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Distributions of deposited energy and ionization clusters around ion tracks studied with Geant4 toolkit

Lucas Burigo$^{1,2}$, Igor Pshenichnov$^{1,3}$, Igor Mishustin$^{1,4}$, Gerhard Hilgers$^5$ and Marcus Bleicher$^{1,6}$

$^1$ Frankfurt Institute for Advanced Studies (FIAS), Johann Wolfgang Goethe University, 60438 Frankfurt am Main, Germany
$^2$ Deutsches Krebsforschungszentrum (DKFZ), 69120 Heidelberg, Germany
$^3$ Institute for Nuclear Research, Russian Academy of Sciences, 117312 Moscow, Russia
$^4$ Kurchatov Institute, Russian Research Center, 123182 Moscow, Russia
$^5$ Physikalisch-Technische Bundesanstalt (PTB), 38116 Braunschweig, Germany
$^6$ Institut für Theoretische Physik, Johann Wolfgang Goethe University, 60438 Frankfurt am Main, Germany

E-mail: L.Burigo@dkfz.de

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Abstract

The Geant4-based Monte Carlo model for Heavy-Ion Therapy (MCHIT) was extended to study the patterns of energy deposition at sub-micrometer distance from individual ion tracks. Dose distributions for low-energy $^1$H, $^4$He, $^{12}$C and $^{16}$O ions measured in several experiments are well described by the model in a broad range of radial distances, from 0.5 to 3000 nm. Despite the fact that such distributions are characterized by long tails, a dominant fraction of deposited energy (∼80%) is confined within a radius of about 10 nm. The probability distributions of clustered ionization events in nanoscale volumes of water traversed by $^1$H, $^2$H, $^4$He, $^6$Li, $^7$Li, and $^{12}$C ions are also calculated. A good agreement of calculated ionization cluster-size distributions with the corresponding experimental data suggests that the extended MCHIT can be used to characterize stochastic processes of energy deposition to sensitive cellular structures.

Keywords: nanodosimetry, track structure, Monte Carlo simulation, Geant4

(Some figures may appear in colour only in the online journal)
1. Introduction

Radiobiological studies establish the connections between physical quantities which characterize a certain kind of ionizing radiation and biological effects induced by such radiation in specific cells or tissues. It is generally accepted that the survival fraction of cells after irradiation depends not only on the absorbed dose, but also on the radiation quality. Accelerated nuclei (ions) represent densely ionizing radiation with high linear energy transfer (LET) and they are characterized by a higher relative biological effectiveness (RBE) compared to sparsely ionizing radiation as photons or high-energy protons. However, there is no universal relation between LET and RBE for a given biological end point that is valid for all projectiles and cell types. This suggests that the description of microscopic spatial distributions of energy deposition in cells is crucial for explaining the observed difference between biological effectiveness of photons and ions and between ions of different charge and energy. The simulations of track structure of ionizing particles help to evaluate the damage caused to relevant biological targets and shed light on the difference in RBE. Studies presented in Goodhead (1994) and Grosswendt (2006) suggest that clustered damage in nanometer-size volumes represent a primary mechanism of lethal damage in targets as DNA molecules, nucleosomes or chromatin.

The final biological consequences of radiation impact depend on spatial and temporal distributions of DNA damage due to ionizing radiation (Goodhead 1994). The complexity of the DNA damage increases in the vicinity of tracks with high density of secondary electrons (Goodhead 2007). The probabilities of single and multiple ionizations inside nanometer-sized volumes were estimated in Grosswendt (2006) on the basis of nanodosimetry measurements and Monte Carlo simulations of the electron transport. As demonstrated in this study, the probabilities of single and multiple ionizations as functions of projectile energy are correlated with the yields of single- and double-strand breaks in the DNA predicted by a sophisticated realistic DNA target model (Friedland et al 1998). It was also shown (Grosswendt 2006) that the ionization cluster-size distributions in macroscopic dilute gas volumes are equivalent to the ionization cluster-size distributions expected in nanometer-sized volumes of liquid water. Therefore, the calculations with track structure codes in liquid water help to relate the radiation quality with respective biological consequences.

