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

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Abstract

Depth and radial dose profiles for therapeutic $^1$H, $^4$He, $^{12}$C and $^{16}$O beams are calculated using the Geant4-based Monte Carlo model for Heavy-Ion Therapy (MCHIT). $^4$He and $^{16}$O ions are presented as alternative options to $^1$H and $^{12}$C broadly used for ion-beam cancer therapy. Biological dose profiles and survival fractions of cells are estimated using the modified Microdosimetric Kinetic model. Depth distributions of cell survival of healthy tissues, assuming 10% and 50% survival of tumor cells, are calculated for 6 cm SOBPs at two tumor depths and for different tissues radiosensitivities. It is found that the optimal ion choice depends on (i) depth of the tumor, (ii) dose levels and (iii) the contrast of radiosensitivities of tumor and surrounding healthy tissues. Our results indicate that $^{12}$C and $^{16}$O ions are more appropriate to spare healthy tissues in the case of a more radioresistant tumor at moderate depths. On the other hand, a sensitive tumor surrounded by more resistant tissues can be better treated with $^1$H and $^4$He ions. In general, $^4$He beam is found to be a good candidate for therapy. It better spares healthy tissues in all considered cases compared to $^1$H. Besides, the dose conformation is improved for deep-seated tumors compared to $^1$H, and the damage to surrounding healthy tissues is reduced compared to heavier ions due to the lower impact of nuclear fragmentation. No definite advantages of $^{16}$O with respect to $^{12}$C ions are found in this study.
Keywords: theory and algorithms in physics of heavy-ion therapy, Monte Carlo applications, simulation, microdosimetry, RBE, biological SOBP

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

1. Introduction

The advantage of charged particles, in particular, protons and carbon nuclei, used for radiation therapy of deep seated tumors consists in elevated dose delivered at the end of projectile range in tissues. The plateau of the depth-dose distribution at the entrance of a monoenergetic beam terminates with a sharp Bragg peak which can be targeted at the tumor. Such a dose profile helps to spare healthy tissues located in front of the tumor as well as beyond the projectile range. Since a set of beam energies is typically used in treatments to cover the whole tumor volume, the resulting dose distribution is characterized by a spread-out Bragg peak (SOBP) (Kase et al 2006b, Gueulette and Wambersie 2007, Schardt et al 2010) with a wide domain of elevated dose.

The damage to healthy tissues during therapy can be essentially reduced if the ratio between the relative biological effectiveness (RBE) values at the SOBP region and beam entrance is favorable. As recognized almost 40 years ago in radiobiological experiments with SOBP beams of light nuclei performed at Berkeley (Chapman et al 1977), this RBE ratio is greater than 1 and increases with the ion charge up to carbon. It was also found that this ratio decreases for Ne and becomes less than 1. In 1994 first patient treatments with beams of $^{12}$C nuclei started in Japan at the National Institute of Radiological Sciences (NIRS) (Kanai et al 1999) and in 1997 in Germany at Gesellschaft für Schwerionenforschung (GSI) (Schardt et al 2010). Later the advantages of $^{12}$C with respect to $^{3}$He and $^{20}$Ne were confirmed in experiments at NIRS with these nuclear beams (Furusawa et al 2000). As explained (Matsufuji et al 2007), the RBE of 135 MeV $u^{-1}$ $^{12}$C beam with linear energy transfer (LET) of 65 keV $\mu$m$^{-1}$ was found similar to the RBE of neutrons which have been used for treatment at NIRS already for 20 years. This similarity also motivated the choice of $^{12}$C nuclei for treatments at NIRS. In the last decades localized tumors have been successfully treated with beams of $^{12}$C nuclei at several facilities constructed in Japan and Germany (Tsujii et al 2004, Schulz-Ertner and Tsujii 2007, Combs et al 2010, Durante and Loeffler 2010, Jensen et al 2011, Kamada 2012).

Biological models applied at these facilities for estimation of RBE for ion beams include the Microdosimetric Kinetic (MK) model (Hawkins 2003) and Local Effect Model (Scholz and Kraft 1996, Elsässer and Scholz 2007).

Despite of the broad clinical experience collected worldwide with proton and carbon-ion beams, other light nuclei can be also considered as future therapy options. The choice of ion species and their energies at each new particle therapy facility (Brahme et al 2001, Svensson et al 2004, Lundkvist et al 2005) essentially depends on LET and RBE of the projectiles under consideration. The distributions of dose, LET and dose-averaged LET of $^{1}$H, $^{4}$He, $^{6,7}$Li, $^{8}$Be, $^{10}$B, $^{12}$C, $^{14}$N and $^{16}$O nuclei of therapeutic energies were studied (Kempe et al 2007, Kantemiris et al 2011) by means of Monte Carlo simulations with SHIELD-HIT and FLUKA codes, respectively. Similar depth distributions for $^{1}$H, $^{3}$He, $^{12}$C, $^{20}$Ne and $^{58}$Ni were calculated (Pshenichnov et al 2008) with the Geant4 toolkit to study their dependence on the ion energy and compare them for these ion species. A study suggested (Kempe et al 2007) that ions with LET above 20 keV $\mu$m$^{-1}$ should be used for efficient cancer therapy as such projectiles induce on average two or more double strand breaks in DNA close to each other. However, as pointed out in the same work, this limit is not sharp and ought to vary with ion charge and
energy. This indicates that the RBE of respective ions has to be additionally considered for an accurate comparison of their biological action. Indeed, as shown in our recent work (Burigo et al. 2014), there is no direct correspondence between RBE and the frequency-mean lineal energy $\bar{y}$, which represents LET, for monoenergetic beams of therapeutic energies. Similar RBE values were estimated (Burigo et al. 2014) at the peak and beam entrance regions which are characterized, however, by very different $\bar{y}$.

