice is to avoid the dependence on biological parameters that may introduce uncertainties in the characterization. Nevertheless, assumptions had to be made for the definition of biologically-relevant ionization cluster sizes and the dimensions of the radiation target. Namely, cluster sizes from 4 to 15 were supposed to be important for induction of DNA clustered damages leading to late radiation effects. The lower limit of four ionizations was set in order to consider only ionization clusters large enough to produce complex DNA damages. In fact, carcinogenesis is mainly caused by genetic and chromosomal aberrations due to errors in DSB repair [7]. While simple DSBs are mostly repaired by the non-homologous end-joining repair mechanism, repair of DSBs combined with additional damages is more error-prone leading to chromosomal rearrangements [97]. The upper limit of fifteen ionizations was set as larger cluster sizes are assumed to be less effective in producing clustered damages (see section 2.2.3 and 3.4). Moreover, the frequency of larger ionization clusters is small and the use of a higher threshold does not significantly alter the conclusions. A length of 16 nm was used for the biologically-relevant target. This choice is in agreement with a previous work of Schulte et al. [167], but differs from other nanodosimetry studies suggesting a shorter size of 3.4 nm (see section 3.4). The larger target length was preferred in order to score large cluster extending beyond 3.4 nm potentially leading to complex DNA damages. A larger size of 10 nm for the biological relevant target was also suggested in [81] and [182].

As previously mentioned, in addition to nanodosimetry, microdosimetry can be used for the characterization of radiation biological effectiveness based on measurable quantities. Average quality factors and dose equivalents can be directly obtained from measured microdosimetric spectra [102].
4.4. Discussion and summary

Microdosimetry is a well established experimental technique and has been used in proton therapy for the characterization of both in-field and out-of-field radiation quality (see for example [186], [54], and [151]). However, as discussed in section 1.3.2 nanodosimetry quantities have a more direct relation with the initial biological damage than microdosimetric spectra measured in micrometric volumes.
5.1 Introduction

Particle therapy is becoming increasingly more common for the treatment of cancer. Charged particles have advantages compared to photon therapy due to the favorable depth-dose distribution (Bragg peak). Protons, to some degree, and heavy ions, in particular, are characterized by an enhanced biological effectiveness in the Bragg peak. While this feature may be useful for the treatment of radio-resistant and hypoxic tumors, it also poses a challenge. Treatment planning for ion beams is based on absorbed dose multiplied by the relative biological effectiveness (RBE). This quantity depends on many physical and biological factors, e.g., particle type, linear energy transfer (LET), cell type, biological endpoint and is, therefore, difficult to determine and subject to uncertainties.

In proton therapy, the current clinical practice is to apply a constant generic RBE value of 1.1, neglecting the tendency of larger RBE in the distal part of the spread-out Bragg peak (SOBP). Although there are no firm clinical data indicating that this practice should be changed, one can expect based on clinical evidence reviewed in [138], that the RBE of clinical proton beams is depth-dependent. On average, there will be an increase in RBE of roughly 5% at 4 mm and roughly 10% at 2 mm proximal to the distal edge of the SOBP, relative to the RBE at the mid-point of the SOBP. A higher RBE can be expected for the stopping low energy protons on the distal fall-off of the SOBP, where the dose decreases rapidly, effectively extending the clinically significant dose range by 1-2 mm. Nevertheless, this uncertainty of RBE can have clinical consequences due to the hesitance of the clinician to aim the beam at organs at risk or due to unexpected side effects. RBE variations are substantially larger in heavy ion therapy and can not be neglected. In this
case, the RBE dependence on dose, type of tissue, and LET are included in the treatment planning process. The current practice is to calculate a depth-dependent RBE value using a biophysical model and adjust the absorbed dose in order to ensure uniform biological effectiveness at each position of the SOBP. Different biophysical models are available to derive biological weighting factors, i.e., the local effect model (LEM), the microdosimetric kinetic model (MKM) or the semi-empirical passive scattering model [120]. Each model introduces a set of different parameters, which are extracted from experimental data. The use of different models and different delivery modalities produces differences in the estimated biological weighted dose up to 20%, making it difficult to compare clinical results from therapy centers using different models [8]. Since the present approaches are obviously insufficient for providing a satisfactory method to equalize biological effectiveness at each position of the SOBP, a new system of measurable radiation quality descriptors is needed [10], [141].

The goal of the work presented in this chapter is to test the feasibility of a novel approach to optimize biologically-weighted particle therapy plans using nanodosimetric quantities. The basic idea behind this approach is to optimize the fluences of individual pencil beams (PB) in order to create a mixed radiation field with equal nanodosimetric descriptors of track structure at each position of the SOBP. Simple proton and carbon-ion treatment plans with a single or two-opposing fields were simulated in a water phantom with Geant4 and nanodosimetric parameters at many positions throughout the target volume were calculated. Under the reasonable assumption that nanodosimetric descriptors of radiation quality are related to the initial DNA damage, this approach may produce optimized biologically-weighted treatments for particle therapy.

5.2 Materials and Methods

5.2.1 Monte Carlo simulations of treatment plans

The simulations presented in this work were performed with the Geant4 Monte Carlo toolkit version 10.00 [14], including the Geant4-DNA extension [101].

In order to prove the principle of the proposed optimization method, a simple linear target geometry and beam arrangement was simulated for the proton and the carbon-ion plans (figure 5.1). A macroscopic target volume, comprising a row of five cubic voxels of 5 mm side length, was created inside a cubic water phantom of 20 cm side length. To introduce a non-symmetric target position, the target center was shifted in beam direction
5.2. Materials and Methods

by 3.75 cm from the phantom center. As a consequence, the target was at 5 cm and 9.5 cm from the left and right side of the phantom, respectively. Two additional voxels, were added at the right and left edge of the target to get dosimetry information outside the target volume, i.e., in normal tissue. Beam arrangements with either a single-field or two-opposing fields impinging on the lateral aspect of the phantom were simulated. Each field consisted of ten monoenergetic Gaussian PBs with a size (sigma) of 3 mm. The energies of the PBs where chosen from a calibration curve of Bragg peak depth in water versus PB energy in order to create a SOBP with Bragg peak spacing of 2.5 mm in depth, i.e., two PBs aimed at each target voxel for single-field plans. In order to achieve an acceptable homogeneity of the SOBP, range shifters and ripple filters where included in the simulations. In the proton plan simulations, twenty-four polyethylene range shifters of 0.45 cm thickness each where placed along the beam, at 10 cm from the phantom surface (figure 5.1 (a)). The PB energy selected in order to cover the target ranged from 151 MeV to 186 MeV. In the carbon-ion plan simulation, two ripple filters designed as in [30] where placed along the beam path, at 35 cm from the phantom surface (figure 5.1 (b)). The PB energies ranged from 154 MeV/u to 246 MeV/u.

The Geant4-DNA extension was used for the simulation of the radiation track structure. Using this extension, protons, carbon ions and their secondaries were transported step-by-step in water down to very low energies. A cut-off of 11 eV was set for electrons. The spatial distribution of the ionization events was obtained from the simulations.

Figure 5.1: Sketch of the simulation set-up. Top: proton simulations with range shifters and the water phantom shown. Bottom: carbon-ion simulations with two ripple filters and the water phantom shown. Red-colored voxels represent the target region.
The macroscopic target was divided into a series of sub-volumes, defined as regions (figure 5.2). The step-by-step transportation was activated in the sensitive volume plus a surrounding shell of micro-metric thickness, while the standard Geant4 condensed history transportation with region specific production cuts, was used for the rest of the volumes. In the world and water phantom regions the Livermore electromagnetic (EM) physics models were activated and a production cut of 100 µm was set for secondaries. As shown in figure 5.2, three slabs of 5 × 5 mm² area and 20 µm thickness (outer shell) were placed in each of the five target voxels and in the two normal-tissue voxels at three different locations (proximal, center, distal). The Livermore EM models with a production cut of 1 µm were used in the outer-shell regions. The Livermore EM models with a production cut of 10 µm was used in the rest of the voxel volume. An additional region (inner shell) comprising a volume of 5 × 5 mm² area and 2 µm thickness was embedded at the center of each outer shell. In these volumes, the step-by-step transportation using the DNA EM models were activated. Finally, a two-dimensional array of 10⁴ × 10⁴ cylindrical volumes of 500 nm diameter and 500 nm height was created at the center of each inner-shell region and set as sensitive volume (scoring cylinders). The x, y and z coordinates of the ionization events produced by the primary particles and their secondaries were collected in the scoring cylinders. The hadron physics models and radioactive decay physics were activated in addition to the EM physics models in order to take nuclear interactions into account.

For the proton plans, 10⁵ histories per PB were simulated, while for the carbon-ion plans 5 × 10⁴ histories were simulated due to the larger computation time necessary for carbon-ion tracking. The calculation time for the entire plan was of the order of days for protons of weeks for carbon ions.
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Figure 5.3: Representation of the track sampling procedure. The big cylinder represents one of the sensitive volumes. Small cylinders with random position and orientation represent the targets used for the track sampling.

5.2.2 Calculation of nanodosimetric quantities

The radiation tracks obtained in the simulations were analyzed with the track sampling approach presented in section 3.1. Each cylindrical sensitive volume was sampled with $10^4$ random cylinders, and the number of ionizations collected in each microscopic target volume was stored for the ICSD computation (figure 5.3).

For each pencil beam $i$ and voxel $j$, the following ICSDs were computed:

1. **Absolute ICSD**, $P_{i,j}(v|Q)$: represents the probability of generating a cluster of $v$ ionizations normalized to the total number of initial primary particles. $Q$ represents the radiation quality of the radiation field produced by the PB $i$ in the voxel $j$.

2. **Conditional ICSD**, $P_{i,j}^*(v|Q)$: represents the probability of generating a cluster of $v$ ionizations normalized to the number of primary particles generating at least one ionization in the microscopic target volume.

ICSDs were computed at three depths (proximal, central and distal) in each voxel and the results were averaged in order to obtain a representative ICSD for PB $i$ and voxel $j$. From the absolute distributions the following nanodosimetric descriptors were derived:

1. **Mean absolute ionization cluster size (ICS)**:

\[
(M_1)_{i,j} = \sum_{v=0}^{\infty} v P_{i,j}(v|Q)
\]  

(5.1)

This quantity is the first moment of the absolute ICSD and represents the mean number of ionizations produced in the microscopic target by the PB $i$ in voxel $j$. 

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2. Yield of small clusters:

\[(Y_{SC})_{ij} = \sum_{\nu=2}^{3} P_{ij}(\nu|Q) \quad (5.2)\]

Small clusters were defined as those clusters comprising two or three ionizations. Such clusters are generally assumed to be responsible for isolated or simple DNA DSBs.

3. Yield of large clusters:

\[(Y_{LC})_{ij} = \sum_{\nu=4}^{10} P_{ij}(\nu|Q) \quad (5.3)\]

Large clusters were defined as those clusters comprising four to ten ionizations. Such clusters are generally assumed to be responsible for complex DSBs or other complex damages. Very large clusters with more than ten ionizations were not included in the computation.

The listed nanodosimetric quantities were calculated for unit PB fluence, i.e., one primary particle per PB, and were used as starting conditions for the optimization of the treatment plans. Furthermore, the following quantities were calculated for each voxel \( j \) in order to evaluate the radiation quality of the composite radiation fields created by all PBs:

1. Mean conditional ICSD:

\[
(M^*_{1})_{ij}(Q) = \frac{\sum_{\nu=2}^{\infty} \nu P^*_{ij}(\nu|Q)}{\sum_{\nu=1}^{\infty} P^*_{ij}(\nu|Q)} \quad \left( P^*_{ij}(\nu|Q) = \sum_{i=1}^{\#PBs} P^*_{ij}(\nu|Q) \right) 
\]

(5.4)

This quantity is the first moment of the conditional ICSD \( P^*_{ij}(\nu|Q) \) produced by the mixed field generated by the contribution of all PBs in the voxel \( j \).

2. Biologically effective mean ICS:

\[
(M^{bio}_{1})_{ij}(Q) = \frac{\sum_{\nu=2}^{10} \nu P^*_{j}(\nu|Q)}{\sum_{\nu=2}^{10} P^*_{j}(\nu|Q)} 
\]

(5.5)

This quantity was defined for evaluating the radiation quality of the mixed radiation field in terms of clusters of 2-10 ionizations.

The maximum statistical error was less than 1% for all the calculated nanodosimetric quantities.
5.2.3 Plan optimization

The Matlab® function `lsqlin` was used to solve the constrained linear least-squares problem associated with the PB fluence optimization. Two different optimization strategies with different goals were used.

1. **Uniform \( M_1 \):** the PB fluences \( w_i \) where optimized with the goal to obtain a uniform mean absolute ionization yield in the macroscopic target.

2. **Uniform cluster yields:** the PB fluences \( w_i \) where optimized with the goal to obtain uniform yields of small and large clusters in the macroscopic target.

The first optimization strategy is equivalent to achieving a uniform absorbed dose plan. Indeed, the mean ionization yield \( M_1 \) is related to the macroscopic absorbed dose according to equation 5.6, where \( W \) is the mean energy required to form an ion pair upon the complete slow down of ionizing particles and \( m \) is the mass of the microscopic target.

\[
D = \frac{M_1 W}{m} \quad [Gy]
\]  

(5.6)

The optimization of single- and two-field proton and carbon-ion plans were analyzed in two steps. First, conditional and absolute ICSDs produced in the irradiated volume were calculated in each voxel of interest for unit fluence. Secondly, the PB fluences were optimized to obtain either uniform \( M_1 \) or uniform cluster yields in the target and the optimized plans were evaluated in terms of nanodosimetric quantities.