Electrons ejected in ionizations of water molecules due to the passage of ions can deliver their energy far away from the ion path at radial distance up to few micrometers. This characteristic radial spread of energy around the ion path is a key component of amorphous (average) track structure models (Cucinotta et al 1999). In particular, in the local effect model (LEM) (Elsässer et al 2008) the dose distribution as a function of the distance from the ion trajectory is used together with the survival data for photons to predict biological effects of ion beams. As shown (Kase et al 2008), a detailed representation of the radial dose profile including the domain of extremely high local dose in the center of the ion track is crucial for reliable estimations of respective biological endpoints in LEM and microdosimetric kinetic model (MKM).

In recent years several Monte Carlo models have been used to study the propagation and interactions of various particles in tissue-like media. In particular, in Pshenichnov et al (2007), (2008), Pshenichnov et al (2010) we have presented the Monte Carlo model for heavy-ion therapy (MCHIT) which is based on the Geant4 toolkit (Agostinelli et al 2003, Allison et al 2006). The Geant4-DNA extension (Incerti et al 2010) of the toolkit makes possible to simulate the track structure of protons and ions at the nanometer scale. This extension was used recently to calculate radial dose distributions around such tracks at energies relevant to radiotherapy (Incerti et al 2014, Wang and Vassiliev 2014). The results were compared with measured radial dose profiles and results of amorphous track models (e.g. Cucinotta et al (1999))
and Scholz and Kraft (1996)) as well as Monte Carlo track structure codes (e.g. Uehara et al (2001)). In the present study we use the Geant4-DNA models in our MCHIT simulations of the radial dose distributions around individual tracks of $^1\text{H}$, $^4\text{He}$, $^{12}\text{C}$ and $^{16}\text{O}$ ions and benchmark the model with experimental data.

Our results are also given in terms of the ratio LET$^r$/LET$_{\infty}$ of the spatially-restricted linear energy transfer LET$^r$, which gives the energy deposited per track length within a distance $r$ from the ion track, to the unrestricted linear energy transfer LET$_{\infty}$ calculated for $r \to \infty$. This ratio represents the fraction of energy deposited inside a cylinder with a given radius $r$ surrounding the ion track and helps to estimate the radius where the most of deposited energy is confined.

In Lazarakis et al (2012) the Geant-DNA models have been used for evaluating nanodosimetry parameters for tracks of electrons, protons and alpha particles propagating through water cylinders representing a DNA segment or a nucleosome. A good agreement between the ionization cluster size distributions calculated by the Geant4-DNA models and the PTra code (Grosswendt 2002), a dedicated code for nanodosimetry, was reported for fast projectiles. However, it was found that at low projectile energy the Geant4-DNA models tend to overestimate the cluster size compared to PTra. In our study we verify the reliability of the Geant4-DNA models for calculating ionization cluster-size distributions by comparing MCHIT/Geant4-DNA results directly with results of nanodosimetric measurements (Conte et al 2012, 2014, Hilgers et al 2015).

2. Materials and methods

2.1. Experimental data on radial dose profiles and ionization cluster size distributions

Radial dose profiles around ion tracks in tissue-equivalent gas were measured in several experiments and results were reported for example in Schmollack et al (2000), Varma et al (1977) and Wingate and Baum (1976). In particular, the data for 3 MeV protons and 0.75 MeV $u^{-1}$ $^4\text{He}$ from Wingate and Baum (1976), 2.57 MeV $u^{-1}$ $^{16}\text{O}$ from Varma et al (1977), 25 MeV $u^{-1}$ $^4\text{He}$, 25 MeV $u^{-1}$ $^{12}\text{C}$ and 21.2 MeV $u^{-1}$ $^{16}\text{O}$ from Schmollack et al (2000) are relevant to charged particle therapy. The information regarding the stochasticity of ionization events in sub-nuclear cell structures is important for estimating the complexity of DNA damage, but it is missing in these data. In order to fill this gap, the track structure of light ions has been investigated by nanodosimetric methods. This technique is applied to evaluate the ionization cluster-size distributions where cluster size $\nu$ is defined as the number of ionizations in the sensitive volume per beam particle. Several kinds of nanodosimeters have been developed to date, which differ basically by particles which are detected after being created by the ionization of gas molecules in the medium. Such detectors are usually classified into electron-counting (Nardo et al 2002, Conte et al 2012) and ion-counting (Garty et al 2002) nanodosimeters. The electron counting devices count the number of electrons produced via ionization of atoms by the incident beam ions inside a sensitive dilute gas volume, which is equivalent to a nanometer-size intracellular domain of water density. The ion counting devices count the number of ions in the medium and they allow to simulate even smaller sensitive volumes of water.