In a recent work (Remmes et al. 2012) the authors studied the possibility to reduce the damage to healthy tissues by properly selecting ion species for therapy. In addition to $^1$H, $^4$He, $^{12}$C they considered $^7$Li, $^9$Be, $^{20}$Ne ions and calculated the dose to normal tissue delivered by these beams. However, the option of $^{16}$O was not considered, while the Heidelberger Ionenstrahl-Therapiezentrum (HIT) in Heidelberg, Germany, was designed to provide $^{16}$O beams of therapeutic energies (Haberer et al. 2004, Combs et al. 2010) in addition to $^1$H, $^4$He, $^{12}$C. Treatments at this facility are performed presently only with $^1$H and $^{12}$C ions, but $^4$He and $^{16}$O can be also used following respective pre-clinical studies.

The radiobiological properties of $^1$H and $^{12}$C beams were compared in several studies, see e.g. (Wilkens and Oelfke 2008, Suit et al. 2010). However, less attention has been paid so far to $^4$He or $^{16}$O and to their comparison with $^1$H and $^{12}$C. There exist several clinical rationale behind the use of $^4$He and $^{16}$O for therapy:

(a) $^4$He and $^{16}$O beams have a reduced lateral spread of the dose distribution compared to $^1$H;
(b) their RBE in the target volume is higher compared to $^1$H;
(c) lower dose in the tail region is expected for $^4$He compared to $^{12}$C due to reduced nuclear fragmentation of projectiles;
(d) $^{16}$O is a promising option for hypoxic tumors as it provides a higher dose-averaged LET in the target volume compared to $^{12}$C.

As demonstrated (Burigo et al. 2013b, Burigo et al. 2014), microdosimetry spectra and the respective average quantities for monoenergetic $^1$H, $^4$He, $^{12}$C and $^{16}$O nuclei propagating in a water phantom can be accurately described with our Monte Carlo model for Heavy-Ion Therapy (MCHIT) (Pshenichnov et al. 2010), and this model coupled with a modified MK model (Kase et al. 2006a) can be used to calculate the respective RBE and cell survival profiles. The modified MK model has been successfully applied elsewhere in the treatment planning for scanned $^{12}$C beam (Inaniwa et al. 2010). In the present work we evaluate $^4$He and $^{16}$O for cancer therapy as complementary options to $^1$H and $^{12}$C by considering the biological dose distributions with a 6 cm SOBP delivered by these four projectiles. Two cases of tumors centered at depth of 130 mm and 240 mm are investigated. This study helps to plan radiobiological experiments with $^4$He and $^{16}$O SOBP beams and extend existing treatment planning systems to operation with new projectiles. Our study complements the results of Remmes et al. (2012) by considering $^{16}$O beams and also by comparing cell survival profiles in $^1$H, $^4$He, $^{12}$C and $^{16}$O treatments in addition to biological dose profiles.

The experimental data (Kase et al. 2006a) collected at HIMAC for the 6 cm SOBP obtained by the modulation of a 290 MeV u$^{-1}$ $^{12}$C beam are used as a reference. The results of microdosimetry simulations are validated by comparison with experimental microdosimetry data collected for $^1$H, $^4$He and $^{12}$C SOBP beams (Kase et al. 2006a). A previous study has shown that MCHIT can reproduce microdosimetric quantities for monoenergetic $^{16}$O beam (Burigo et al. 2013b). These results give us confidence in the estimation of microdosimetric quantities for a $^{16}$O SOBP beam. This makes possible to predict the RBE and cell survival profiles for $^{16}$O beams and compare all four ion species in a common framework for the first time in the literature.
2. Materials and methods

2.1. Monte Carlo modeling of propagation of ions in water

With the Monte Carlo model for Heavy-Ion Therapy (MCHIT) (Pshenichnov et al. 2005, Pshenichnov et al. 2010) the propagation of accelerated protons and light nuclei of therapeutic energies in tissue-like media can be simulated. The model is based on the Geant4 toolkit (Agostinelli et al. 2003, Allison et al. 2006) and takes into account all major physics processes relevant to the interactions of beam particles with these materials. The Geant4 version 9.5 with patch 02 is used to build the present version of MCHIT, which also simulates the interactions of various particles with walled and wall-less Tissue Equivalent Proportional Counters (TEPC) thus providing respective microdosimetry distributions.