5.3 Results

5.3.1 Proton plans

5.3.1.1 Single-field optimization

In figure 5.4, the composite ICSDs obtained for the single-field proton plan with PB unit fluences are shown. The plots in the left panel, represent the composite absolute ICSDs produced by all PBs in the five target voxels (2-6) and in the two normal-tissue voxels (1 and 7). Due to the single-field arrangement, the fluence decreases with depth. This leads to lower absolute frequencies of clusters. The probability to obtain one or more ionization in the microscopic target is larger for the superficial voxels of the macroscopic target and is lower in the most distal voxel, where only the tail of the most
penetrating Bragg peak is present. In the right panel, the composite conditional ICSDs are shown. The conditional ICSDs and their first moments $M^*_1$ are representative of the radiation quality present in each voxel. The larger clusters occur with larger frequencies in the distal voxels (6 and 7) where the dose is delivered exclusively by stopping protons. $M^*_1$ increases with increasing depth; e.g., $M^*_1$ is 18% larger in the distal voxel than in the entrance voxel. This behavior is due to the increasing contribution of stopping protons towards the distal end of the field.

Figure 5.5 shows the composite $M_1$, $Y_{SC}$ and $Y_{SC}$ values for the two PB fluence optimization strategies as a function of the voxel depth. As expected, the uniform $M_1$ optimization strategy produces a uniform $M_1$ distribution in the macroscopic target (figure 5.5 (a)). However, the yields of both small and large clusters increase with depth (figure 5.5 (c)). In figure 5.5 (e) the frequencies of small and large clusters relative to the total yield of clusters produced in the voxels are shown. The relative frequency of large clusters slightly increases with depth and a steeper increase is observed in the last two voxels, where the contribution of low energy proton increases. For the uniform cluster yield optimization strategy the optimization algorithm decreases the small and large cluster yields in the distal voxels assigning lower weights to the most penetrating PBs (figure 5.5 (d)). However, an optimal solution providing a uniform yield of both large and small clusters could not be found due to the insufficient number of degrees of freedom for this optimization problem. Figure 5.5 (f) shows that $M^{bio}_1$ increases with increasing depth despite the PB fluence optimization.
5.3. Results

Figure 5.5: Nanodismetric quantities calculated for the single-field proton plans as a function of the voxel depth. Results of the uniform $M_1$ optimization and uniform cluster yield optimization are shown in the left and right column, respectively. (a), (b), composite $M_1$. (c), (d) composite $Y_{SC}$ (squares) and $Y_{LC}$ (triangles). (e) frequency of small clusters, $Y_{SC}$ (squares) and large clusters, $Y_{LC}$, (triangles) relative to the total yield $Y_{SC} + Y_{LC}$. (f) composite $M_{bio}^1$.

5.3.1.2 Two-opposing field optimization

In figure 5.6, the composite ICDSs obtained for a proton plan with two-opposing fields using unit PB fluences are shown. The absolute ICDSs (left panel) have similar frequencies for all the macroscopic target voxels. The ionization frequency is smaller in the normal tissue voxels, where a lower particle fluence is present and the radiation field is mainly comprised of fast protons. The conditional ICSDs (right panel) are almost overlapping, indicating that the mixed field radiation quality is similar at all the target depths. $M_1^*$ in the normal-tissue voxels at the macroscopic target edge has the same values as in the target due to the distal Bragg peak penumbra of the most penetrating PBs.
Both the uniform $M_1$ and uniform cluster yield optimization were successful in this case. Figure 5.7(c) and (d) show that uniform distributions of both $Y_{SC}$ and $Y_{LC}$ are obtained in the optimized plans. This result is due to the opposing-beam configuration. The dose is delivered by the same number of Bragg peaks and plateaus in each target voxel. Therefore, radiation fields of similar quality are present at all depths. The relative frequency of small and large clusters displayed in figure 5.7(e) confirms that all voxels are irradiated with the same share of densely and sparsely ionizing radiation. The distribution of $M_{1}^{\text{bio}}$ is also uniform in the target and it slightly decreases in the normal-tissue voxels (figure 5.7(f)).

5.3.2 carbon-ion plans

5.3.2.1 Single-field optimization

Figure 5.8 shows the composite ICSDs obtained for the single-field carbon-ion treatment plan. The absolute ICSDs (left panel) show a larger frequency of all clusters per unit particle fluence compared to protons. The densely ionizing effect of carbon ions is apparent in the conditional ICSD plots (right panel) demonstrating much larger relative frequencies of larger ionization clusters and $M_{1}^{*}$ values compared to protons, in particular in the more distal voxels. A percentage difference of 82\% for $M_{1}^{*}$ is found between the proximal and distal voxel. This is explained by the rapid increase of LET with penetration depth for carbon ions. carbon-ion fragments also contribute to the $M_{1}^{*}$ increase in the distal voxels.

Figure 5.9(c) demonstrates that the uniform $M_1$ optimization of the single field plan leads to a nonuniform distribution of small and large cluster yields in the macroscopic target. The small cluster yields decreases with increasing
Figure 5.7: Nanosimetric quantities calculated for the two-field proton plans as a function of the voxel depth. Results of the uniform $M_1$ optimization and uniform cluster yield optimization are shown in the left and right column, respectively. (a), (b), composite $M_1$. (c), (d) composite $Y_{SC}$ (squares) and $Y_{LC}$ (triangles). (e) frequency of small clusters, $Y_{SC}$, (squares) and large clusters, $Y_{LC}$, (triangles) relative to the total yield $Y_{SC} + Y_{LC}$. (f) composite $M_{bio}^1$.

As in the case of protons, the optimization of uniform cluster yields does not converge to an acceptable solution (figure 5.9 (b), (d) and (f)).
Figure 5.8: Composite ICSDs obtained in the five target voxels (2-6) and in the two normal-tissue voxels (1 and 7) for the single-field carbon-ion plan with unit PB fluence. Left panel: absolute distributions (frequencies of zero-clusters not shown). Right panel: conditional distributions. The voxel numbering scheme is the same as figure 5.4. The legend box in the right panel shows the $M_1^*$ values for each voxel.

curves was larger than for the two-field proton plan (figure 5.10), indicating a larger variation of the radiation quality with depth. The difference between the minimum and maximum $M_1^*$ in the macroscopic target was of 11%.

In this case, the uniform $M_1^*$ optimization leads to a slightly nonuniform distribution of $Y_{SC}$ and $Y_{LC}$ in the target as shown in figure 5.11 (c) and (e). On the other hand, the uniform cluster yield optimization produces a plan with a flat distribution of both large and small clusters (figure 5.11 (d)). Although not included in the optimization objectives, a uniform $M_1$ distribution was also obtained in this case (figure 5.11 (b)). The $M_1^{bio}$ calculated for the optimized plan was constant in the target and lower in the normal tissue (figure 5.11 (f)).

### 5.4 Discussion and summary

A common approach to take into account the changing biological effectiveness of therapeutic ion beams has been to modify the physical dose according to the RBE concept. This requires knowledge of RBE for relevant target cells and for the dose delivered. Moreover, different biophysical models for calculating RBE – such as the LEM or the MKM – can lead to differences in the prescribed dose up to 20%, which is unacceptable.

In this work, a novel optimization strategy for particle therapy treatment planning has been proposed. The approach is based on the optimization of nanodosimetric quantities assumed to be related to the radiobiological effect. The nanodosimetry-based optimization is independent of RBE and does not require a specific biophysical model. The approach rather depends on physical quantities that can be simulated with MC track structure codes.
5.4. Discussion and summary

Figure 5.9: Nanosimetric quantities calculated for the single-field carbon-ion plans as a function of the voxel depth. Results of the uniform $M_1$ optimization and uniform cluster yield optimization are shown in the left and right column, respectively. (a), (b), composite $M_1$. (c), (d) composite $Y_{SC}$ (squares) and $Y_{LC}$ (triangles). (e) frequency of small clusters, $Y_{SC}$, (squares) and large clusters, $Y_{LC}$, (triangles) relative to the total yield $Y_{SC} + Y_{LC}$. (f) composite $M_1^{bio}$.

and benchmarked with experimental measurements. The feasibility of this planning strategy was tested for simplified proton and carbon-ion plans calculated in a water phantom with Geant4 MC simulations.

In the case of the single-field plans, the uniform cluster yield optimization approach did not produce an acceptable result. This is expected due to the insufficient number of degrees of freedom of the optimization problem. Due to the beam configuration, the mixed radiation field in the macroscopic target varies with depth. Only high-LET radiation, producing dense clusters, is present at the distal end while a mixture of high and low-LET is found in the other voxels. This makes the simultaneous equalization of $Y_{SC}$ and $Y_{LC}$ at different target depths unfeasible. The optimization was successful for
the two-opposing beam plans. Uniform distributions of $Y_{SC}$ and $Y_{LC}$ were obtained in the macroscopic target for both proton and carbon-ion plans. Although not included in the optimization, a uniform $M_1$ distribution was also obtained. In this case, the beam configuration is favorable for the equalization of the biologically relevant radiation components, since a balanced mixture of high- and low-LET radiation is present in all the target voxels. This result increases the confidence of the feasibility of the proposed optimization approach and it points out the importance of the beam configuration in treatment planning of ion beams. The results are valid for the specific simple geometry of the simulated plans. Further testing is necessary to validate this approach for more realistic scenarios with a three-dimensional target geometry and inclusion of tissue heterogeneity. This would produce more complex mixed radiation fields that may challenge the optimization.

The proposed optimization strategy is based on the assumption that nanodosimetric descriptors of the track structure directly relate to the radiation biological effect. In this work, the yields of large and small clusters per primary particle were defined as estimators of the initial biological damage. Single ionizations were neglected in the computation of the biological damage, as those are assumed to produce isolated DNA breaks that are efficiently repaired by the DNA repair system. On the other hand, clusters with two or more ionizations can produce clustered DSBs, which are considered potentially irreparable lesions, with reparability decreasing with increasing degree of lesion clustering [80]. Following these assumptions, $Y_{SC}$ may be related to simple DSBs that are usually repaired, while $Y_{LC}$ may be related to clustered damages leading to chromosomal aberrations or cell death. Both quantities were included in the treatment plan optimization as both lethal and sub-lethal damages were assumed to be relevant for the cell killing endpoint. Clusters larger than ten ionizations were not taken into account in
5.4. Discussion and summary

Figure 5.11: Nanodosimetric quantities calculated for the two-field carbon-ion plans as a function of the voxel depth. Results of the uniform \( M_1 \) optimization and uniform cluster yield optimization are shown in the left and right column, respectively. (a), (b), composite \( M_1 \). (c), (d) composite \( Y_{SC} \) (squares) and \( Y_{LC} \) (triangles). (e) frequency of small clusters, \( Y_{SC} \) (squares) and large clusters, \( Y_{LC} \) (triangles) relative to the total yield \( Y_{SC} + Y_{LC} \). (f) composite \( M_{bio}^1 \).

the optimization, due to the low frequency of occurrence.

Nanodosimetry-based plan optimization allows the delivery of biologically-weighted treatment plans, which are experimentally verifiable. Indeed, ionization cluster yields can be simulated in the patient with track structure codes and the results can be benchmarked – for the gas phase – with nanodosimetric measurements. The next step necessary before the clinical application of this approach is to perform a series of radiobiological experiments to provide clear evidences of a relation between nanodosimetric quantities and the biological effectiveness of radiation in a number of tumor systems both in vitro and in vivo.

The accuracy of the ionization cluster yields calculated in this work relies
on the physics interaction models implemented in Geant4-DNA. At the nanometer scale, step-by-step transportation of electrons down to a theoretical limit of zero eV is important. At these low energies ($\ll 100$ eV), the cross sections for liquid water are uncertain. Corrections to the plane wave Born approximation, used to calculate excitation and ionization cross sections, have to be applied. Different correction methods are present in literature and used in different MC track structure codes [58]. Semi-empirical corrections as described by Emfietzoglou and Nikjoo [56] are implemented in Geant4-DNA. Alternative models for the calculation of the liquid water dielectric response function based on more recent experimental data are available in the literature [58]. The implementation of these models could improve the accuracy of the ionization and excitation cross sections used for the simulations and as a consequence of the ionization cluster yield calculation. The yields obtained in this work may indeed be overestimated as Vassiliev et al. [181] noticed that Geant4-DNA underestimates the W-value of electrons.

An alternative approach for including the radiation quality in the proton treatment planning has been proposed by Giantsoudi et al. [77]. The authors investigated the feasibility of LET-guided plan optimization. Using a multicriteria optimization module, they were able to select among multiple dose optimized plans those producing a favorable LET distribution. More recently, Unkelbach et al. [179] presented proton therapy plans reoptimized including both absorbed dose and LET-based objectives. This approach has the advantage of being based on a physical quantity (LET) that can be both predicted with MC simulations and measured. On the other hand, the LET is a non-stochastic parameter describing the energy loss per unit of path length rather than the stochastic energy loss in sub-cellular volumes (see section 1.3). Thus, LET is only an approximation of the underlying physics of radiation interaction and can not be directly related to the radiation track structure and the yield of biologically effective lesions.
6.1 Introduction

In chapter 4 and 5, two examples of applications of nanodosimetry in particle therapy were presented. It was shown that the analysis of ICSDs produced in nanometric volumes of water can provide useful information for the characterization of the mixed radiation fields produced both inside and outside the particle treatment field. This information can eventually be used to assess the biological effect of the treatment. Unfortunately, the development of an instrument needed for such applications is particularly challenging.