Measurements of ionization cluster-size distributions were performed for protons and helium ions with energies ranging from 0.1 to 20 MeV using an ion-counting nanodosimeter (Hilgers et al 2015, 2007). An electron-counting nanodosimeter was used for 1.35 MeV $u^{-1}$ $^4\text{He}$ (De Nardo et al 2002), 20 MeV $^1\text{H}$, 8 MeV $u^{-1}$ $^2\text{H}$, 8 MeV $u^{-1}$ $^6\text{Li}$, 3.81 MeV $u^{-1}$ $^7\text{Li}$ (Conte et al 2012), 8 MeV $u^{-1}$ and 20 MeV $u^{-1}$ $^{12}\text{C}$ (Conte et al 2014) ions.
The aforementioned measurements with the ion-counting nanodosimeter were performed in 120 Pa propane and also in nitrogen gas. In the present work we consider only the data obtained with a cylindrical sensitive volume of propane of $0.27 \, \mu g \, cm^{-2}$ in diameter and $3.9 \, \mu g \, cm^{-2}$ in height corresponding to a cylinder of 2.7 nm in diameter and 39 nm in height at 1 g cm$^{-3}$ density. The beam hits the target in the center, with the beam axis being perpendicular to the central axis of the target cylinder. The trajectories are distributed uniformly in a beam spot having an equivalent diameter of 2.2 nm in water.

In the measurements with the electron-counting nanodosimeter (De Nardo et al. 2002, Conte et al. 2012, 2014), the sensitive volume was constructed as a wall-less cylinder of 3.7 mm in diameter and height placed inside a chamber filled with propane-based gas at low pressure. The measurements with $^4$He ions were conducted with the propane gas pressure of 300 and 350 Pa resulting to the equivalent diameters of 20.6 and 24.0 nm, respectively, at the density of 1 g cm$^{-3}$. In the measurements with other ions the pressure was set to 300 Pa. The ion beam traverses the gas chamber at a given impact parameter $b$ respective to the center of the sensitive volume. The collimated beam had a diameter of 0.8 mm corresponding to 4.4 nm at the density of 1 g cm$^{-3}$. Electrons were collected from the top of the sensitive volume. The efficiency of single electron counting depends on the position of the electron inside the sensitive volume and the gas pressure. The efficiency of counting events with $\nu > 1$ was additionally limited by the time resolution of the detector due to a possible overlap of signals from individual electrons. The distribution of the arrival time of electrons was reported to be a Gaussian-shaped with the standard deviation of 700 ns, while the time resolution of the detector was 30 ns (Conte et al. 2012).