The ionization of atoms and multiple Coulomb scattering on nuclei of the media are the most important electromagnetic processes to simulate the energy loss and straggling of primary and secondary charged particles. Two predefined physics lists for electromagnetic processes are employed in MCHIT, namely, G4EmStd (which uses the ‘Standard Electromagnetic Physics Option 3’) and G4EmPen (which uses the Penelope models for low-energy processes). The low-energy thresholds for production of δ-electrons are 990 eV for G4EmStd and 100 eV for G4EmPen. However, in order to reduce the CPU time, such energy thresholds are set differently for water, plastic of the TEPC wall and the TEPC sensitive volume filled with tissue-equivalent gas (Burigo et al. 2013a). A customized physics list, G4EmPen + IonGas, which is based on G4EmPen and the models describing the ionization of gas media by ions, can be also used in calculations. As demonstrated (Burigo et al. 2014), G4EmStd and G4EmPen provide statistically equivalent results for microdosimetry spectra, which agree well with the distributions measured for 4He (Tsuda et al. 2012), excluding the domains of low lineal energy, $y < 1$ keV $\mu m^{-1}$ and around the maximum at $y \sim 15$ keV $\mu m^{-1}$. However, the agreement between the data and calculations is improved when G4EmPen + IonGas is used. Therefore, G4EmPen + IonGas is used in MCHIT also in the present work to simulate electromagnetic processes inside the TEPC volume.

A therapeutic nuclear beam is attenuated in tissues due to the loss of beam nuclei in nuclear fragmentation reactions, which generate secondary projectile and target fragments (Pshenichnov et al. 2010). Nuclear reactions are taken into account in MCHIT to reproduce this effect. As shown (Pshenichnov et al. 2010), the build-up of secondary fragments produced by 200 MeV $u^{-1}$ and 400 MeV $u^{-1}$ 12C beams is generally well described with a customized physics list based on the Light Ion Binary Cascade model (G4BIC) (Folger et al. 2004) coupled with the Fermi break-up model (G4FermiBreakUp) (Bondorf et al. 1995) responsible for subsequent decays of excited nuclear fragments created at the first fast stage of nucleus-nucleus collisions. In the present work G4BIC is used for 1H and 4He beams, while the Quantum Molecular Dynamics model (G4QMD) (Koi 2010) is involved in simulations with 12C and 16O beams. More details on the physics processes and respective Geant4 models involved in modeling with MCHIT are given in our recent publications (Pshenichnov et al. 2010, Burigo et al. 2013a, Burigo et al. 2014).

2.2. Microdosimetry simulations and calculations of RBE for monoenergetic beams

Microdosimetry data collected with TEPCs provide information relevant to the stochastic energy deposition to subnuclear structures of mammalian cells during irradiation. The design and materials of specific TEPC models were thoroughly introduced in MCHIT. This made possible to simulate the microdosimetry spectra measured with a walled TEPC at several
positions inside a water phantom irradiated by 185 MeV u⁻¹ ⁷Li and 300 MeV u⁻¹ ¹²C beams (Martino et al 2010) and study the impact of nuclear fragmentation reactions on these spectra (Burigo et al 2013a, Burigo et al 2014). The influence of the positioning of the TEPC with respect to the beam axis and the distortion of the spectra due to the pile-up of individual events were investigated. After correcting for such effects the calculated microdosimetry spectra agree well with the experimental data.

Following the validation of MCHIT for microdosimetry of monoenergetic ¹H, ⁴He, ⁷Li and ¹²C beams (Burigo et al 2013a, Burigo et al 2014), in the present work this model is applied to microdosimetry of SOBP dose distributions. In the measurements performed at HIMAC with a 6 cm SOBP for 160 MeV ¹H, 150 MeV u⁻¹ ⁴He and 290 MeV u⁻¹ ¹²C (Kase et al 2006a) the data for frequency-mean lineal energy, 〈y_f〉, dose-mean lineal energy, 〈y_d〉 and saturation-corrected dose-mean lineal energy, 〈y^*〉 (ICRU 1983) were collected. The microdosimetry spectra were measured with a walled TEPC corresponding to a tissue-equivalent sphere of 1 µm in diameter.

According to the linear-quadratic (LQ) model the survival fraction of cells S after the impact of the radiation dose D is calculated as

\[ S = \exp[-\alpha D - \beta D^2] \]  

(1)

Following the modified MK model (Kase et al 2006a) applied to human salivary gland (HSG) tumor cells the parameter 〈y^*〉 is estimated as

\[ \alpha = \alpha_0 + \frac{\beta}{\rho r_d^2 y^*} \]  

(2)

with the constant term \( \alpha_0 = 0.13 \text{ Gy}^{-1} \) representing the initial slope of the survival fraction curve in the limit of zero LET and \( \beta = 0.05 \text{ Gy}^{-2} \). \( \rho = 1 \text{ g cm}^{-3} \) is the density of tissue and \( r_d = 0.42 \text{ µm} \) as the radius of a sub-cellular domain in the MK model. The dependence of the \( \alpha \)-parameter of the LQ model on \( y^* \) rather than on \( y_d \) reflects the reduction of the RBE known as the saturation effect. It means that an excessive local energy deposition does not boost biological effects induced by high-LET particles (ICRU 1983). As demonstrated (Kase et al 2006a), the same value of parameter \( \beta = 0.05 \text{ Gy}^{-2} \) can be used to fit the data on S with equation (1) for x-rays and ions. This justifies the assumption of the MK model that \( \beta \) is independent of LET.