In order to perform routine measurements in particle therapy, a nanodosimeter should have the following characteristics:

- portable device of small dimensions suitable for measurements in phantoms;
- relatively easy and low-cost manufacturing for mass production;
- suitable for measurements in mixed radiation fields;
- sensitive area dimensions adjustable in a large size range i.e., large sensitive area for measurements of low intensity fields outside the primary beam;
- high counting rate capabilities for measurements in the primary beam.

The existing nanodosimeters do not fulfill any of the listed requirements (see section 2.2.1). In fact, those devices are complex and bulky detectors, whose applicability is limited to research studies on track structure.

The idea for a new generation of nanodosimeters was suggested by Schulte
et al. [168]. They suggested the realization of a compact detector for imaging the three-dimensional structure of radiation track segments. The first step towards the construction of such device was achieved by Bashkirov et al. [23] with the invention of a two-dimensional single-ion detector working in low pressure gas. However, to date, the ion detector is still at the prototyping stage and no systematic characterization and optimization of its performance has been done. A complete 3D track imaging detector (TIDe) could be built using the ion-detector for the 2D localization of the ionizations produced by radiation in low pressure gas and using ion drift time measurements to reconstruct the third spatial dimension. The design and working principle of such detector is presented in section 6.2.1 of this chapter.

Having the important features of being compact, low-cost, and able to image arbitrary long track segments, the TIDe seems a promising device for performing nanodosimetric measurements in particle therapy. Therefore, the development of this detector was one of the main goals in this thesis work.

In this chapter, the results of the characterization of a TIDe detector prototype are presented. Starting from the design proposed by Bashkirov et al., two versions of the detector were built using different electrode materials. Measurements of the detector response to alpha particle tracks were performed and the results were compared to simulations in order to assess the detector performance.

6.2 Materials and Methods

6.2.1 Detector working principle

The TIDe consists mainly in a drift chamber where ionizing radiation interacts with low pressure gas, and a 2D single-ion detector for the localization of the ions produced in the interaction. In the original design proposed by Bashkirov et al., the ion detector comprises a dielectric board with a thickness of roughly 3 mm, which is mechanically drilled with sub-millimeter diameter holes. One side of the board is copper-clad with the printed circuit board (PCB) technology and the other side is in contact with an electrode of high volume resistivity. This structure is similar to the RPWELL detector which combines the working principle of THGEMs and RPCs (see section 2.6 and 2.5).

A sketch of the TIDe design is shown in figure 6.1. The anode plate placed at an adjustable distance between 1 and 5 cm above the 2D detector defines the ion drift region. The anode is biased with a positive voltage of the order of few tens of volts, while the resistive electrode is biased with a negative high voltage (HV) of the order of few hundreds of volts. The copper electrode
6.2. Materials and Methods

Figure 6.1: Schematic representation of the detector design. From top to bottom: copper anode providing a drift field ($E_d$) through the gas volume, THGEM-like structure with readout electrode on the top, high-resistivity cathode in contact with the bottom side of the board and biased with negative HV, insulating material embedding the cathode. The enlarged view shows the signal generation principle.

on the top of the board is kept at ground potential. The electric field configuration obtained in the detector for a positive voltage of 20 V applied over 1 cm drift region and a negative voltage of 800 V on the resistive electrode was calculated with the QuickField software [6] and is shown in figure 6.2. Operating the detector at gas pressures of the order of few mbar, a strong reduced field ($E/P$) of the order of few $V \, cm^{-1} \, Pa^{-1}$ is produced in the PCB holes. The TIDe working gas is low pressure propane. The choice of the gas is motivated by previous works on microdosimetry and nanodosimetry. Propane and propane based mixtures were found to perform well in gaseous detectors and were extensively used in tissue equivalent proportional counters (TEPC). Propane was also used for measurements of ionization cluster size distributions performed with the ion-counting nanodosimeter [76], the jet-counter [146], and the single electron counter [55]. Moreover, the equivalence of radiation interaction in low pressure propane and water concerning the ionization process was proven by Grosswendt [84].

The TIDe working principle can be outlined as follows: electron-ion pairs, composing the radiation track in the gas volume, are divided by the drift field ($E_d$) present the region above the ion detector upper surface. While electrons drift towards the anode, ions drift into the detector holes due to the focusing effect of the electric field configuration (see figure 6.2). The ions in the holes are accelerated by the strong reduced field and can produce impact ionization of the gas. In addition, the ions can collide with the hole walls or the cathode, resulting in secondary electron emission. The
resulting electrons are exposed to the strong electric field and create an electron avalanche that develops into a controlled discharge (i.e. a streamer). The discharge is confined in time due to the high volume resistivity of the cathode and in space by the dielectric walls of the holes. Therefore, each hole operates as an independent ion counter. Because of the high electron gain, the signal induced in the readout electrodes can be acquired with standard electronics. The 2D spatial coordinates of the counting holes can be reconstructed by segmenting the readout electrode. Because the diffusion displacement of ions in the gas is of the order of the size of the holes, the coordinates of the counting holes correspond to the time projection of the initial ionization events. The relative position of the ionization events along the third dimension can then be encoded measuring the difference in the ion arrival time.

The TIDe spatial resolution in the horizontal plane depends, on the diameter and pitch of the THGEM holes, on the pressure and type of working gas, and on the type of primary radiation. Because of the large mass of ions, such particles have a small initial energy and a limited diffusion in low pressure gas. Therefore, the ions created in the gas volume preserve information on their initial position during their drift towards the ion detector. The RMS transversal displacement of ions due to the diffusion in propane gas can be calculated using equation 2.14 and 2.13, and the $D/\mu$ values of propane ions obtained in [171] and reported in section 2.4.1:

$$x_{rms} = \sqrt{\frac{2D}{\mu E}}$$  

(6.1)

For an electric field $E$ of 20 V cm$^{-1}$, a drift length $x$ of 0.5 cm, and a pressure of 1.33 mbar, a spatial distribution with a FWHM value of 1 mm is obtained.
This value is of the order of the THGEM holes. Using equation 2.3, the dimensions in gas can be scaled to water-equivalent dimensions obtaining a transversal spatial resolution of 2.8 nm for tracks produced by $^{241}$Am alpha particles in 1.33 mbar of propane. Along the drift direction, the spatial resolution depends again on the ion diffusion, in the ideal case. However, the resolution is additionally affected by the time resolution of the single-ion detector and the data acquisition system (DAQ). Moreover, the vertical spatial distribution is broadened by the stochastic nature of the position of the ion-impact interaction in the THGEM hole diameter. The 3D spatial resolution can be easily tuned by varying the gas pressure and the drift field intensity. The possible pressure and voltage ranges are however, limited by experimental restrictions as shown in the next sections.

6.2.2 Detector design

In order to characterize the performance of the TIDe, a detector prototype was built based on the design proposed by Bashkirov et al. [23].

In figure 6.3, a drawing of the top and side view of the detector prototype is shown.

![Figure 6.3: Drawings of the detector prototype, top and side view. The dimensions shown are in millimeters. The copper anode is represented in orange, the copper clad is represented with the dashed lines in the top view and the dielectric board (FR-4 material) is represented in yellow. In the side view, the glass resistive cathode (black) embedded in an insulating plastic box (dashed black) is shown.](image)

A few PCB boards were manufactured by a standard PCB company according to the requested specifications. The boards were made of FR-4 material copper-clad on one side and had a thickness of 3.3 mm. The copper layer was additionally plated with gold to avoid the metal oxidation. 576 holes arranged in 24 lines of 24 holes each were mechanically drilled in the board. The hole pitch (distance between the hole centers) was of 2 mm along each
6. CHARACTERIZATION OF A TRACK IMAGING DETECTOR PROTOTYPE

The lines of holes were staggered (see the picture in figure 6.4), therefore, the holes covered a rectangular area of 24 mm × 48 mm. This area corresponds to the detector sensitive area in the ideal case of 100% efficiency of ion focusing into the holes. Two different PCB designs were produced, with a different hole diameter and different configurations of read-out electrodes on the upper surface. In the first PCB design (left hand side of the picture in figure 6.4) the holes were 0.8 mm in diameter and the readout electrode was common to all the holes. In the second design (right hand side of the picture in figure 6.4) the holes were 1 mm in diameter and the top readout electrode was segmented in strips connecting the lines of holes. In this design, two additional layers of read-out strips were embedded in the board at a depth of 127 µm and 254 µm, respectively. The two embedded layers of strips were oriented orthogonally to each other and at 45 degrees with respect to the strips of the top layer (see scheme in figure 6.4). As result, the signal generated in each hole is read-out individually and the counting hole can be localized in the 2D space.

Figure 6.4: Left hand side: picture of two PCBs with different designs. Right hand side: scheme of the readout strip configuration of the second PCB design. The central and the lower layers are formed by orthogonal strips – common to each row and column of holes, respectively – providing 2D readout of signal generated in the individual holes. The top layer of strips is oriented at 45 degrees with respect to the other two layers and is added to resolve hit ambiguities.

PCBs with design 1 were used for the measurements presented in this chapter. With these boards, the total signal generated in all the holes is easily acquired with a single channel DAQ. Conversely, the read-out scheme of design 2 requires a complex multichannel DAQ and data post-processing for the encoding of the 2D hole location. Therefore, such read-out will be implemented only in a second step, after the characterization and optimization of the TIDe performance.

Two versions of the prototype were built using the two different cathodes shown in figure 6.5. Cathode 1 is a plate made of standard soda-lime float glass, while cathode 2 is made of a semi-conductive glass developed by Schott Glass Technologies Inc. The characteristics of the two cathodes are
6.2. Materials and Methods

reported in table 6.1. The volume resistivity values listed in the table are obtained from the literature. These should be taken as indicative values as the actual volume resistivity may vary for different samples of the same glass. As explained in section 2.5, resistive electrodes prevent the propagation of discharges in the whole gas volume. On the other hand, the long recharge time of these materials limits the detection rate.

One side of the glass electrode was in contact with the lower surface of the PCBs. Both the glass and the FR-4 were polished in order to maximize the contact between the surfaces of the two materials and prevent the flow of currents on the cathode surface. The other side of the cathode was connected to the HV power supply with a copper electrode. Both the glass and the copper electrode were embedded in a plastic plate for insulation of the HV components.

![Figure 6.5: Picture of the two resistive cathodes used in the two versions of the TIDe prototype. Left panel: cathode made of float glass. Right panel: cathode made of Schott glass.](image)

Table 6.1: Specifications of the resistive cathodes shown in figure 6.5. The volume resistivity values ($\rho$) are values at room temperature taken from the literature. Values of the conductance per unit of area ($G$) are calculated as $G = \rho^{-1} t^{-1}$, where $\rho$ is the volume resistivity and $t$ is the plate thickness.

<table>
<thead>
<tr>
<th>Glass</th>
<th>$\rho$ [Ωcm]</th>
<th>Area [cm$^2$]</th>
<th>$t$ [cm]</th>
<th>$G$ [1/Ωcm$^2$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Float</td>
<td>$4 \times 10^{12}$ [13]</td>
<td>3.5 $\times$ 6.0</td>
<td>0.14</td>
<td>$1.8 \times 10^{-12}$</td>
</tr>
<tr>
<td>Schott</td>
<td>$1 \times 10^{11}$ [28]</td>
<td>3.3 $\times$ 5.8</td>
<td>0.3</td>
<td>$3.0 \times 10^{-11}$</td>
</tr>
</tbody>
</table>

Finally, a copper anode was set up at 10 mm above the upper surface of the PCB. The anode dimensions were slightly larger than the detector sensitive area in order to avoid edge effects causing distortion of the drift field.
6.2.3 Experimental set-up

The TIDe prototype was set up into a gas-tight chamber installed in the Loma Linda University Radiation Research laboratory. The chamber was designed for previous experiments [76] and was provided with a gas flow system consisting in an oil pump and a proportional valve (MKS 248A), regulating the gas inlet. The valve was controlled with a pressure control system (MKS 250E) fed with the signal from a Baratron gauge (MKS 128) monitoring the pressure in the chamber. A picture of the chamber and experimental set-up is shown in figure 6.6. Propane gas of 99.5% purity was used for the most part of the experiments presented in this chapter. Furthermore, the TIDe operation with argon, nitrogen and air was also tested. The measurements were performed varying the gas pressure in a range from 1.33 to 6.5 mbar.

![Figure 6.6: Picture of the experimental set-up. The TIDe prototype shown in the insert was setup inside the gas-tight chamber.](image)

A $^{241}$Am source was used as primary radiation field for the prototype characterization, providing alpha particles of 4.6 MeV. The source was incorporated into the gas-tight chamber and was collimated in order to provide a needle beam of 2 mm diameter and 1.4 particles per second. The beam crossed the TIDe drift region at 5 mm above the PCB upper surface. The primary particles were detected with a silicon photo-diode (Hamamatsu S1223-01) with the entrance window removed in order to detect alpha particles. The photo-diode was combined with a charge sensitive preamplifier (ORTEC 142) and the output signal was sent to the DAQ and used as trigger for the signal acquisition.
The TIDe setup inside the chamber is shown in figure 6.7. The anode was connected to a positive power supply via a 1 MΩ resistor. The value of the applied voltage was optimized in order to maximize the ion focusing into the holes and varied in a range from 5 to 30 V. The signal induced in the electrode was read-out through a 1 MΩ impedance (AC mode oscilloscope). The cathode was connected to an independent negative power supply. The value of the voltage applied was optimized to maximize the signal to noise ratio and ranged from $-650 \text{ V}$ to $-900 \text{ V}$. Only the cathode area corresponding to the PCB holes was exposed to the working gas. The other surfaces of the cathode and the HV components were carefully insulated from the low pressure environment to prevent the development of uncontrolled discharges. The electrode on the top of the PCB was read-out in a single channel (i.e. the total signal coming from the all the holes was merged into one channel). The copper cladding on the upper surface of the PCB was grounded.