2.2. Monte Carlo modeling with MCHIT

In the present work radial dose profiles and ionization cluster-size distributions in the vicinity of tracks of individual ions in water are calculated by the Monte Carlo method using our MCHIT model (Burigo et al. 2013) based on the Geant4 toolkit (Agostinelli et al. 2003, Allison et al. 2006) of version 9.6 with patch 04. MCHIT has been used to describe a wide set of experimental data of ion irradiation, including depth and radial energy deposition profiles for protons and carbon nuclei in tissue-like materials, energy spectra and angular distributions of secondary neutrons, yields of secondary nuclear fragments and distribution of positron-emitting nuclei after irradiation. Recently we have extended this model to describe microdosimetry spectra and RBE of ion beams (Burigo et al. 2013, 2014, Burigo et al. 2015). In the present study the MCHIT code was adapted for track structure simulations. Nuclear reactions induced by projectile nuclei in water are neglected in the calculations that follows and only liquid water is considered as the medium. Electromagnetic interactions are simulated with the Geant4-DNA models which account for the elastic scattering, ionization, electronic excitation, vibrational excitation and molecular attachment processes for electrons; for the ionization, electronic excitation and charge exchange processes for protons and alpha particles; and for the ionization process for heavier ions. All the processes are simulated on a step-by-step basis by means of the detailed history Monte Carlo modeling. Other details of the implementation of the Geant4-DNA models can be found in Incerti et al. (2010). All electrons created by a primary ion or secondary $\delta$-electrons are transported until they are slowed down to 7.4 eV. Below this energy threshold interactions of electrons in water are not simulated and their remaining kinetic energy is considered to be deposited locally. The ionization of water molecules by carbon and oxygen ions is modeled by means of a relativistic extension of the Rudd model (Plante and Cucinotta 2008). The same approach is also used in MCHIT to account for the ionization of water molecules by $^2$H, $^6$Li and $^7$Li nuclei. Such an extension was necessary
for conducting the present study because the modeling of interactions of $^2$H, $^6$Li and $^7$Li is not yet implemented in the Geant4-DNA models of the version 9.6. The present implementation of ion-induced ionization in Geant4-DNA does not take into account the momentum conservation in ionization events, i.e. the changes in the direction of ion propagation after ejecting electrons are neglected. Simulations of ion propagation at the scale of few micrometers are not affected by such a simplification. However, simulation results in more thick media can be deteriorated. The model of ion-induced ionization was modified in Geant4-DNA to impose the momentum conservation. This improvement makes possible to simulate the lateral spread of ion tracks during their propagation through the medium.

In the present work the radial dose profiles and ionization cluster-size distributions were calculated in water at 1 g cm$^{-3}$. We compare our results with the distributions (section 2.1) originally measured in dilute gas and then rescaled to the water density. As discussed in Grosswendt (2002), the mean cluster size in tissue-equivalent gas due to the passage of 1.25 MeV u$^{-1}$ $^4$He is greater than that in liquid water, if $^4$He hits the cylindrical sensitive volume of the detector. In contrast, the mean cluster size in gas is smaller for ion trajectories at larger

Figure 1. Radial dose profiles for $^1$H, $^4$He, $^{12}$C and $^{16}$O ions in water. MCHIT/Geant4-DNA results for various ions are shown by different lines as explained in the legend. Results for 25 MeV u$^{-1}$ $^4$He presented by green dash-dotted and dotted lines were obtained, respectively, by simulations with and without imposing momentum conservation in ionization events. Experimental data (Wingate and Baum 1976, Varma et al 1977, Schmollack et al 2000) are shown by symbols of various colors and shapes as explained in the legend.
impact parameters which are entirely outside the cylinder. Such differences are due to longer ranges of secondary electrons in water compared to gas because of the difference in the ionization cross sections in these materials. In particular, more secondary electrons which are ejected from a distant ion track hit the sensitive volume in water compared to gas. In order to provide the equivalence of the ionization cluster-size distributions measured in propane gas to those calculated in water the diameters of the sensitive volumes were scaled by the ratio of the respective ionization cross sections following the prescription of Grosswendt (2002).

The average counting efficiency $\bar{\varepsilon}$ for electrons collected at an arbitrary position in the sensitive volume of the electron-counting nanodosimeter were reported in Conte et al (2012) and De Nardo et al (2002). Both $\bar{\varepsilon}$ and the time resolution of the detector for events with $\nu > 1$ were taken into account in our simulations following Conte et al (2012) and De Nardo et al (2002). In the case of ion-counting nanodosimeter, the counting efficiency of 100% was assumed.