According to the LQ model the RBE is calculated using the following relation:

\[ \text{RBE} = \frac{D_R}{D} = \frac{2\beta D_R}{\sqrt{\alpha^2 - 4\beta \ln(S) - \alpha}}, \]  

(3)

where D is the physical dose of ions at cell survival level S and \( D_R \) is the dose of the reference radiation at the same survival fraction. The 10% survival dose \( D_{10,R} \) of the reference radiation (200 kVp x-rays) for HSG cells is 5.1 Gy (\( \alpha_x = 0.19 \text{ Gy}^{-1} \)) (Kase et al 2006a) while only 2.3 Gy is required to kill 50% of such cells.

2.3. Composing SOBP profiles from a library of pristine Bragg peaks

The computing time required for treatment planning in carbon-ion therapy can be reduced by using pre-computed libraries of dose, \( \alpha \) and \( \beta \) distributions for monoenergetic beams (Krämer and Scholz 2000, Krämer et al 2000, Jäkel et al 2001, Krämer and Durante 2010). The aim of the treatment planning is to find an optimum superposition of many beams with their individual energy, position and intensity in order to obtain the prescribed biological SOBP dose.
profile. It is expected that a similar approach will be also suitable for other therapeutic beams, like ³He and ¹⁶O. Therefore, we implemented a common algorithm to calculate the relative weights of pre-defined monoenergetic beams of ¹H, ³He, ¹²C and ¹⁶O to obtain flat biological SOBP distributions for each projectile as a product of the physical dose and RBE calculated for mixed radiation field.

A library of depth-dose profiles and the corresponding microdosimetry spectra for different beam energies and nuclei were calculated by Monte Carlo simulations with MCHIT. It contains profiles with a 1 mm increment of the Bragg peak positions which are within 90–175 mm and 200–280 mm depth in water. They are used as input data for a procedure similar to one implemented at NIRS (Matsufuji et al 2007). According to this procedure based on the theory of dual radiation action (Zaider and Rossi 1980) the survival fraction of cells exposed to mixed radiation is calculated as:

\[
S_{\text{mix}}(D) = \exp(-\alpha_{\text{mix}}D - \beta_{\text{mix}}D^2);
\]

\[
\alpha_{\text{mix}} = \sum f_ia_i;
\]

\[
\sqrt{\beta_{\text{mix}}} = \sum f_i\sqrt{\beta_i}.
\]

Here \(f_i\) is the weight coefficient (fraction) of the local physical dose of the \(i\)th monoenergetic beam which contribute to the total physical dose \(D\), while \(\alpha_i\) and \(\beta_i\) are the parameters of the LQ model specific to the \(i\)th monoenergetic beam. The parameters \(\alpha_i\) and \(\beta_i\) are calculated along the beam axis using MCHIT coupled with the modified MK model as described in section 2.2. The resulting RBE_{\text{mix}} for the mixed radiation is calculated from the survival fraction of cells \(S_{\text{mix}}(D)\) and it also depends on the depth. Finally, the biological dose \(D_{\text{bio}}\) is calculated from RBE_{\text{mix}} and physical dose:

\[
D_{\text{bio}} = \text{RBE}_{\text{mix}} \times D.
\]

A dedicated algorithm to obtain \(f_i\) for a given biological SOBP was developed. It starts with the determination of the weight at the distal edge of the SOBP distribution and then calculates weights for less energetic beams by adjusting their contribution to provide a flat biological SOBP. These weights make up the beam energy profile used as input for SOBP calculations with MCHIT.

The set of discrete beam energies for ¹H, ³He, ¹²C and ¹⁶O was optimized to yield 6 cm-wide SOBP dose distributions in a target volume centered at 130 mm and 240 mm in depth. Two biological endpoints of 10% survival and 50% survival of tumor cells at the SOBP was chosen in the calculations. Parallel beams of 5 cm in diameter with uniform spatial distribution were modeled. Longitudinal profiles of biological dose and cell survival were calculated inside a cylinder of 2.5 cm in diameter centered at the beam axis to ensure negligible variations of dose and radiation quality in the radial direction inside this cylinder.

Distributions of biological dose are obtained as the product of physical dose calculated with MCHIT and RBE obtained with the MK model on the basis of microdosimetric modeling using MCHIT. Longitudinal distributions of cell survivals are calculated for different tissue radiosensitivities. Throughout this paper the parameters for HSG cells were taken as \(\alpha_0 = 0.13\ \text{Gy}^{-1}\) and \((\alpha/\beta)_{\text{x-rays}} = 3.8\ \text{Gy}\) (Kase et al 2006a). Two other tissues are modeled with corresponding parameters taken following Kase et al (2011). The latter two cases correspond to late responding tissue (\(\alpha_0 = 0.04\ \text{Gy}^{-1}\), (\(\alpha/\beta)_{\text{x-rays}} = 2\ \text{Gy}\) which is radioresistant
and early responding tissue \((\alpha_0 = 0.44 \text{ Gy}^{-1}, (\alpha/\beta)_x - \text{rays} = 10 \text{ Gy})\), which is very sensitive to radiation.

3. Results and discussion

3.1. Pristine Bragg peaks

Simulation results for monoenergetic 152.7 MeV \(^{1}\text{H}\), 152.1 MeV \(^{4}\text{He}\), 290 MeV \(^{12}\text{C}\) and 345.4 MeV \(^{16}\text{O}\) beams are shown in figure 1. The beam energies were chosen to place the Bragg peaks of all four beams at the depth of \(\sim 162 \text{ mm}\).