A scheme of the DAQ system is shown in figure 6.8. The signal induced in the readout electrode was amplified with a fast preamplifier (ORTEC VT120), digitalized with a constant fraction discriminator (ORTEC 584 with 10 ns delay), and analyzed with a field-programmable gate array (FPGA). The primary particle signal obtained from the photo-diode was amplified with a spectroscopy amplifier, digitalized, and used to trigger a pulse generator producing the acquisition gate and to reset the FPGA clock. The width of the acquisition gate was tuned according to the drift field and pressure values in a range from 600 µs to 1 ms. The FPGA (Xilinx Virtex4 board) was used to register the arrival time of the ion signal and to count the number of registered ions per trigger.
6. Characterization of a track imaging detector prototype

Figure 6.8: Scheme of the DAQ system. The signal generated by the primary particle crossing the detector sensitive volume triggers the ion signal acquisition. The detector signal is amplified, discriminated and registered by a FPGA. All the signals, together with the signal induced in the anode, are displayed on an oscilloscope.

6.2.4 Measurements for the detector characterization

In order to characterize the detector response and optimize the values of the working parameters, measurements of the following quantities were performed:

- *ion signal rate*: number of detector pulses counted with the FPGA per unit of time;
- *absolute number of ion counts per primary particle*: number of pulses counted with the FPGA per nominal number of primary particle crossing the volume;
- *conditional number of ion counts per primary particle*: number of ion counts per primary particle producing at least one ion signal (i.e. excluding the empty triggers). This value was measured counting the number of pulses registered with the FPGA per number of FPGA clock resets;
- *alpha detection efficiency*: percentage ratio of the rate of alpha particles producing at least one ion signal to the nominal alpha particle rate;
- *dark count rate*: detector signal, measured without the alpha source, per unit of time;
- *ion drift time*: arrival time of the ion signal with respect to the trigger measured with the FPGA.

The nominal rate of alpha particles crossing the volume was measured by counting the number of particles detected with the photo-diode with an independent counter.
6.2.5 Track structure simulations

MC simulations were performed with the PTra track structure code (see section 2.3.2) in order to estimate the number of ionizations produced in the detector drift region. A needle beam of 4.6 MeV alpha particles interacting with a volume of propane was simulated. The beam diameter was of 2 mm and the dimension of the gas volume was 24 mm × 48 mm × 10 mm. Simulations for propane gas at a pressure of 2.5 mbar and 4 mbar were performed. The number of the ionizations produced per primary particle and the spatial coordinates of the ionization events were obtained from the simulations. In order to estimate the detector geometrical efficiency, the coordinates of the ionization events were superimposed onto the hole structure of the PCB. Moreover, an estimate of the ion detection efficiency, including a detector dead time of the order of the inverse of the primary particle rate, was performed. In this case, only the first ion collected in each hole per primary particle were considered in the computation of the detected ionizations. The electric field configuration in the detector and the ion transport in the gas were neglected in the simulations.

6.3 Results

6.3.1 Analysis of the detector output

The signal obtained with the TIDe prototype assembled with the PCB with a common top electrode (design 1) and the float glass cathode (cathode 1) is shown in figure 6.9. The signal displayed on channel 1 corresponds to the signal produced by an alpha particle track in propane at a pressure of 4 mbar applying a $E_d$ of 20 V cm$^{-1}$ and an accelerating filed ($E_a$) of either 2.1 kV cm$^{-1}$ (upper pictures) or 2.4 kV cm$^{-1}$ (lower pictures). The signal consists in a train of negative pulses registered few tens of µs after the primary particle signal obtained with the photo-diode (channel 2). Each pulse corresponds to a discharge initiated by an ion entering one of the detector holes. The large variation of the pulse amplitude at a given value of $E_a$ indicates that the discharge region in the counting hole is limited and its size depends on the location of the initial ion-induced ionization along the hole axis. The pulse average amplitude increases with $E_a$ intensity and the pulse duration is roughly 400 ns. Considering an average amplitude of 5 mV on a 50 Ω load (for an HV of 700 V) and a pulse duration of 400 ns, the estimated average charge per avalanche is of the order of 20 pC corresponding to roughly $10^8$ electrons. Therefore, the number of electrons per avalanche is above the Raether limit for avalanche to streamer transition (see section 2.4.3). In figure 6.10, the average amplitude of the ion signal is plotted as a func-
Figure 6.9: Oscilloscope screen-shots of the detector response to an alpha particle track in propane at 4 mbar. Channel 1 represents the detector signal on a 50Ω load before the amplification. Channel 2 represents the photo-diode signal after the charge sensitive preamplifier. The upper pictures were obtained applying a voltage of 20 V and -700 V to the anode and the cathode, respectively. The lower pictures were obtained applying 20 V and -800 V. The pictures on the rights hand side are the time expanded views of the pictures on the left.

Figure 6.10: Average amplitude of the ion signal measured with the oscilloscope as a function of the electric field in the detector holes. The line represents the linear fit of the data.
A rather stable ion signal was observed applying a voltage larger than 600 V and at values of propane pressure in a rage from 3.3 to 6.6 mbar. Below 3.3 mbar an unstable signal was observed that was disappearing after few seconds of acquisition (see section 6.3.2.2). Moreover, no signal was observed for pressure values smaller than 2 mbar. This behavior could have been caused by the presence of impurities (oxygen) in the gas, quenching the signal. Impurities could have been present due to a leak in the chamber or out-gassing of the detector components. Additionally, sparks could develop at low pressure in case of local distortions of the electric field caused by manufacturing imperfections of conductive detector components. Such sparks could cause the detector shutdown for an indeterminate time.

The detector response to alpha particle tracks in different working gases is shown in figure 6.11. In the case of argon, the output signal is a combination of a series of negative short pulses and a long integrated signal. The proportion between the two signals varies with pressure, at a pressure value smaller than 4 mbar, the integrated signal is predominant. This behavior could confirm the presence of impurities in the gas. For nitrogen and air, the signal corresponding to the alpha particle track is an integrated signal of about 40 µs duration. Due to the electronegativity of these two gases, the observed signal is likely to be caused by electron attachment processes occurring before the electrons of the streamer reach the top of the hole.

6.3.2 Ion counting efficiency

6.3.2.1 Simulated detector response

In figure 6.12, the results of the simulated detector response are shown. In the first plot of the figure, the distributions of the estimated number of ionizations per primary particle, produced in the gas volume of the detector at
6. Characterization of a track imaging detector prototype

Figure 6.12: Distributions of the expected number of detected ions per primary particle obtained from MC simulations for two values of propane pressure. (a): distributions of the detected ions in the case of an ideal detector. (b): distributions obtained including the detector geometrical efficiency in the simulations. (c): distributions obtained including both the detector geometrical efficiency and the detector dead time in the simulations.

a pressure of 2.5 mbar and 4 mbar of propane, are shown. The average number of ionizations reduces by 35% when decreasing the propane pressure from 4 to 2.5 mbar. In the second plot, the distributions obtained considering only the ionization events produced right above the PCB holes are show. The average number of detected ions per primary particle is the 25% of the ionizations produced in the gas volume. This value corresponds to the geometrical transparency of the PCB (i.e. the ratio of the total area of the PCB holes to the PCB sensitive area). The distributions are characterized by two peaks: the higher peak is produced by the primary track while the lower peak is produced by delta electrons leaving the main track. In the last plot of the figure, the distributions obtained considering only the first ions collected in each hole per primary particle are shown. In this case, the estimated number of detected ions per primary particle is 35 for both the pressure values. This means that, on average, all the holes along the track (24) detect at least one ion. Moreover, additional holes detect the ions produced by delta electrons away from the primary track (see figure 6.13). The estimated value of detected ions corresponds to the 3% and 2% of the ions
6.3. Results

Figure 6.13: Red points represent a simulated track of an alpha particle of 4.6 MeV interacting with a volume of 4 mbar of propane. The gray structure represents the 2D array of holes of the ion detector.

produced in the gas volume at 2.5 mbar and 4 mbar, respectively.

In the simulations, the ion focusing effect, created by the electric field configuration in the detector, and the ion drift in the gas were neglected. These two processes work in favor of an ion detection efficiency larger than the estimated values. In fact, the PCB ion transparency (i.e., the ratio of the number of ions entering the PCB holes to the number total ions in the gas) is expected to be larger than the pure geometrical transparency due to the focusing effect of the electric field lines (see figure 6.2). On the other hand, the ion diffusion in the gas, causes a spread of the spatial distribution of the ion. As a consequence, the number of PCB holes involved in the ion detection – and, therefore, the number of detected ions – is expected to be larger than the number obtained in the simulations including the detector dead time. Finally, the probability of detecting the ions entering the PCB holes was assumed to be equal to 100%. This assumption may be unrealistic given that the probability to initiate the electron avalanche in the hole is low for low energy ions. This point is further discussed in section 6.4.

6.3.2.2 Ion counts as a function of $E/P$

Float glass prototype version:

In figure 6.14, the results of the measurements performed with the first version of the TIDe prototype are shown. The voltage applied to the cathode ranged from -600 V to -800 V and the pressure in the chamber was kept at 4 mbar. $E_d$ was set to 20 V cm$^{-1}$. The nominal primary particle rate, mea-
sured with the photo-diode, was 1.4 Hz and the acquisition gate for the ion signal was 800 µs. In panel (a) of the figure, the net ion count rate and the dark count rate are plotted as a function of the reduced field $E/P$. Both signals increase with increasing values of the cathode voltage. The dark count rate reaches a value of 50 Hz at -800 V, which corresponds to the 0.3% of the counts registered within the acquisition gate. Therefore, a large signal to noise ratio is obtained. The ion count rate is, however, rather low reaching a maximum value of only 13 Hz. In panel (b) of the figure, the average values of the conditional and absolute number of counts per primary particle are shown. The two numbers are different at each $E/P$ value indicating that a number of primary particles do not produce a signal in the detector. This behavior is clearly visible in the last plot of the figure where the alpha detection efficiency is shown. The percentage of the primary particles producing a signal in the detector increases with increasing $E/P$. However, the maximum percentage reached is only 76%. In figure 6.15 the results of the measure-
6.3. Results

Figure 6.15: Results of the measurements performed with the detector prototype assembled with the float glass cathode at different values of propane pressure. (a): net ion count rate and dark count rate as a function of E/P. (b): conditional and absolute number of ion counts per primary particle as a function of E/P. (c): percentage alpha detection efficiency as a function of E/P.

measurements performed at the fixed HV value of -800 V and varying the propane pressure in a range from 2 to 6.6 mbar are shown. Both the ion count rate and the dark count rate (panel (a) of the figure) increase with decreasing pressure down to a pressure of 3.3 mbar (E/P equal to 7.3 V cm\(^{-1}\) Pa\(^{-1}\)). After this value, the two signals drop. The same trend is observed for the conditional and absolute number of ion counts per primary particle shown in panel (b) of the figure. Conversely, the alpha detection efficiency (panel (c) of the figure) increases with increasing pressure and reaches a plateau at 80% for large pressure values.

The drop of the ion detection efficiency at low pressure was observed to correlate with the instability of the detector response already discussed in section 6.3.1. The signal instability can be observed in figure 6.16, where the ion count rate is plotted as a function of the detector on-time for pressure values of 4 mbar, 2.5 mbar, and 2 mbar. The ion signal is rather stable at a pressure of 4 mbar (panel (a)). At 2.5 mbar the signal rate slightly decreases with time (panel (b)). At 2 mbar, it decreases rapidly, vanishing after few seconds after the detector activation (panel (c)). Below a pressure value of
6. CHARACTERIZATION OF A TRACK IMAGING DETECTOR PROTOTYPE

Figure 6.16: Ion count rate as a function of the on time of the detector at three pressure values: 4 mbar (a), 2.5 mbar (b), and 2 mbar (c).

2 mbar, neither ion counts or dark rate counts were observed.

Schott glass prototype version:
In figure 6.17, the results of the measurements performed with the prototype version assembled with the Schott glass cathode are shown. For this set of measurements, the HV had a fixed value of -800 V and the pressure varied in a range from 2 to 6.6 mbar. The other working parameters of the detector were the same as described above. The behavior of the ion signal rate and of the absolute and conditional number of counts per primary particle as a function of E/P is similar to the behavior obtained for the float glass prototype. All the three quantities increase with decreasing pressure up to a maximum and rapidly decrease afterwards. However, the maximum is shifted to larger pressure values when the Schott glass cathode is used. In this case, the signal drops already at a pressure of 3.3 mbar (E/P equal to 7.3 V cm$^{-1}$ Pa$^{-1}$). An unstable signal was observed at this pressure and no signal was registered at 2 mbar. An other difference that was observed between the two prototype versions is the behavior of the dark rate. A rapid increase of the dark rate, up to almost 200 Hz, occurs in coincidence with the ion signal drop at 3.3 mbar for the Schott glass cathode. For lower pressure
6.3. Results

Figure 6.17: Results of the measurements performed with the detector prototype assembled with the Schott glass cathode at different values of propane pressure. (a): net ion count rate and dark count rate as a function of $E/P$. (b): conditional and absolute number of ion counts per primary particle as a function of $E/P$. (c): percentage alpha detection efficiency as a function of $E/P$. The alpha detection efficiency is defined as the percentage ratio of the rate of alpha particles producing at least one ion signal to the nominal alpha particle rate.

values the dark rate decreases similarly to the ion signal.