3. Results and discussion

3.1. Radial dose profiles

Radial dose profiles for $^1$H, $^4$He, $^{12}$C and $^{16}$O ions calculated with MCHIT are presented in figure 1 together with the corresponding measured profiles from Varma et al (1977), Wingate and Baum (1976) and Schmollack et al (2000), top and bottom panel, respectively. A very good agreement between the MCHIT results and measurements is seen in the top panel of figure 1 for 0.6 nm to 300 nm distance from the ion track for 3 MeV $^1$H, 0.75 MeV $u^{-1}$ $^4$He and 2.57 MeV $u^{-1}$ $^{16}$O ions. As seen in the bottom panel of figure 1, the calculation result for 25 MeV $u^{-1}$ $^4$He agrees well with the data (Schmollack et al 2000) only after the momentum conservation in ion ionization reactions is imposed. Similar results are obtained for 25 MeV $u^{-1}$ $^{12}$C and 21.2 MeV $u^{-1}$ $^{16}$O (calculations without momentum conservation not shown). Neglecting the changes in ion direction results in underestimation of the dose values obtained in Schmollack et al (2000) at small radii, from 20 to 150 nm. The effect of elastic scattering of ions is neglected in the calculations due to the experimental set-up which was designed to select events with small net scattering (Schmollack et al 2000).

One should bear in mind that different measurement techniques were used in different experiments. In Varma et al (1977) and Wingate and Baum (1976) the measurements with stationary ionization detectors were performed at different distances from the ion track by changing the pressure of tissue-equivalent gas. In contrast, in Schmollack et al (2000) a movable detector was employed to measure dose at different radii in a larger gas vessel. The smallest simulated diameter of the sensitive volume for microdosimetry measurements was set to 150 nm, and, as stated by the authors, it was difficult to obtain information for radial distances smaller than 100 nm due to a restricted spatial resolution of the experiment (Schmollack et al 2000). Schmollack et al (2000) compared their data with theoretical models only at radii larger than 150 nm. In order to reproduce the measured radial dose profile in simulations, Plante and Cucinotta (2010) represented the uncertainty of the initial position of ion tracks by a Gaussian distribution with $\sigma = 200$ nm. We propose an alternative solution to this problem. We obtained the agreement between data and MCHIT for 20–150 nm distances from the ion track just by imposing momentum conservation in the ion-induced ionization events simulated by Geant4-DNA. Therefore, there is no need to introduce an additional spread in the initial positions of ion tracks.

One can note that a huge dose calculated at small radii ($r < 1$ nm), see figure 1, is explained by the direct ionization of water molecules by ions. This accounts for a large fraction ($\sim 30–40\%$) of the total deposited energy (see figure 2). The energy dissipation further away from the
track is associated with secondary interactions of produced electrons with water molecules. As seen, due to higher energy of secondary electrons the radial dose distributions measured for more energetic ions of 21.2–25 MeV u\(^{-1}\) extend well beyond 1 \( \mu \)m radius, while the dose delivered by slow ions of 0.75–3 MeV u\(^{-1}\) is negligible at large radial distances.

3.2. Spatially-restricted linear energy transfer

Linear stopping power is identical to unrestricted linear energy transfer, LET\(_\infty\), which includes all energy losses per unit track length at all radial distances up to \( r = \infty \). In Incerti \textit{et al} (2010) it was calculated with the Geant4-DNA models for protons and helium nuclei with kinetic energy up to 10 MeV and benchmarked to ICRU 49 data (ICRU 1993). Our simulations with MCHIT/Geant4-DNA show a very good agreement with ICRU 49 data for helium nuclei at 0.75 MeV u\(^{-1}\), but our calculations for 3 MeV protons overestimate the data by about 10%. In the case of 25 MeV u\(^{-1}\) helium, the calculated LET\(_\infty\) underestimates the ICRU 49 data by about 10%. We have also compared LET\(_\infty\) for 25 MeV u\(^{-1}\) 12C and 2.57 and 21.2 MeV u\(^{-1}\) 16O with ICRU 73 data (ICRU 2005). In these cases, the values of LET\(_\infty\) are also underestimated by \( \sim \)10%. One should keep in mind that the Geant4-DNA models do not include the processes of excitation of water molecules by ions heavier than helium, thus underestimating the energy loss in the core of ion tracks. However, this practically does not affect the production of secondary electrons by ions in ionization events and their energy dissipation in the medium. Also, the effect of excitation on the mean free path of ions heavier than helium is neglected in this study.