As expected, the \(^{12}\text{C}\) and \(^{16}\text{O}\) beams deposit much higher energy per ion at the Bragg peak compared to \(^{1}\text{H}\) and \(^{4}\text{He}\). However, higher energy deposition by \(^{12}\text{C}\) and \(^{16}\text{O}\) is observed also at the entrance and tail regions. Therefore, no clear advantages of therapeutic \(^{12}\text{C}\) and \(^{16}\text{O}\) beams with respect to \(^{1}\text{H}\) and \(^{4}\text{He}\) beams regarding healthy tissues can be inferred exclusively from the analysis of these depth-dose distributions.
The $\alpha$ profiles estimated for HSG cells after irradiation with the considered $^1$H, $^4$He, $^{12}$C and $^{16}$O beams are shown in the bottom panel of figure 1 and they differ from each other. They were calculated with the MK model basing on microdosimetry data generated by Monte Carlo simulations with MCHIT. Experimental (Kase et al 2006a) $\alpha$ values for $^{12}$C beam obtained by two different methods are also shown for comparison. In the first case, $\alpha$ is also calculated with the MK model, but on the basis of measured $y^*$ values. In the second case, $\alpha$ is obtained from the LQ fitting of survival curves of HSG cells with $\beta$ fixed to $0.05 \text{ Gy}^{-2}$. The $\alpha$ profile for $^{12}$C beam calculated with MCHIT coupled with the MK model agrees well with both sets of experimental data. A prominent difference between $\alpha$ profiles for $^{12}$C and $^{16}$O and the profile for $^4$He is seen in the insert of figure 1. The backward shift of the maximum of $\alpha$ of $^{12}$C and $^{16}$O with respect to the position of the $^4$He maximum is due to the saturation effect. It is also found that $^{12}$C and $^{16}$O nuclei are characterized by higher $\alpha$ values along the whole irradiated medium. At the same time the $\alpha$ values for $^4$He are relatively low at the entrance and tail regions and demonstrate a steep rise at the Bragg peak position. Before the Bragg peak the $\alpha$ values for $^4$H beam are slightly below the value for the reference radiation and increase to 0.5 well after the distal edge of the $^4$H Bragg peak. This rise of $\alpha$ for $^4$H beam is explained by the presence of secondary nucleons, in particular, neutrons, produced by primary $^1$H in water and propagating beyond the Bragg peak. However, their contribution to the total dose is very small.

Figure 2. Energy deposition profiles for $^{12}$C in water in 10 mm steps (top panel) and the corresponding $y^*$ profiles calculated with MCHIT (bottom panel).
3.2. SOBP optimization for $^1$H, $^4$He, $^{12}$C and $^{16}$O

As explained in section 2.3, a given biological SOBP dose distribution is composed from a set of depth-dose and depth-$\gamma$ profiles from a library precalculated with MCHIT for monoenergetic beams. Seven pristine Bragg peaks for $^{12}$C covering a 60 mm domain in depth and the corresponding $\gamma^*$ distributions are shown in figure 2 to illustrate the content of this library. The microdosimetry variables stored in the library as functions of depth are used to estimate RBE profiles according to the MK model, see section 2.3. As seen in figure 2, the height of the Bragg peak noticeably diminishes with depth, while the maximum $\gamma^*$ remains almost constant ($\sim 80$ keV $\mu$m$^{-1}$) over the considered depth range.

A 6 cm-wide SOBP profile of biological dose for 290 MeV u$^{-1}$ $^{12}$C beam, which was built according to the above-described procedure is shown in the top panel of figure 3. In the following such profiles are calculated also for other ion species to yield exactly 10% survival of HSG cells at the SOBP in order to facilitate the comparison of different projectiles. The resulting distribution has a flat SOBP with negligible fluctuations due to the presence of individual Bragg peaks. In contrast, the corresponding SOBP distribution of the physical dose, which is also shown in figure 3, is not flat, but rather decreases with depth. The respective RBE$_{\text{mix}}$ amounts to $\sim 1.6$ at the proximal edge of the SOBP, while it is slightly above 2.6 at the distal edge, see the bottom panel of figure 3. The uncertainties of RBE$_{\text{mix}}$ calculated by MCHIT + MK model which are due to the statistical uncertainty in the calculated depth-$\gamma^*$ profiles are below 1% at all depths for $^4$He, $^{12}$C and $^{16}$O ions and below 1% from the beam entrance down to the distal edge of the SOBP for $^1$H. In the tail region the uncertainty for $^1$H is larger (up to 10%) due to much smaller number of events in the TEPC which is not directly irradiated by the primary $^1$H beam. The uncertainty increases for lighter ions due to less secondary particles penetrating beyond the distal edge of the SOBP. However, such calculational uncertainties are much smaller compared to the uncertainties of the LQ parameters extracted from cell irradiation experiments or related to variations of radiosensitivity of specific cell lines (Friedrich et al 2010). The insert in the bottom panel of figure 3 demonstrates the calculated relative weights for monoenergetic beams used to build the SOBP distribution of biological dose shown in figure 3.