Unlike to what was observed in the measurements with the float glass cathode, the absolute and conditional number of counts per primary particle were similar up to 4 mbar ($E/P$ equal to 6.1 V cm$^{-1}$ Pa$^{-1}$) for the Schott glass measurements (see panel (b) of figure 6.17). This indicates that a similar number of ions is detected for all the alpha particles crossing the gas volume. In fact, the percentage of alpha particles producing a signal in the detector (panel (c) of figure 6.17) is constantly equal to 95% for all the pressure values for which the detector has a stable response. A slightly larger conditional number of ions per primary particles is measured with the Schott glass prototype. The maximum number of ions is detected for a reduced field of 6.1 V cm$^{-1}$ Pa$^{-1}$ and it is 33% larger than the maximum number of ions detected with the float glass prototype.

In figure 6.18 the conditional distributions of the number of ion counts per primary particle measured with the two prototype versions are compared.
6. Characterization of a track imaging detector prototype

Figure 6.18: Comparison of the conditional distributions of the number of ion counts per primary particle measured with the two versions of the detector prototype. The black line represents the distribution obtained with the float glass prototype and the blue line represents the distribution obtained with the Schott glass prototype. The two distribution were obtained at a gas pressure of 4 mbar, a HV of -800 V, and a $E_d$ of $20 \text{ V cm}^{-1}$.

The two distributions have different shapes. While for the float glass prototype single counts are the most frequent, the distribution obtained with the Schott glass prototype peaks at 14 ions per primary particle.

These results suggest an improvement of the detector performance reducing the volume resistivity of the cathode. Nevertheless, the number of ions detected with the best performing prototype is only 1% of the number of ions produced in the gas volume estimated with the track structure simulations (see section 6.3.2.1). In order to investigate the causes of this low efficiency, the maximum value of the ion counts per primary particle measured at 4 mbar was compared to the expected value obtained from the simulations including the PCB geometrical transparency and the detector dead time.

Considering the worst case scenario of geometrical efficiency in the simulations (i.e. neglecting the focusing effect of the electric field) the measured number of ions is still only 5% of the value obtained in the simulations. Considering, in addition, a dead time of the order of the alpha particle rate in the simulations, the measured number of ions is 57% of the expected value. From this comparison appears that the holes along the alpha track detect less than one ion per primary particle. Therefore, a poor ion collection efficiency and a long recovery time of the electric field in the holes is not enough to explain the low ion detection efficiency observed. The other possible causes for the low efficiency are discussed in section 6.4.
6.3. Results

6.3.3 Distributions of the ion drift time and drift field optimization

In the left panel of figure 6.19, the distributions of the ion arrival time measured with the FPGA at a pressure of 3.3 mbar for two different values of the applied drift field are shown. As expected, the most frequent arrival time moves towards larger values when decreasing $E_d$. This behavior confirms that the signal registered by the detector originates at a given position in the drift chamber and thus, is produced by the alpha particle track.

The measured distributions were compared with the calculated distributions shown in the right hand panel of figure 6.19. The latter were obtained as follows: alpha particle tracks produced in propane at 3.3 mbar were simulated with the PTra code and the coordinates of the ions obtained from the simulations were superimposed to the electric field map calculated with the QuickField software [6]. The parameters measured in [171] and reported in section 2.4.1 were used for the transport of ions in propane. The values of these parameters were measured in experimental conditions similar to the measurements of this work and are averaged values over all the ion species produced in propane. The ion drift time was calculated by summing the drift time obtained in a sequence of segments of length $\Delta y = 0.2$ mm, using the procedure suggested in [166]. For each segment, the drift along the field lines was combined with a random transversal displacement sampled from a Gaussian distribution with:

$$\sigma_{ti}^2 = \frac{2\Delta y}{E_i} \cdot \left( \frac{D}{\mu}_i \right)$$  \hspace{1cm} (6.2)
The local ion mobility $\mu_i$ and the ratio of transversal diffusion to the mobility $(D/\mu)_i$ were calculated using equation 2.15 and 2.16, respectively. The electric field maps including the detector geometry were calculated for a nominal $E_d$ of 20 V cm$^{-1}$ and 10 V cm$^{-1}$, and a HV of -800 V applied to the cathode.

As shown in figure 6.19, both the calculated and measured distributions are characterized by an asymmetric shape. The calculated and measured most frequent arrival time are in agreement for both the drift field values. However, the measured distributions are broader than the calculated distributions. This difference could be caused by the simplistic transport model used for the drift time calculations. A more detailed description of the ion diffusion is necessary to obtain more accurate results. The distribution of the ion interaction point in the hole – neglected in the calculations – also may influence the ion arrival time. The ion arrival time distribution in the case of a uniform drift field in the detector, i.e. neglecting the penetration of the accelerating field in the drift region, was also calculated (blue line in the right plot of figure 6.19). By comparing this distribution with the distribution obtained at the same $E_d$ value but including the focusing effect (black line in the right plot of figure 6.19), one can see that the nonuniform electric field configuration present in the detector causes a shift of the distribution peak towards lower values of arrival time and the appearance of a tail at larger times. From these results it appears that the ions produced in the detector experience the focusing effect.

Figure 6.20: Calculated trajectories of the ions in the drift region for two values of drift field: 20 V cm$^{-1}$ (left panel) and 40 V cm$^{-1}$ (right panel).

The drift field value was optimized in order to maximize the efficiency of ion collection in the holes. In figure 6.20, the calculated trajectories of the ions in the drift region are compared for two different values of $E_d$. A drift field in a range from 10 V cm$^{-1}$ to 20 V cm$^{-1}$ produced the best calculated ion collection efficiency for a negative HV of 800 V applied to the cathode. A
value of 20 V cm\(^{-1}\) was used in the measurements. Nevertheless, the actual ion collection efficiency in the THGEM holes may be not optimal and it can additionally be improved e.g., by increasing the geometrical transparency of the PCB.

### 6.4 Discussion and summary

In the work presented in this chapter, the working principle of the TIDe proposed by Bashkirov et al. [23] was studied. Furthermore, measurements for the characterization of a prototype of the detector were performed in order to investigate the possibility of using this device for nanodosimetric measurements in particle therapy. The detector combines the working principle of RPCs and THGEMs, which are well established particle detectors at the forefront of technology. Therefore, the detector development can use the advanced technology of such devices and the large amount of studies on their performance. Moreover, the TIDe design is attractive due to its simple manufacturing and the versatility of its dimensions. However, the characterization measurements revealed a few issues in the detector operation.

The prototype response was tested using low energy alpha particles producing dense tracks in the low pressure gas. A response correlated with the passage of the primary particle was registered, indicating the feasibility of the ion detection principle. The working parameters of the prototype were optimized in order to maximize its performance:

**HV applied to the cathode**

In section 6.3.2.2, results of the measurements of the ion counts as a function of the HV applied to the cathode showed that the ion detection efficiency increases with increasing HV value. This is explained with the increasing probability for ion-impact ionization with increasing ion energy (increasing E/P). However, the exact behavior of the ion-impact cross section as a function of the reduced field is unknown for slow propane ions in gas. Therefore, the ion detection efficiency may exhibit a maximum at a given E/P value. The increase of the HV value causes also an enhancement of the ion collection efficiency due to the larger penetration of the accelerating field in the drift region. On the other hand, the dark count rate rapidly increases with the HV value. Therefore, a trade-off value should be used for maximizing the signal to noise ratio. A negative HV value of 800 V was found to produce the largest ion count maintaining the dark rate at an acceptable level for the two prototype versions used in this work. The optimal HV value may, however, vary for different gas pressure, cathode material, and THGEM geometry.
6. Characterization of a track imaging detector prototype

Drift field
Large drift field values allow to minimize the ion diffusion and to maximize the primary particle rate capability of the detector. However, the maximum applicable value of $E_d$ is limited to $40 \text{ V cm}^{-1}$. For larger drift field values, the electrons drifting towards the anode may produce secondary ionizations as observed in [76]. The $E_d$ value should also be optimized in order to maximize the ion collection efficiency. As shown in section 6.3.3, a strong drift field causes a reduction of the ion focusing into the holes.

Gas type and pressure
As shown in section 6.3.1, an individual signal from each hole is obtained when propane is used as working gas. Conversely, the use of nitrogen, argon and air causes the loss of the single hole resolution. In order to achieve a water-equivalent resolution of the order of nanometers, the working gas pressure should be less than $1 \text{ mbar}$. However, the characterization measurements revealed an instability of the detector operation for pressure values smaller than $3.3 \text{ mbar}$ and $4 \text{ mbar}$ for the float glass and Schott glass version of the prototype, respectively. This behavior is likely to be related to technical issues. Possible causes can be ascribed to a leak in the gas-tight chamber and the development of uncontrolled discharges in the detector. The second hypothesis is supported by the fact that the signal instability is observed for smaller values of $E/P$ when the cathode with a lower volume resistivity is used (see section 6.3.2.2).

Volume resistivity of the cathode material
The comparison of the measurements performed with the two versions of the prototype showed an improvement of the ion detection efficiency reducing the cathode resistivity of one order of magnitude (see section 6.3.2.2). As explained in section 2.5, this is due to the fact that by increasing the conductivity of the electrode, the recovery time of the local electric field in the THGEM hole decreases. In fact, the development of the electron discharge in one of the THGEM holes causes a reduction, or even the shut down, of the local electric field. This causes a distortion of the electric field lines in the hole proximities. Therefore, the ions approaching the hole before the nominal field is restored are not collected in the holes or, if they are collected, they do not acquire enough energy to produce impact ionization and are not detected. As a consequence, the faster recharge time of the Schott glass cathode allows to achieve larger rate capabilities for the ion detection. On the other hand, the use of the Schott glass cathode causes an increasing of the dark count rate and makes the detector prone to the development of uncontrolled discharges.

Even in the case of the optimal prototype configuration, the number of detected ions per primary particle was a small fraction of the estimated number of ions produced in the detector sensitive volume. The main causes for
6.4. Discussion and summary

the low ion detection efficiency may be the follow:

Dead time

The detector dead time is caused by the recovery time of the electric field in the THGEM holes. This time depends on the charge collection time, which is of the order of µs and the recharge time, which depends on the cathode material. The recharge time for high resistivity materials can be of the order of hundreds of milliseconds and therefore, drastically affects the ion detection rate capability. The different alpha detection efficiency measured with the two prototype versions indicates that a dead time longer than the inverse of the alpha rate (≈ 700 ms) affects the performance of the float glass version. Conversely, because almost 100% of the alpha particles are detected with the Schott glass, a shorter dead time can be assumed for this version. However, the small improvement of the conditional ion collection efficiency obtained with the lower resistivity cathode may indicate that a further reduction of the dead time duration is necessary to allow the detection of more than one ion per hole per primary particle.

Considering the maximum ion count rate registered and an average of 35 counting holes (obtained from the simulations) the maximum measured ion rate per area is roughly 110 Hz cm$^{-1}$. This low value suggests that additional sources of dead time may affect the detector performance. The additional dead time is likely to be caused by the upcharging of the dielectric walls of the holes. In fact, this process has been observed in THGEM and RPWELL detectors (e.g. in [46] and [125]).

The dark count rate also contributes to extend the dead time of the detector as it causes the discharge of the holes in the same manner as the ion counts. A constant fraction of the dark counts is caused by cosmic and background radiation. Other components can be caused by field emission from imperfections of the cathode surface and scintillation of water molecules in the gas.

Ion-impact ionization probability

The cross sections for ionizing ion-gas collisions depend on the type of gas, gas pressure, and on the electric field strength across the holes. Cross-section data for low energy propane ions are unknown. Some data are available for He, N$_2$, and Ar and show that the probability for impact ionization of the gas is low [143] [139]. Therefore, the path length of the ions in the THGEM holes has to be long enough to obtain at least one ionization. The comparison of the measured ion counts per primary particle with the simulations of the expected detector response (shown in section 6.3.2.2) suggests that a height of 3.3 mm for the detector holes may not be enough to obtain the impact ionization interaction for all the collected ions. In fact, even when both the PCB geometrical transparency and the detector dead time are considered in the simulations, the measured number of ions per primary particle is
only the 57% of the simulated value. This indicates that other factors, not included in the simulations, affect the detector efficiency.

The results presented in this chapter show that the ion detection efficiency of the TIDe is insufficient to allow the registration of the radiation track structure of densely ionizing radiation. However, a larger efficiency could be obtained for sparsely ionizing radiation. In this case the ions would reach the detector well separated in time allowing the full recovery of the THGEM holes. In the next chapter further studies aiming to enhance the ion detection efficiency of the detector are presented.
Chapter 7

Optimization of the TIDe ion detection efficiency

7.1 Introduction

In the previous chapter, the measurements performed to assess the performance of a track imaging detector prototype were presented. Such measurements highlighted a few critical points in the detector design and operation, leading to an instability of the detector response and a low ion detection efficiency for densely ionizing primary radiation. In this chapter, the work performed for the optimization of the detector efficiency is presented. Several versions of a simplified TIDe were built in order to study the dependence of the ion detection efficiency on the THGEM thickness, the THGEM hole pitch and the cathode resistivity. The efficiency dependence on the quality of the primary radiation and the primary particle rate was investigated using a microbeam delivering low energy alpha particles and protons. The ion collection efficiency was also studied with the same setup. Furthermore, a new gas-tight chamber was designed and built with the aim to improve the stability of the experimental conditions.