A quantity of interest for radiation biology is the spatially-restricted linear energy transfer LET, which gives the energy deposited per track length within a radius \( r \) from the ion track. The ratio LET/LET\(_\infty\) allows to characterize the concentration of the energy deposition in the medium around the track. LET is calculated by the \( rdr \) integration of the dose distributions calculated with MCHIT, which are presented above in figure 1. The resulting values of LET/LET\(_\infty\) are shown in figure 2 for 3 MeV \(^1\)H, 0.75 and 25 MeV u\(^{-1}\)He, and 25 MeV u\(^{-1}\) 12C. Particles

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Ratio LET/LET\(_\infty\) for 3 MeV protons, 0.75 and 25 MeV u\(^{-1}\)He, and 25 MeV u\(^{-1}\) 12C as a function of radial distance \( r \) calculated with MCHIT/Geant4-DNA.}
\end{figure}
at such energies are characterized by a short range in tissues of about water density, i.e. \( \sim 15 \mu \text{m} \) (6 mm) for 0.75 (25) MeV \( ^{4}\text{He} \). Results obtained for other nuclei of the same energy per nucleon (not shown) are represented by similar curves as verified by comparing the results for \( ^{4}\text{He} \) and \( ^{12}\text{C} \) at 25 MeV u\(^{-1}\).

The results for \( \text{LET}_{r}/\text{LET}_{\infty} \) reveal two important features. Firstly, this ratio starts from a finite value of \( \sim 0.3–0.4 \) at \( r < 0.3 \text{ nm} \). This very focused energy deposition is attributed to the prompt ionization and excitation processes induced directly by beam particles. Such processes are concentrated in the domain around the ion track which is comparable to the size of a water molecule. Secondly, the energy deposition around the ion track becomes more narrow as the kinetic energy of the beam ions is reduced. This is a direct consequence of smaller kinetic energy of secondary electrons produced in ionizations of water molecules by slower ions. Our results for \( \text{LET}_{r}/\text{LET}_{\infty} \) indicate that the main part of energy deposition (\( \sim 0.8 \)) is confined within a radius of 10 nm, but less than half of the energy is deposited within a radius of 1 nm.

### 3.3. Cluster size distributions

Now we apply MCHIT with Geant4-DNA models to calculate the probability distributions of ionization clusters in nanometer-sized volumes which have been measured by a technique known as nanodosimetry. Following the notations of De Nardo et al (2002) we denote such probability distributions as \( P(k; b, D, \varepsilon) \) which gives the number of ionizations \( \nu \) (a.k.a. cluster size) for a given kind of radiation \( k \) in a volume with the diameter \( D \) at a given impact parameter \( b \) and taking into account the average single ionization detection efficiency \( \varepsilon \). Such probability distributions are presented in figures 3–6 for \( ^{1}\text{H} \), \( ^{2}\text{H} \), \( ^{4}\text{He} \), \( ^{6}\text{Li} \), \( ^{7}\text{Li} \) and \( ^{12}\text{C} \) ions. All these distributions characterize the core of the ion track because ions cross the sensitive volume with impact parameter \( b \) smaller than the sensitive volume radius: \( b < D/2 \).
In figure 3 we show the calculated ionization cluster-size distributions for protons of 0.38, 2.5 and 10 MeV together with the corresponding distributions measured in Hilgers et al (2015) with the ion-counting detector. The simulation results agree well with the experimental data for cluster size \( \nu \) up to 16 for 0.38 MeV protons and up to smaller cluster sizes for higher energies. One can see that the calculations underestimate the experimental data at larger \( \nu \). It is worth mentioning that Monte Carlo simulations reported in the same publication show a similar disagreement with the data, but the authors were able to restore the agreement between measurements and Monte Carlo simulations by taking into account additional ionizations produced in the ion-counting nanodosimeter, see Hilgers et al (2015) for details. In addition to the cluster size distributions simulated with MCHIT and the measured distributions, figure 3 shows the simulated cluster size distributions corrected for additional ionizations produced in the ion-counting nanodosimeter. This background correction was carried out using the same procedure and the same parameters as in Hilgers et al (2015). It leads to a noticeably improved agreement between simulation and measurement. In the background corrected distributions, a shoulder appears in the range of cluster sizes \( \nu \) between \( \nu \sim 10 \) and \( \nu \sim 20 \), which is not seen in the measurements. This shoulder is due to the model underlying the description of the background of additional ionizations and can also be observed in background corrected distributions presented in Hilgers et al (2015) for 120 Pa propane. The slope of the probability distribution after the maximum is almost constant in the simulated distributions, whereas in the measurements the slope is reduced for large clusters. The background correction of the simulation results reduces the slope of the distribution in the range of cluster sizes \( \nu \) between \( \nu \sim 10 \) and \( \nu \sim 20 \), thus reducing the deviation from measurements. However, it leads to an additional structure in the shape of the simulations that is not visible in the measurements.