The $\alpha_{\text{mix}}$ profiles corresponding to 6 cm-wide SOBPs for 152.7 MeV $^1$H, 152.1 MeV u$^{-1}$ $^4$He, 290 MeV u$^{-1}$ $^{12}$C and 345.4 MeV u$^{-1}$ $^{16}$O beams are presented in figure 4. They were calculated with the MK model basing on microdosimetry data generated by Monte Carlo simulations with MCHIT. The reliability of these profiles can be proven by comparing them with $\alpha_{\text{mix}}$ obtained in experiments by two different methods as described in section 3.1. The profiles based on MCHIT simulations agree very well with the $\alpha_{\text{mix}}$ estimated by both methods, see figure 4. In order to make such comparison, experimental values corresponding to $^1$H and $^4$He were shifted in depth due to a slight difference of beam energies used in measurements and simulations. It should be mentioned that in the experiments by Kase et al (2006a), a ridge filter was used to spread the Bragg peak of a monoenergetic beam while in our calculations a beam energy profile was applied simulating beam energies extracted from a synchrotron. The average traversed water-equivalent length of the ridge filter required to modulate a 6 cm SOBP beam is around 2 cm. The presence of the ridge filter in the experiments leads to the production of some secondary particles which can irradiate the TEPC located downstream the phantom. The effect of nuclear fragmentations within the ridge filter is not considered in our simulations because the number of fragmentation events in the ridge filter is small compared to the number of such events in the phantom, and their effect on the calculated $\alpha_{\text{mix}}$ is marginal.

A good agreement with the experimental data for $^1$H, $^4$He and $^{12}$C beams suggests that this method can be also applied to $^{16}$O beam as it was demonstrated that MCHIT is able to...
reproduce microdosimetry parameters for $^{16}$O beam (Burigo et al 2013b). The distribution of $\alpha_{\text{mix}}$ for $^{16}$O obtained on the basis of microdosimetry simulations with MCHIT is shown in figure 4 for comparison. The shapes of $\alpha_{\text{mix}}$ profiles for $^4$He, $^{12}$C and $^{16}$O are found to be similar. They are characterized by an increase of $\alpha_{\text{mix}}$ at the proximal edge of the SOBP distribution, which translates in a respective increase of RBE. Similarly to the case of monoenergetic $^1$H beam, see section 3.1, a characteristic rise of $\alpha$ (RBE) for $^1$H beyond 162 mm depth at the distal region of the SOBP is found. At the entrance region $\alpha_{\text{mix}}$ values are similar for $^1$H and $^4$He beams. The ratio between $\alpha_{\text{mix}}$ values at the proximal (depth of ~102 mm) and distal (depth of ~162 mm) regions is closer to unity for $^{16}$O compared to $^{12}$C. The $\alpha_{\text{mix}}$ profile for $^{16}$O demonstrates the most pronounced tail with respect to other projectiles.

3.3. SOBP dose distributions

Radial profiles of physical dose at the center of 6 cm-wide SOBP of $^1$H, $^4$He, $^{12}$C and $^{16}$O beams for two different target depths are shown in figure 5. The corresponding depth profiles of biological dose are shown in figure 6. The biological endpoint of 10% survival of HSG cells at the SOBP was chosen in these calculations.
Carbon ions are preferred over protons for irradiation of deep-seated targets close to organs at risk due to the reduced lateral scattering which leads to better dose conformation to the target. Figure 5 demonstrates the lateral spread of the dose delivered by $^1\text{H}$, $^4\text{He}$, $^{12}\text{C}$ and $^{16}\text{O}$ beams at different depth values. As seen, $^{12}\text{C}$ and $^{16}\text{O}$ ions present a much steeper dose fall-off compared to $^1\text{H}$. The lateral penumbra $P_{80/20}$ can be used to characterize the radial distance between the points in which the dose level decreases from 80% to 20% of the nominal dose in the target. $P_{80/20}$ values at the proximal edge, center and distal edge of SOBP are presented in table 1. For the target centered at 130 mm, the penumbra is considerably smaller for $^{12}\text{C}$ and $^{16}\text{O}$ ions as compared with $^1\text{H}$ and $^4\text{He}$. However, for the deeper target position the difference between $^4\text{He}$ and the heavier ions is reduced. At the same time $P_{80/20}$ values are very similar for $^{12}\text{C}$ and $^{16}\text{O}$ ions at both tumor positions.

The longitudinal biological dose profiles $D_{bio}$ for SOBP at 100–160 mm are shown in the left panel of figure 6. In this case the dose distributions produced by different ions are rather close to each other, the maximum difference at the entrance is within 15%. The lowest doses are estimated there for $^4\text{He}$ and $^{12}\text{C}$, while the highest doses—for $^1\text{H}$ and $^{16}\text{O}$. In the second case of SOBP at 210–270 mm depth, MCHIT + MK model predicts higher biological dose at the beam entrance from $^{12}\text{C}$ and $^{16}\text{O}$ ions compared to doses from lighter projectiles. The reason is that the effect of nuclear fragmentation becomes more significant for these heavier ions when irradiating deeply-seated tumors. The stopping power of the primary ion is higher than the sum of the stopping powers of the fragments. Therefore, in order to reach the same dose level at deeper penetration, a higher number of primary ions are required. This increases the dose at the entrance compared to the first case and explains the non-monotonous behavior of the biological dose for $^{12}\text{C}$ and $^{16}\text{O}$ ions seen in the right panel of figure 6. This effect is not visible for lighter projectiles due to lower nuclear reaction cross sections for $^1\text{H}$ and $^4\text{He}$ compared to $^{12}\text{C}$ and $^{16}\text{O}$.