7.2 Material and methods

Different versions of a simplified TIDe prototype consisting of a dielectric board with only few holes were built in order to study the dependence of the efficiency on the geometrical parameters and building materials of the detector. The various tests were performed in different laboratories and slightly different setups were used for different set of measurements, depending on the instrument availability of the different locations.
7. Optimization of the TIDe ion detection efficiency

7.2.1 Efficiency as a function of THGEM thickness

Three versions of the simplified prototype with different THGEM thicknesses were built in order to study the ion detection efficiency as a function of the path length of the ions in the accelerating field. The detectors were made of an acrylic board of 110 mm × 80 mm area and either 3.3 mm, 6.5 mm, or 8.7 mm thickness. Each board had four holes of different diameters ranging from 0.5 to 1.5 mm and a hole pitch of 10 mm. An anode was placed at 10 mm above the top of the THGEM and a cathode made of float glass was used. The signal generated in the holes was read out using copper tape electrodes. For this set of measurements, the signal obtained from the 1.5 mm-diameter hole was read out. One of the detector versions is shown in the left panel of figure 7.1. The detectors were setup in a gas-tight chamber installed at Loma Linda University Radiation Research laboratory (the chamber is described in section 6.2.3). The chamber was provided with a continuous flow of propane and a $^{241}\text{Am}$ calibration source. The source was collimated in order to obtain a needle beam with a width of 2 mm (FWHM) traversing the gas volume at 5 mm above the THGEM and aligned with the row of holes. A silicon photo-diode was used to detect the primary particles and measured an alpha rate of 1.6 Hz. A drawing of the experimental setup is shown in the right panel of figure 7.1. The signal induced in the readout electrodes was amplified, discriminated, and sent to a counter. The primary particle signal was used to trigger an acquisition gate. The acquisition gate was centered on the arrival time distribution of the ion signal acquired with an oscilloscope. A gate width of 800 µs was enough to include the distribution tails. In figure 7.2, a screen-shot of the signals on the oscilloscope is shown. Channel four shows the signal of the primary particle obtained with the photodiode, while the other channels show the signal generated in the THGEM holes.

![Figure 7.1](image)

**Figure 7.1:** Left panel: picture of one of the detector versions made of acrylic. The readout electrodes on the top of the board are made of copper tape. A copper anode and a float glass cathode provide the drift field and the accelerating field, respectively. Right panel: drawing of the measurement setup. The holes in the board are indicated by the red dashed lines. The copper readout electrode is indicated in blue.
7.2. Material and methods

![Image of oscilloscope screen](image)

**Figure 7.2**: Screen-shot of the detector signals on the oscilloscope. Channel four shows the signal of the primary particle obtained with the photo-diode. Channel one and three show signals from single holes of the 8.7 mm thick THGEM while channel two shows the signal from two connected holes. Signals were acquired in persistence mode in order to get the ion arrival time distribution.

The performance of the three detector versions was compared in terms of number of alpha particles producing a detected ionization. This number was obtained by counting the number of coincidences between the detector signal (obtained from one hole) and the acquisition gate. The reduced electric field (E/P) in the detector was varied by changing the high voltage (HV) applied to the cathode and the pressure of the working gas. In order to maintain similar value of E/P for the different detector thicknesses, the HV was increased accordingly. A HV range from 750 V to 1400 V was used and the propane pressure was varied from 1.3 mbar to 2.7 mbar. The drift field was adjusted according to the pressure in order to maintain a similar ion arrival time for all the pressure values.

7.2.2 Efficiency as a function of hole pitch and cathode resistivity

Five other versions of the simplified detector prototype were built in order to test the detector efficiency as a function of the THGEM hole pitch and the cathode resistivity. Two 1 cm-thick THGEMs with an area of 52 mm × 62 mm and a different hole pitch were produced at the CERN PCB workshop. The boards were made of single side copper-clad FR-4 and were pierced with two rows of five holes each. In one board the hole pitch was 6 mm while in the second board the pitch was of 4 mm. The hole diameter was of 1.5 mm for both the THGEMs. The design of the 6 mm-pitch THGEM is shown in figure 7.3. The two THGEMs were combined with the three different cathodes listed in table 7.1.

For this set of measurements, a new portable gas-tight chamber was built and installed at the Gaseous Detector Development Laboratory of CERN.
7. Optimization of the TIDe ion detection efficiency

![Figure 7.3](image_url)

**Figure 7.3**: Left panel: drawing of the THGEM with a hole pitch of 6 mm. The copper readout electrodes are also shown. The readout electrodes are separated by 0.2 mm. For the measurements described here, the signal induced in the two electrodes was put together in order to have a single channel readout. The hole diameter is 1.5 mm. The rest of the FR-4 board surface is copper-clad and grounded. The distance between the grounded layer and the readout electrodes is again 0.2 mm. An equivalent design was produced with a hole pitch of 4 mm. Right panel: picture of the THGEM with a hole pitch of 6 mm.

<table>
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<th>$\rho$ [(\Omega cm)]</th>
<th>Area [cm$^2$]</th>
<th>$t$ [cm]</th>
<th>$G$ [1/(\Omega cm^2)]</th>
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<tr>
<td>Float</td>
<td>$4 \times 10^{12}$ [13]</td>
<td>$3.5 \times 6.0$</td>
<td>0.2</td>
<td>$8.5 \times 10^{-13}$</td>
</tr>
<tr>
<td>Schott</td>
<td>$1 \times 10^{11}$ [28]</td>
<td>$3.3 \times 5.8$</td>
<td>0.3</td>
<td>$3.0 \times 10^{-11}$</td>
</tr>
<tr>
<td>Chinese</td>
<td>$3.5 \times 10^{10}$ [184]</td>
<td>$3.3 \times 5.8$</td>
<td>0.1</td>
<td>$2.9 \times 10^{-10}$</td>
</tr>
</tbody>
</table>

Table 7.1: Specifications of the resistive cathodes used in the measurements. The volume resistivity values ($\rho$) are values at room temperature taken from the literature. The values of the conductance per unit of area ($G$) are calculated as $\rho^{-1}t^{-1}$, where $\rho$ is the volume resistivity and $t$ is the plate thickness. The Chinese glass was provided by Prof. Wang Yi at Tsinghua University.

In order to reduce the exposure of the HV components to the low pressure environment, the THGEMs were embedded into the lid of the gas-tight chamber (see figure 7.4). With this setup, only one side of the glass cathode was exposed to the low pressure, while the other side of the glass and the HV connection were at atmospheric pressure. This helped to reduce the occurrence of spurious discharges in the gas. A copper anode was placed at 22 mm from the THGEM surface. A beam of $^{241}$Am alpha particles was used as primary particle source. Unlike the previous setup, the beam was not collimated in this case, due to the low intensity of the source. This resulted in a divergent beam with the axis at 1.6 cm from the THGEM surface. A silicon detector with a sensitive area of 2.5 cm diameter was used to measure the primary particle rate and trigger the data acquisition gate. The measured alpha rate was 5 Hz. The width of the acquisition gate was set to 1.5 ms for this setup, due to the larger ion drift distance compared to the setup.
described in the previous section. The signal generated in the ten holes of the THGEMs was read out with a single channel.

![Detector Setup Diagram](image)

**Figure 7.4**: Scheme of detector setup. The THGEM is embedded in the gas-tight chamber. Dashed lines represent the THGEM holes.

The performance of the different detector versions was compared by measuring the mean number of detected ions per primary particle (counts per trigger) and the alpha detection efficiency. The number of detected alpha particles was obtained by counting the number of coincidences between the acquisition gate and the pulse started by the first ion detected per primary particle. The dark count rate (i.e., the detector count rate measured without radiation source) was also measured.

### 7.2.3 Efficiency as a function of primary radiation rate and quality

The prototype version assembled with the 1 cm-THGEM with 6 mm hole pitch and the Schott glass cathode was tested with a microbeam at the Physikalisch-Technische Bundesanstalt (PTB) in Braunschweig (Germany). The detector was set up in the lid of the portable gas-tight chamber as described in the previous section. The chamber was provided with an entrance window made of a mylar foil of 10 µm of thickness. Due to the interaction with the mylar, the micrometric beam was scattered, thus, the beam size inside the chamber depended on the beam radiation quality and was of the order of millimeters.

The irradiation setup at the microbeam was simulated with Geant4 MC toolkit in order to estimate the beam size at the entrance of the detector sensitive volume (i.e., the first THGEM hole). The simulation results were benchmarked with measured profiles of the beams. The profiles were obtained by irradiating gafchromic films positioned inside the chamber. The beam sizes obtained for the radiation qualities used in the measurements are listed in table 7.2. In the same table, the radiation qualities are described in terms of number of ions produced in 2.7 mbar of propane per track length. These numbers were obtained from track structure simulations performed with the PTra code.
7. Optimization of the TIDe ion detection efficiency

Table 7.2: Characteristics of the particle beams used in the measurements. The number of ionizations per millimeter was obtained from simulations performed with the PTra track structure code for propane at a pressure of 2.7 mbar.

<table>
<thead>
<tr>
<th>Radiation quality</th>
<th>Ions/mm</th>
<th>Beam width (FWHM) [mm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>α 10 MeV</td>
<td>17</td>
<td>5.1</td>
</tr>
<tr>
<td>α 20 MeV</td>
<td>9</td>
<td>1.7</td>
</tr>
<tr>
<td>p 10 MeV</td>
<td>1</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Measurements of the mean number of detected ions per primary particle were performed for the three different radiation qualities. A negative voltage of 1 kV across the THGEM and a propane pressure of 2.7 mbar were used in the measurements. The primary particle rate was set to 6 Hz. For this set of measurements, the beam was aligned with the central axis of the THGEM (i.e., between the two rows of holes). Geant4 simulations were performed to obtain the expected number of ions created in the whole sensitive volume of 28.5x6.7x22 mm³ taking the beam geometry into account. The Livermore low-energy physics models were used in the simulations and the number of ions produced in the propane volume was calculated from the ratio of the energy deposited to the W-value. The number of counting holes per primary particle – considering the THGEM geometry and a detector dead time of the order of the inverse of the primary particle rate – was also estimated. In this case, the number of holes collecting an energy larger than the ionization threshold was scored for each primary particle traversing the sensitive volume and detected by the silicon detector.

In order to assess the detector rate capability, measurements of the mean number of counts per trigger were preformed varying the rate of the 20 MeV alpha particle beam from 1 Hz to 400 Hz.

The uniformity of the ion collection efficiency within the sensitive volume was tested using the 20 MeV alpha beam. For this aim, the mean number of counts per trigger was measured either aligning the beam with the two rows of holes of the THGEM or centering the beam in between the two rows.

7.3 Results

7.3.1 Efficiency as a function of THGEM thickness

Results of the measurements performed with the THGEMs of different thicknesses are shown in figure 7.5. The alpha detection efficiency – measured as percentage of the ratio of the number of alpha particles producing a signal in the detector to the nominal alpha particle rate – is plotted as a function of the reduced field E/P. From the plots, it can be observed that the efficiency...
7.3. Results

Figure 7.5: Plots of measured alpha detection efficiency as a function of reduced field strength (E/P). The alpha detection efficiency is defined as the ratio of the number of alpha particles producing a detected ionization to the total number of alpha particles crossing the sensitive volume. Green, blue, and red colors represent the results obtained with the THGEM of 3.3 mm, 6.5 mm and 8.7 mm, respectively. Different data series represent data collected at different propane pressure. The error bars represent the statistical errors.

is larger for thicker dielectric boards (i.e., longer path of the ions in the electric field). For a given pressure, the efficiency increases with E/P for all the board thicknesses. This trend is similar to what observed in the characterization measurements shown in the previous chapter (see section 6.3.2). At a given E/P, the efficiency is higher for larger pressure values. This could be due to the larger number of ions produced when alpha particles interact with propane at higher pressure. However, this would mean that – at least for low E/P values – the probability to obtain at least one impact ionization in the holes is still less than 100% despite the use of a 8.7 mm-thick THGEM. On the other hand, the ion collection efficiency could be different at different gas pressure.

It should also be noted that, at variance with the measurements performed with the 3.3 mm PCB board (see chapter 6), a detector signal could be observed at pressure values lower than 2 mbar. This was ascribed to the simpler design of the detector used for the measurements reported in this section. This makes the detector less prone to imperfections and makes it easier to insulate the HV connections of the cathode.
7. Optimization of the TIDe ion detection efficiency

7.3.2 Efficiency as a function of hole pitch and cathode resistivity

In figure 7.6, the results of the measurements performed with the 1 cm-thick THGEMs with different hole pitch are shown. In the left panel, the plots of the mean number of detected ions per alpha particle (counts per trigger) as a function of E/P are shown. The E/P value was varied by adjusting the HV in a range from 960 V to 1560 V, while the pressure was kept at 2.7 mbar. The Schott glass was used as a cathode for these measurements. It can be observed that the plots have a similar behavior for the two THGEM designs. However, the values of the counts per trigger are larger for the THGEM with a larger hole pitch. In the right panel of figure 7.6, the dark count rate is plotted as a function of reduced field E/P. The dark count rate increases with increasing E/P and the rate values are larger for the design with the larger pitch.