Calculated ionization cluster-size distributions for 0.525 and 4.9 MeV \( u^{-1} \)\(^4\)He ions are presented in figure 4 together with the distributions measured with the ion-counting nanodosimeter.
As seen from this figure, the calculated distribution for 0.525 MeV $u^{-1}$ $^4$He ions agrees well with the data up to $\nu = 36$. At the same time, the calculated probability of larger cluster sizes is lower compared to the measured values, as expected due to additional ionizations in the detector as explained above. In the case of 4.9 MeV $u^{-1}$ $^4$He ions, the cluster-size distributions agree only up to $\nu = 7$. The contribution of additional ionizations in the detector is more pronounced at higher projectile energies where smaller cluster sizes are produced in the sensitive volume. In addition to cluster size distributions simulated with MCHIT and the measured distributions, figure 4 also shows the simulated cluster size distributions corrected for additional ionizations. For 0.525 MeV $u^{-1}$ $^4$He ions, the accounting for additional ionizations leads to a significant overestimation of large ionization clusters as compared to the measurement, whereas for $^4$He ions of 4.9 MeV $u^{-1}$ the agreement between simulation and measurement is improved similarly as for 2.5 MeV and 10 MeV protons shown in figure 3.

It should be noted, that $^4$He ions of 0.525 MeV $u^{-1}$ are within the energy range showing the maximum deviation between background corrected simulations and measurement with respect to the mean cluster size (Hilgers et al 2015), however, the optimization of the parameters characterizing the production of additional ionizations was carried out using all data sets for 120 Pa propane (Hilgers et al 2015). One can also note that events with very large $\nu$ have a limited influence on the general biological impact of ion radiation on cell nuclei. Firstly, the probability of events with $\nu$ much higher than the mean cluster size is relatively small. Secondly, due to a well-known saturation effect (Sato et al 2011) most of events with such $\nu$ are lethal and, therefore, their biological endpoints are not very sensitive to specific values of $\nu$ in each particular event.

Calculation results for the ionization cluster-size distributions measured with the electron-counting nanodosimeter are presented in figure 5 for protons, deuterons and lithium ions, and in figure 6 for carbon ions. All these distributions were calculated for ions crossing the sensitive volume at central incidence. In our simulations the efficiency for single electron
counting was taken as reported in Conte et al (2012) and Conte et al (2014), $\bar{\epsilon} = 0.162$.

The experimental ionization cluster-size distributions for protons, deuterons and lithium ions are well reproduced by simulations following the scaling procedure described in Grosswendt (2002). Without such a scaling (results are not shown) the calculated mean cluster sizes will be slightly shifted to smaller values compared to the experimental data.

As seen from figure 6, the shape of ionization cluster-size distributions calculated for carbon ions is very similar to the shape of distributions measured with the electron-counting nanodosimeter (Conte et al 2014). However, the calculated distributions are shifted to larger values. One possible reason for such discrepancy might be an inaccurate rescaling procedure used to connect the measurements performed in gas to calculations performed for water.