As seen from figure 6, in the case of $^1\text{H}$ the tail of the dose distribution beyond the distal edge of the SOBP is negligible for both target volume locations. In contrast, the tail cannot
be neglected for $^4$He, $^{12}$C and $^{16}$O beams. This indicates that the $^1$H beam is the best option if very sensitive organs are located behind the tumor volume. However, due to their larger lateral penumbra $^1$H cannot be recommended if organs at risk are located alongside. A fast increase of $\alpha_{\text{mix}}$ with depth, observed in figure 4 for $^{12}$C ions near the proximal edge of the SOBP, leads to a more steep rise of the biological dose just before the SOBP as compared with $^1$H, see figure 6. The distributions of $D_{\text{bio}}$ for $^4$He demonstrate favorably smaller dose at the entrance and tail regions compared to $^{12}$C with a rather similar lateral spreading. The biological dose delivered by $^{16}$O to normal tissue is larger compared to $^{12}$C both in front of the target volume and behind it. However, $^{16}$O ions are better for sparing organs at risk around the tumor. From our consideration of lateral penumbra and biological dose distributions one can conclude that $^4$He presents the best choice compared to $^1$H, $^{12}$C and $^{16}$O when healthy and tumor tissues both have radiosensitivity similar to HSG cells.

3.4. Depth distributions of cell survival

Using the combined MCHIT + MK model we have performed calculations of survival fractions of cells $S_{\text{mix}}$ as a function of depth, after exposing them to $^1$H, $^4$He, $^{12}$C and $^{16}$O SOBP
beams for tissues of different radiosensitivity. This makes possible to compare the respective biological outcomes of the irradiation.

Distributions of $S_{\text{mix}}$ for 10% and 50% cell survival were calculated for HSG cells for two positions of the target volume as shown in figure 7. Hereafter the radiosensitivity of HSG cells is considered as normal. This serves as a natural reference point for comparison with late responding tissue and early responding tissue shown in figure 8.

On the basis of performed simulations we came to the following conclusions. In the case of normal radiosensitivity (HSG cells), the beams of 4He and 12C spare tissues equally well at the beam entrance for a target located at 100–160 mm depth, while the harmful impact of 1H is the strongest there, see panels (a) and (c) of figure 7. As expected, the main difference between light 1H, 4He and heavier 12C, 16O ions is revealed beyond the distal edge of the SOBP profile, due to the contribution of secondary fragments from 12C and 16O. 4He beam better spares normal responding tissues at the entrance compared to 1H and 16O ions and it also improves substantially the survival rate at the tail compared to 12C ions. In the case of a target located at 210–270 mm, panels (b) and (d) of figure 7, the increase of the target depth makes the effect of nuclear fragmentation on the cell survival even more important. Similar to what is observed in the previous target position at 100–160 mm, 4He ions better spare the normal responding tissues.

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**Figure 6.** SOBP biological dose profiles for 1H, 4He, 12C and 16O nuclei obtained as a product of physical dose calculated with MCHIT and RBE with the MK model for HSG cells. The results are given for SOBP at 100–160 mm (left panel) and 210–270 mm (right panel).

**Table 1.** Lateral penumbra $P_{80/20}$ at the proximal edge, center and distal edge of SOBP of 1H, 4He, 12C and 16O beams of 5 cm in diameter.

| Ion beam | $P_{80/20}$ (mm) |
|----------|------------------|
|          | Proximal | Center | Distal | Proximal | Center | Distal |
| 1H       | 3.0      | 4.2    | 5.2    | 6.5      | 7.8    | 8.8    |
| 4He      | 1.5      | 2.0    | 2.5    | 3.2      | 3.8    | 4.2    |
| 12C      | 1.0      | 1.2    | 1.5    | 2.0      | 2.8    | 3.0    |
| 16O      | 1.0      | 1.0    | 1.5    | 2.0      | 2.5    | 3.0    |
tissues in the beam entrance compared to $^1$H and $^{16}$O ions. However, the advantage of $^{12}$C ions with respect to $^1$H seen in the previous cases disappears for the case of 10% survival at the deeper target (panel (d)). In such a case, $^1$H kill less healthy cells compared to $^{12}$C until the depth of 100 mm, while $^{12}$C produce less damage downstream until the target volume. To achieve the best therapeutic results one may even use a combined irradiation scheme including both $^4$He and $^{12}$C beams.

In figure 8 we present simulation results for various combinations of radiosensitivity of the target volume located at 100–160 mm depth and surrounding healthy tissues, obtained for 10% survival in the target volume. The cases of early responding tissues and tumor with $(\alpha/\beta)_\text{tumor} = 10$ Gy, as well as resistant tissues and tumor with $(\alpha/\beta)_\text{tumor} = 2$ Gy are considered. In the cases presented in panels (a) and (d) of figure 8 the radiosensitivity of surrounding healthy tissues is the same as the tumor sensitivity and the shapes of cell survival distributions are rather similar to the case of normal (HSG cells) radiosensitivity presented in panel (c) of
However, in the case of early responding tumor surrounded by radioresistant tissues, see panel (b) of figure 8, the calculation results suggest a better treatment using 1H and 4He ions with the worst survival fraction of healthy tissues with 16O ions. In contrast, when the tumor is resistant to radiation and surrounded by radiosensitive tissues, see panel (c) of figure 8, these tissues are better spared by 12C and 16O ions, but more severely damaged by 1H. In all cases, the relation between the survival fractions estimated for 1H, 4He, 12C and 16O beyond the distal edge of the SOBP are quite similar to the case of normal radiosensitivity. This is because of the fact that the dose in the tail region is defined by the secondary fragments, which are more abundant for 12C and 16O beams compared to the lighter ions. Similar results are obtained for 50% survival in the target volume (results not shown) with a slightly better performance of 16O ions over 12C ions in the entrance region for the case of a radioreistant tumor surrounded by radiosensitive healthy tissues.