In table 7.3, the maximum alpha detection efficiency measured with four different versions of the detector prototype is reported. The efficiency increases with decreasing resistivity of the cathode material. Moreover, the combination of the Chinese glass with the 6 mm-pitch THGEM leads to a larger efficiency than the combination of the Chinese glass with the 4 mm-pitch THGEM. In the left panel of figure 7.7, the plots of the mean number of counts per trigger measured with the 4 mm-pitch THGEM and the three different cathodes are shown. The largest mean value of counts per trigger was obtained with the Chinese glass cathode. In the same plot, the results obtained with the Chinese glass cathode combined with the 6 mm-pitch THGEM are shown. Like to what observed for the Schott glass cathode, a larger number of counts per trigger is obtained with the 6 mm-pitch THGEM. The dark count rate obtained with the different detector versions is shown in the right panel of figure 7.7. For all the versions, the dark count
7.3. Results

Table 7.3: Maximum alpha detection efficiency measured with the detector prototype assembled with different cathode materials and THGEMs with different hole pitch. The alpha detection efficiency is defined as the ratio of the number of alpha particles producing a detected ionization to the total number of alpha particles crossing the sensitive volume.

<table>
<thead>
<tr>
<th>THGEM pitch (mm)</th>
<th>Glass type</th>
<th>α detection efficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Float</td>
<td>(7 ± 1)%</td>
</tr>
<tr>
<td>4</td>
<td>Schott</td>
<td>(45 ± 3)%</td>
</tr>
<tr>
<td>4</td>
<td>Chinese</td>
<td>(65 ± 2)%</td>
</tr>
<tr>
<td>6</td>
<td>Chinese</td>
<td>(89 ± 5)%</td>
</tr>
</tbody>
</table>

Figure 7.7: Left panel: mean values of counts per trigger as a function of E/P. Different colors represent the data obtained with different versions of the simplified detector prototype. Right panel: dark rate as a function of E/P measured with the four detector versions.

rate increases with increasing E/P. The dark count rate increase is more rapid for the Chinese cathode versions.

7.3.3 Efficiency as a function of rate and quality of primary radiation

In the left panel of figure 7.8, the measured number of ions per primary particle and the number of ions expected in the sensitive volume – obtained from the simulations – are plotted as a function of the radiation quality of the microbeam (measured in terms of ions per mm of track length). Both the measured and expected number of ions decrease with decreasing ionization density. However, the measured number of ions decreases less rapidly than the expected value in the case of the proton irradiation (1 ion/mm/primary). This trend can be better observed in the plot on the right hand side of the figure (black line), where the percentage ratio of the number of detected to expected ions is shown. Initially, the ion detection efficiency decreases with decreasing ionization density. However, the efficiency is the same for the 20 MeV alpha beam and the 10 MeV proton beam. This behavior could be explained considering both the geometry of the different beams and the ionization density produced by the primary particles. In the case of the
7. Optimization of the TIDe ion detection efficiency

Figure 7.8: Left panel: the blue line represents the measured number of ions per primary particle as a function of the primary particle quality measured as ions produced in 2.7 mbar of propane per unit of track length. The black line represents the number of ions expected in the detector sensitive volume ($28.5 \times 6.7 \times 22$ mm) per primary particle. Right panel: the black line represents the ion detection efficiency calculated considering all the ions produced in the sensitive volume. The red line represents the ion detection efficiency calculated considering the worst case scenario of ion collection efficiency and a dead time of roughly 200 ms.

alpha particle beams, the 5.1 mm width of the 10 MeV beam is enough to cover the two rows of holes. Conversely, the 20 MeV beam – with a width of 1.7 mm – covers only the central part of the THGEM, where no holes are present. This fact, in addition to the nonuniform ion collection efficiency observed in figure 7.10, leads to the detection of a larger number of ions for the 10 MeV alpha beam. On the other hand, the beam size of the 20 MeV alpha beam and the 10 MeV proton beam is similar. Therefore, the ion collection efficiency is similar for the two irradiations and the difference of the ion detection efficiency depends only on the ionization density produced by the two radiation qualities. The number of the detected ions is of course very small ($\approx 0.1\%$) compared to the number of ions produced in the volume due to the simplified detector design (few holes and large pitch) in addition to the detector dead time. The red plot in the right panel of figure 7.8 represents the ion detection efficiency calculated including both the THGEM geometry and the dead time in the simulated response of the detector. In this case, the detection efficiency increases with decreasing ionization density. The efficiency is larger than 100%. This indicates that the simulated ion collection efficiency is underestimated in the simulations as expected (the focusing effect is not included in the simulation).

The mean number of counts per trigger measured as a function of the primary particle rate is shown in the left panel of figure 7.9. It can be observed that the number of detected ions per primary particle is constant below 20 Hz then rapidly decreases while increasing the primary particle rate. In the right panel of the figure, the rate of the total signal registered in the detector as a function of the primary particle rate is shown. The total signal is
7.3. Results

Figure 7.9: Left panel: plot of the mean number of counts per trigger as a function of the primary particle rate. Right panel: plot of the total signal rate as a function the primary particle rate. Measurements performed with the 20 MeV alpha particle beam aligned with one row of holes.

composed by the sum of the signal rate produced by the ions and the dark count rate, which also contributes to the detector dead time. From the plot, it can be observed that the registered signal rate increases with the primary particle rate until 20 Hz and then it reaches a plateau. The saturation value is 17 Hz that is the maximum signal rate that can be registered with the detector setup described in section 7.2.3.

Figure 7.10: Plot of the mean number of counts per trigger measured when the beam is at different positions with respect to the row of holes of the THGEM: beam aligned with the two rows of holes (left and right point) and beam centered between the two rows (central point). Measurements performed with the 20 MeV alpha beam of 1.7 mm of width.

In figure 7.10, the result of the lateral scan of the sensitive volume with the alpha beam of 1.7 mm width is shown. It can be observed that the mean value of counts per trigger is lower when the beam is centered in between the two rows of holes than when the beam is aligned with the
7. Optimization of the TIDe ion detection efficiency

holes. This shows that the ion collection efficiency is not uniform in the sensitive volume.

7.4 Discussion and summary

In order to reconstruct the 3D track structure of radiation with the TIDe detector, ions produced in low pressure gas should be detected with high efficiency. Measurements performed with a TIDe detector prototype built according to the original design showed a low efficiency for the detection of single ionizations produced by high LET radiation (see chapter 6). In the work presented in this chapter, the possible causes of the low detector efficiency were experimentally investigated.

As discussed in the previous chapter, one of the causes for the low ion detection efficiency was ascribed to the low probability for low energy ions to produce impact ionization. In order to enhance the chance of obtaining at least one ionization, one could increase the electric field strength in the THGEM holes. However, this would enhance the dark rate and the occurrence of uncontrolled discharges. Another way to increase the detector performance is to increase the path length of the ions in the electric field. The measurements reported in section 7.3.1 show, indeed, that the rate of the signal generated in one single hole increases with increasing THGEM thickness. Despite this, the alpha detection efficiency of one single hole is less than 50% even in the case of the thickest board. This is due to the large resistivity of the cathode used in these measurements (float glass) as explained in the previous chapter (see section 6.4). Moreover, the charge up of the dielectric board – causing a long dead time – could be larger for thicker boards as observed in [52]. Finally, although the efficiency of the 8.7 mm-thick detector version is larger relatively to the less thick versions, the absolute efficiency of impact ionization could be still smaller than 100%.

In section 7.3.2, it was shown that the detector efficiency depends on the THGEM hole pitch and cathode resistivity. The THGEM with 4 mm hole pitch has a larger geometrical transparency than the 6 mm-pitch THGEM. Therefore, a larger number of ions per primary particle should be collected with the 4 mm-pitch THGEM, if no focusing effect is assumed. However, the measurement results showed that a larger mean number of counts per trigger is obtained with the THGEM of 6 mm pitch. The reason of this result is still under investigation. A possible explanation could be related to the discharge area of the cathode. As shown in figure 7.4, the cathode is common with all the THGEM holes. Therefore, it is possible that when an electron avalanche is generated in one hole, the portion of the cathode above the adjacent holes discharges as well causing a reduction of the effective voltage.
7.4. Discussion and summary

across the holes. This effect was observed both for the Schott glass cathode and the Chinese glass cathode. Measurements performed with different cathodes show that the detector performance improves by decreasing the cathode resistivity. A low cathode resistivity leads to the reduction of the component of the detector dead time related to the cathode recharge time. On the other hand, when the cathode resistivity is too low, uncontrolled discharges are produced. More materials will be tested in a further work in order to obtain an optimal value of resistivity. For example, a few samples of a ceramic material, with a bulk resistivity of the order of $10^{10} \, \Omega \text{cm}$ and developed at the Institute of Materials Science Research of Madrid (described in [126]), were provided by Miguel Morales at University of Santiago de Compostela for testing.

From the measurements performed as a function of the primary particle rate (see section 7.3.3), it is clear that the performance of the detector assembled with the 1 cm-thick THGEM and the Schott glass cathode is strongly affected by a long dead time, of the order of tens of ms. In fact, the number of detected ions per primary particle drastically drops when the primary particle rate is larger than 20 Hz. Furthermore, the measurements performed varying the quality of the primary beam suggest that the main cause of the low detection efficiency is the long dead time rather than the low probability of ion-impact ionization. In fact, the larger efficiency observed for the proton beam indicates that the percentage of detected ions does not scale with the ionization density. However, this result could be affected by the differences in the ion collection efficiency caused by the different size and divergence of the beams of different qualities. Further measurements should be performed providing the same irradiation geometry for all the beam qualities in order to disentangle the dependence of the total efficiency on the ion collection efficiency. This could be done for example, by adding a system of collimators in the chamber. Additionally, to separate the different efficiency components a posteriori, a collection efficiency map could be calculated and validated by scanning the sensitive volume with a needle beam as shown in [166].

The simulations of the detector response to the different radiation qualities of the PTB microbeam were performed with Geant4 due to the versatility of the toolkit in simulating the various irradiation geometries. Because of the unavailability of the Geant4-DNA extension for the step-by-step transport of radiation in propane, the standard condensed history transportation was used. The number of ionizations produced in gas was, therefore, obtained from the ratio of the energy deposited in the gas volume to the W-values of the primary particles in propane (see section 7.2.3). However, this procedure is not accurate when the number of ionizations produced is small. As a consequence, only the total number of expected ions in the sensitive volume was calculated (from tens to hundreds of ions). The inclusion in Geant4-DNA of
7. Optimization of the TIDe ion detection efficiency

the ionization cross-sections for electrons and ions in propane (planned for the future releases [36]) will allow to obtain more accurate results also for the estimation of the ion detection efficiency including the THGEM geometry (i.e., considering the number of ionizations produced in the THGEM holes).

In summary, from the measurements presented in this chapter emerged that a THGEM thickness of roughly 1 cm and a cathode resistivity of the order of $10^{10} \Omega \text{cm}$ would lead to an enhanced performance of the TIDe detector presented in chapter 6. However, the assessment of the absolute ion detection efficiency of a new TIDe prototype with such characteristics has still to be performed. Another point to address for the construction of the next prototype is the pitch of the THGEM holes. On one hand, a small pitch is necessary to obtain a uniform ion collection efficiency in the sensitive volume. On the other hand, the large discharge area of the cathode appears to limit the performance of detectors with a small hole pitch. A solution to this issue would be to use segmented resistive electrodes in order to decouple the THGEM holes. Moreover, the ion collection efficiency could be enhanced by improving the shaping of the electric field lines by biasing the readout electrodes in addition of reducing the hole pitch.
The interest in particle therapy has been rapidly growing for the past years. The irradiation with charged particles can indeed offer a superior dose conformity, a lower integral dose to the patient, and an enhanced biological effectiveness (for heavy ions) compared to standard photon therapy. The attractive clinical advantages of this therapy, along with the technology development, have triggered a substantial increase in the number of particle therapy facilities, almost doubling or tripling the number of patients treated with protons and carbon ions, respectively, within the past five years. At the same time, the lack of clinical data and epidemiologic studies of this new irradiation technique urgently calls for new dosimetric approaches for a thorough characterization of the radiation biological effects in order to predict the treatment outcome. Standard dosimetric quantities are, in fact, insufficient for describing the stochastic nature of the radiation interaction at the microscopic level, which directly determines the initial damage to biological tissue. The capability of nanodosimetry to characterize the patterns of ionizations produced in sub-microscopic volumes is promising for defining new dosimetric quantities directly related to the initial damage to DNA. These quantities may complement the standard dosimetric information for the assessment of the biological effect of the irradiation with particle beams. The aim of this work has been indeed to study the potential of using the nanodosimetric approach in particle therapy and to perform the first stages of the development of a detector for nanodosimetric measurements in the clinical environment.

Two main radiobiological concerns challenge the clinical superiority of the particle therapy treatment over standard photon therapy. The first is the uncertainty in the assessment of the biological effect of the neutron fields produced during the particle therapy treatment. There is indeed an ongoing debate on the contribution of such fields to the risk of the long term effects of radiation therapy, such as radiation induced secondary cancers, caused
by the “low dose bath” delivered out of the primary irradiation field [163].
In chapter 4, it was shown that the complex mixed field produced out of the
primary field in proton therapy can be directly characterized with measurable
quantities related to the track structure of the charged particles compon-
ing the mixed field. This avoids elaborate measurements of the neutron field
component. Moreover, the nanodosimetric characterization contains direct
information on the effectiveness in producing DNA damage for different
radiation qualities thus, removing the need to rely on the controvert use of
RBE-based radiation weighing factors. The nanodosimetric characterization
was built upon a combination of condensed history and track structure sim-
ulations used to obtain the spatial distribution of the ionizations produced
in a macroscopic water phantom irradiated with a mono-energetic proton
field. Nanodosimetry-based quality factors were defined in order to char-
acterize the ionization patterns produced at different locations out of the
primary proton field relative to sparsely ionizing radiation (60Co photons).
This characterization allowed to observe the clustering power of low energy
protons produced in neutron interactions at large distance from the field
edge, where the neutron component of the mixed field is dominant. More-
over, the radiation quality at a given out-of-field location was described in
terms of low-LET radiation for which the biological effect as a function of
the absorbed dose is known. This was done by calculating the quantity 60Co-
dose, which was defined as the amount of photon dose necessary to produce
the same yield of biologically relevant ionization clusters as the radiation of
the mixed field.