4. Conclusions

The MCHIT model with the Geant4-DNA package successfully describes the radial dose distributions around the ion track in water for $^1$H, $^4$He, $^{12}$C and $^{16}$O ions of 0.75–25 MeV u$^{-1}$ measured in Schmollack et al (2000), Varma et al (1977) and Wingate and Baum (1976). This makes us confident in calculating the ratio of the spatially restricted linear energy transfer to the unrestricted LET for such ions. The ratio $\text{LET}_r/\text{LET}_\infty$ characterizes the concentration of the energy transferred to the medium around the ion track. As follows from our simulations, less than half of the energy deposited by slow ions close to the Bragg peak is confined within $r < 1$ nm, about 80% is confined within $r < 10$ nm, while the rest of deposited energy is distributed in a much broader range up to $r \sim 100$ nm. Similar results for the $\text{LET}_r/\text{LET}_\infty$ ratio for 1 MeV protons were obtained recently in Incerti et al (2014) also with the Geant4-DNA package. These results may have important implications for modeling physical conditions around the ion track. In particular, the assumption adopted in Scifoni et al (2010), Surduvich...
et al (2009), (2013) and Toulemonde et al (2009) that most of energy deposition by $^{12}$C ions in water is confined within a cylinder with $r = 3$ nm are not confirmed by our calculations, which demonstrate that only about 60% of the energy is deposited at $r < 3$ nm.

Our modeling of the ionization cluster-size distributions shows that the region of $r < 10$ nm is characterized by a high density of electrons produced in ionization events. This leads to large cluster sizes which may reach, e.g. $\sim 10–20$ for $^{12}$C ions of 20 MeV $u^{-1}$ energy. Such clustered ionization events increase the probability of lethal DNA damage. Our results on ionization cluster-size distributions can be considered as complementary to the results of recent studies (Incerti et al 2014, Wang and Vassiliev 2014), also based on the Geant4-DNA models, where only radial dose distributions around ion tracks were calculated. To the best of our knowledge, the experimental ionization cluster-size distributions in nanometric volumes measured with the two types of nanodosimeters were modeled with Geant4-DNA for the first time.

In conclusion, we have demonstrated that MCHIT with inclusion of Geant4-DNA models can be applied not only for calculating the radial dose profiles, but also for evaluating the ionization cluster-size distributions in nanometer-sized volumes traversed by nuclei with energies relevant to ion-beam cancer therapy. We believe that our study will eventually help in modeling radiobiological effects induced by such ions in human tissues.

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References

Burigo L, Pshenichnov I, Mishustin I and Bleicher M 2014 Microdosimetry spectra and RBE of $^1$H, $^4$He, $^3$Li and $^{12}$C nuclei in water studied with Geant4 Nucl. Instrum. Methods B 320 89–99
Burigo L, Pshenichnov I, Mishustin I and Bleicher M 2015 Comparative study of dose distributions and cell survival fractions for $^1$H, $^4$He, $^{12}$C and $^{16}$O beams using Geant4 and microdosimetric kinetic model Phys. Med. Biol. 60 3313–31
Grosswendt B 2002 Formation of ionization clusters in nanometric structures of propane-based tissue-equivalent gas or liquid water by electrons and α-particles Radiat. Environ. Biophys. 41 103–12
ICRU 1993 Stopping powers and ranges for protons and alpha particles Technical Report ICRU Report No 49 ICRU Bethesda, MD
ICRU 2005 Stopping of ions heavier than helium Technical Report ICRU Report No 73 ICRU Bethesda, MD
Incerti S et al 2010 Comparison of GEANT4 very low energy cross section models with experimental data in water Med. Phys. 37 4692–708
Sardutovich E, Yakubovich A V and Solov’yov A V 2013 DNA damage due to thermomechanical effects caused by heavy ions propagating in tissue Nucl. Instrum. Methods B 314 63–5
Toulemonde M, Surdutovich E and Solov’yov A V 2009 Temperature and pressure spikes in ion-beam cancer therapy Phys. Rev. E 80 031913
Varma M N, Baum J W and Kuehner A V 1977 Radial dose, LET, and \( W \) for \(^{16}\)O ions in N\(_2\) and tissue-equivalent gases Radiat. Res. 70 511–8