The second issue in the use of charged particles in radiation therapy con-
cerns the assessment of the biological effect of such radiation and its vari-
ation within the tumor caused by the energy loss of the charged particles pen-
etrating the biological tissue. In fact, the present RBE-based approaches for
obtaining biologically-weighted treatments are considered insufficient (in
particular for carbon ions) due to the RBE dependence on multiple parame-
ters – both physical and biological – that makes it difficult to determine this
quantity with acceptable accuracy [10]. In chapter 5, it was shown that the
nanodosimetric approach can be used to obtain particle therapy treatments
producing a uniform initial biological damage within the tumor. Simple
proton and carbon ion treatment plans with either a single or two-opposing
field geometry were simulated in a water phantom. Biologically-weighted
plans were calculated optimizing the fluence of the individual pencil beams
in order to create a mixed radiation field with equal nanodosimetric param-
eters throughout the target volume. Uniform distributions of biologically
relevant ionization clusters were successfully obtained both for proton and
carbon ion irradiation with the two-opposing field irradiation geometry.

At variance with previous approaches depending on RBE and biophysical
models, the nanodosimetric approach depends only on physical quantities
that can be simulated with MC track structure codes and directly benchmarked with experimental measurements. On the other hand, the approach relies on two main assumptions:

- the distribution of the number of ionizations produced in a microscopic target of biological tissue (unit density medium) can be estimated from measurements in macroscopic volumes of low pressure gas;

Previous works (reviewed in chapter 2) demonstrated that the values of nanodosimetric quantities measured in cylindrical volumes of gas linearly scale with the density and the primary particle mean free path in the medium. Additional work was performed in order to validate the scaling procedure for a more general irradiation setup. The results presented in chapter 3 show a good agreement between nanodosimetric quantities simulated in gas and water volumes irradiated with protons.

- a correlation exists between the spatial distribution of the ionization events produced within a biologically relevant target and the biological damage induced by radiation.

Most of the literature studies relating the radiation track structure with the initial damage to DNA are based on track structure simulations. Only few investigations have been performed on the relationship between measured nanodosimetric quantities and biological parameters. These works (reviewed in chapter 2) show a correlation between the size of the ionization clusters produced within gas volumes and the complexity of the DNA damages, increasing the confidence in the feasibility of the nanodosimetric approach. However, systematic radiobiological studies have still to be performed before the clinical application of this approach. Dedicated radiobiological experiments should be devised where the radiation quality of the irradiated cells is characterized with nanodosimetric parameters. These experiments are challenging and require advanced techniques in order deliver single particle irradiation and resolve the DNA damage produced in a single cell. Another radiobiological issue to address is the relationship between the initial DNA damage and the biological outcome. In fact, although it is generally accepted that unrepaired or misrepaired double strand breaks (DSB) lead to chromosome aberrations, mutations and cell death, a complete understanding of the pathways from the initial DSB to these endpoints and the role played by DSB of various complexity is still lacking [132], [97]. Challenging atomic and molecular physics experiments would also be needed to study the complexity of DNA damages at the single molecule level [173].

The studies performed in this thesis highlighted the need of further investigations for the improvement the present nanodosimetric approach. In particular the following directions of improvement have been identified:

*The biologically relevant target*
The size of the biologically relevant target is an important parameter in the relationship between nanodosimetric quantities and radiation biological effect. On one hand, nanodosimetric quantities strongly depend on the dimension of the target volume. On the other hand, although DNA is considered the relevant target for the induction of the initial radiobiological damage, it is not known which spatial extension this damage should have in order to be relevant. Moreover, the damage to larger structures may also be relevant for given biological effects. In this work a cylindrical target of 2.3 nm of diameter and 16 nm of height was defined as the relevant target and used for the scoring of ionization clusters. In a further work, the dependence of the results obtained on the target size should be studied. Alternative track sampling approaches should also be considered. A valid alternative is the use of clustering algorithms – such as the density based clustering algorithm DBSCAN – rather than definite sampling volumes, as suggested by Francis et al. [69]. Furthermore, the use of detailed geometrical models of DNA should be investigated. For example, a complex model of a chromatin fiber is available in Geant4-DNA [159]. As suggested by Bueno et al., [35] the geometrical arrangement of the DNA could indeed influence the scoring of the biologically relevant ionization clusters.

The target medium
The target volume used in this work consisted of liquid water as a surrogate of biological tissue. This approximation is commonly applied in track structure simulations due to the lack of data on the cross-sections for the physical interaction in biological material. However, theoretical studies have shown considerable differences between electron and proton energy loss in water and DNA [175], [12]. Recently, cross-section data for the DNA constituents tetrahydrofuran, trimethylphosphate, pyrimidine, and purine have been experimentally obtained (in [20] and [19]) and parametrized for the use in track structure codes (in [37]). Using these data, Bug et al. [39] showed that modeling the DNA medium with liquid water causes the underestimation of the size of the ionization clusters produced by electrons. In light of these findings, the accuracy of the simulations presented in this thesis could be improved by calculating nanodosimetric quantities in DNA medium rather than in water.

Indirect DNA damage
The track structure simulations performed in this study were limited to the physical stage of the radiation interaction with water. The production of radicals by radiolysis of water molecules and the following chemical events leading to indirect damage were neglected. However, such damages are known to be dominant especially for low-LET radiation. Moreover, there is evidence that radiation induced radicals play a key role in cell killing and sublethal cellular effects [106], [152]. As mentioned in chapter 2, a few track structure codes – such as PARTRAC – include models for simulating...
the production of free radicals and follow the diffusion and chemical reactions of those species at different times after the irradiation. Models for the chemical stage simulation are also available in Geant4-DNA even though still at the validation stage [100]. The simulations performed in this work could therefore be extended including such models to convert the clusters of ionizations into DNA damage taking indirect effects into account.

The level of detail needed for the description of the radiation target and the use of biophysical models for the conversion of ionization clusters to DNA damage should be carefully assessed also taking the final aim into account. On one hand, a detailed description of all the steps going from the initial energy deposition to the final biological outcome is necessary for the investigation of the fundamental mechanisms of the radiation interaction with biological tissue. On the other hand, such high level of detail may be unnecessary for correlating measurable nanodosimetric quantities with biological effects in radiation therapy.

**Reduction of the computation time**

An important limitation of the use of the nanodosimetric approach in a clinical situation is the prohibitive computation time needed for track structure simulations in macroscopic volumes. Because of this, the results showed in chapter 4 and 5 were obtained calculating the nanodosimetric quantities only for few representative voxels of the macroscopic water phantom. Further development of this work should focus on the use of analytical models for the parametrization of the biologically relevant nanodosimetric quantities produced in patient geometries in order to obtain the data in a clinically acceptable time. A calculation approach similar to the approach proposed by Alexander et al. [16] could be considered.

The application of nanodosimetry in particle therapy creates also experimental challenges. The existing nanodosimeters (reviewed in chapter 2) are not suitable for measurements in clinical environments due to their bulk structure and the complexity of their operation. Furthermore, in such devices, the size of the simulated biological target corresponds with the size of the detector sensitive volume. Hence, it is limited by experimental conditions. A new nanodosimeter concept has been proposed by Schulte’s group at Loma Linda University [168] and has been studied in this thesis work. The new detector has the potential of registering arbitrary long segments of radiation tracks, which can be analyzed *a posteriori* for obtaining biologically relevant information. Moreover, due to the compact size and the simplicity of its manufacturing, the device is suitable for mass production and routine measurements in particle therapy facilities.

In chapter 6, the innovative concept of the track imaging detector (TIDe) was presented and the results of the detector characterization were shown. The detector aims at the registration of the two dimensional time projections of
the spatial distribution of the ionization events produced in low pressure gas. In order to achieve a spatial resolution of the order of few nanometers at unit density, slow ions with limited ballistic and diffusion are detected, rather than electrons. The ion detection principle is based on the rare event of ion-impact ionization of the gas. Such event is obtained by accelerating the slow ions in a strong reduced field created into the holes of a thick-gas-electron-multiplier-like structure (THGEM). The extracted electrons are then amplified by generating discharges confined into the holes. Such discharges are quenched due to the high resistivity of the biased electrode. As such, an individual signal for each single ion produced in the gas is obtained. Ions produced by low energy alpha particles were successfully detected with two versions of the TIDe prototype that differed in the resistivity of the cathode material. However, a low ion detection efficiency – of the order of few percent – was observed with both prototype versions, with a slightly better performance obtained with the less resistive cathode. The analysis of the measurements revealed that the detector performance is strongly affected by a long dead time mainly caused by the long cathode recharge time. Moreover, the comparison of the results with Monte Carlo simulations of the detector response showed that a combination of additional causes contributes to the low efficiency. The low probability of ion-impact ionization was hypothesized as the main of such additional causes.

In chapter 7, further experimental investigations aiming to enhance the ion detection efficiency of the TIDe were presented. Several simplified versions of the detector were assembled in order to study the efficiency dependence on the detector geometry and building materials. A larger efficiency was obtained increasing the THGEM thickness. This confirmed the hypothesis that a longer ion path in the accelerating field is necessary to obtain at least one impact ionization per ion entering the THGEM holes. An unexpected decrease of the efficiency with decreasing pitch of the THGEM holes was observed. The result was ascribed to a large discharge area of the cathode causing the simultaneous discharge of multiple THGEM holes. Furthermore, a larger efficiency was obtained reducing the cathode resistivity. Measurements of the efficiency as a function of the primary particle quality and rate were performed at the PTB microbeam facility using a 1 cm-thick THGEM assembled with a cathode intermediate resistivity. Preliminary results showed that the detector is more efficient in detecting ions from sparsely ionizing radiation. A long dead time – of the order of tens of ms – was estimated from measurements as a function of the primary particle rate. Finally, a nonuniform ion collection efficiency was observed by scanning the detector sensitive volume with a 20 MeV microbeam.

In summary, the experimental work performed for this thesis lead to an improvement of the TIDe performance by increasing the THGEM thickness and reducing the resistivity of the cathode by two orders of magnitude. Never-
theless, the results achieved are the initial steps towards the realization of a TIDe suitable for nanodosimetric measurements in a clinical environment.

One of the main issues to be addressed in the next stage of the detector development is the reduction of the detector dead time. Two sources of dead time were identified with the measurements performed in this work: the recharge time of the resistive cathode and the charge up of the dielectric material of the THGEM. The aimed rate capability for the TIDe depends on the applications and the quality of the radiation to be characterized. For example, an ion rate per area of the order of $10^4 \text{Hz cm}^{-2}$ would be produced in the gas by measuring radiation tracks at the Bragg peak of a proton beam, supposing to reduce the primary particle fluence down to 1 kHz (minimum achievable in a clinical beam). An ion rate per area from 10 to 100 times larger would be produced in heavier ion beams. Achieving such a rate capability is challenging even with the best performing resistive materials (see section 2.5). An alternative solution to investigate is to replace the glass cathode with resistive pads with embedded resistors similar to what suggested by Chefdeville et al. [47] for resistive Micromegas. Such pads consist of two layers of resistive foils embedded in the dielectric material and connected with a resistive paste. By changing the shape of the resistive paste the resistivity of the pad can be tuned over two orders of magnitudes. Using such structures, particle rates per area of the order $10 \text{MHz cm}^{-2}$ were measured with Micromegas in a spark-free operation [47]. The use of individual resistive pads for each THGEM hole, would have the additional advantage of decoupling the holes, solving the issue of the simultaneous discharge of adjacent holes observed in the measurements. Resistive pads can be created with PCB technology and are currently produced at the CERN PCB workshop [67].

The charge up of the dielectric walls may contribute to a large dead time by reducing the local field in the holes; thus, preventing the process of ion-impact ionization. Although charge up is known to affect the operation of THGEM based detectors, a complete modeling of the process is still lacking. Measurements of THGEM gain stability have shown that the time constant of the process is of the order of hours [154] and the effect increases with increasing thickness of the THGEM [52]. In order to reduce such effect in the TIDe, the replacement of the dielectric material with a slightly conductive material has been considered for the next stage of the detector development. Of particular interest is the photosensitive glass developed by Hoya Corporation, Japan [1], which has been used to produce glass GEMs (G-GEM). Using photo-etching, hole patterns are produced in a glass substrate. Furthermore, the glass is compatible with photolithography techniques. Therefore, electrode patterns can be printed on the glass surface. G-GEMs have shown a stable performance for imaging applications [123]. Although the production technique was developed to create micrometric GEM structures,
the production of plates of 1 cm thickness with holes of 1 mm diameter is also possible [122]. The use of the PEG3 version of the glass with a volume resistivity of $8.5 \times 10^{12} \, \Omega \text{cm}$ [174] should allow a charge up free operation of the TIDe similar to what observed in [124]. In addition, the outgassing free property of the glass would allow a long-term operation for a sealed portable version of the detector.
Bibliography

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