**Figure 8.** Distributions of cell survival fractions for radiosensitive (panels (a) and (b)) and radioresistant (panels (c) and (d)) tumors at 100–160 mm depth surrounded by healthy tissues of various sensitivities after irradiation with 1H, 4He, 12C and 16O SOBP beams. ‘Sensitive’ stands for tissues with \((\alpha/\beta)_{\text{x-rays}} = 10\) Gy (early responding tissue) and ‘resistant’ for tissues with \((\alpha/\beta)_{\text{x-rays}} = 2\) Gy (late responding tissue).
By considering figures 7 and 8 one can conclude that the selection of the optimal projectile from the considered $^1$H, $^4$He, $^{12}$C and $^{16}$O depends (1) on the depth where the tumor is located; (2) on the survival fraction at the target volume, i.e. dose level; and (3) on the radiosensitivity of the tissues located in front of the tumor and its relation to the tumor radiosensitivity. In all cases when the healthy tissues and tumor are equally sensitive to radiation and for a modest tumor depth of 100–160 mm the use of $^4$He and $^{12}$C is well justified. Due to the reduced fragmentation of $^4$He one can benefit from using this projectile when sparing tissues behind the tumor is crucial. At the same time $^{16}$O has no clear advantages compared to $^{12}$C in terms of the impact on healthy tissues. Due to higher ionization and enhanced fragmentation more cells are killed by $^{16}$O or products of its fragmentation outside the tumor volume compared to $^{12}$C. Finally, our results are summarized in table 2, where the best two projectiles are listed for each combination of the radiosensitivity of the tumor and surrounding healthy tissues.

Finally, we would like to note that several fields are typically applied at various directions with their overlap in the target volume in order to alleviate the damage to healthy tissues. This treatment technique used with a proper fractionation scheme improves the contrast between the cell survival fractions outside and inside the tumor volume. However, the superiority of certain projectiles with respect to other species in terms of the reduced damage to healthy tissues can be demonstrated already in the case of a single treatment field, as shown in figures 7 and 8. Further studies are needed to confirm our results for treatment protocols with multiple fields.

### 4. Conclusions

In this work we presented Monte Carlo simulations of propagation and energy deposition by $^1$H, $^4$He, $^{12}$C and $^{16}$O in tissue-like media. Our simulations of microdosimetry spectra using the MCHIT model provided $y^*$ values as input to the modified MK model (Kase et al 2006a) for calculating cell survival fractions. This made possible to calculate RBE for SOBP dose profiles composed from several monoenergetic beams of these projectiles. This method allowed us to calculate $\alpha_{\text{mix}}$ for $^1$H, $^4$He and $^{12}$C which are in full agreement with (1) $\alpha_{\text{mix}}$ calculated also with the MK model, but on the basis of measured $y^*$ (Kase et al 2006a); and (2) $\alpha_{\text{mix}}$ obtained from the LQ fitting of survival curves of HSG cells (Kase et al 2006a). This makes us confident in extending our approach to $^{16}$O beams for which the respective data are not yet available. These simulations provided well-adjusted biological dose distributions for $^1$H, $^4$He, $^{12}$C and $^{16}$O with a very flat SOBP. Thus, the basic properties of mixed radiation fields corresponding to these SOBP distributions have been investigated.

In order to reduce side effects of ion therapy the damage to surrounding healthy tissues should be minimized. We have used the combined MCHIT + MK model to investigate the severity of this damage by calculating the cell survival fractions in healthy tissues for

| Tumor | Sensitive | Normal (HSG) | Resistant |
|-------|-----------|--------------|-----------|
| Healthy tissues | Sensitive Normal (HSG) | $^4$He, $^{12}$C | $^{12}$C, $^{16}$O |
| | Resistant | $^4$He, $^{12}$C | $^4$He, $^{12}$C |

By considering figures 7 and 8 one can conclude that the selection of the optimal projectile from the considered $^1$H, $^4$He, $^{12}$C and $^{16}$O depends (1) on the depth where the tumor is located; (2) on the survival fraction at the target volume, i.e. dose level; and (3) on the radiosensitivity of the tissues located in front of the tumor and its relation to the tumor radiosensitivity. In all cases when the healthy tissues and tumor are equally sensitive to radiation and for a modest tumor depth of 100–160 mm the use of $^4$He and $^{12}$C is well justified. Due to the reduced fragmentation of $^4$He one can benefit from using this projectile when sparing tissues behind the tumor is crucial. At the same time $^{16}$O has no clear advantages compared to $^{12}$C in terms of the impact on healthy tissues. Due to higher ionization and enhanced fragmentation more cells are killed by $^{16}$O or products of its fragmentation outside the tumor volume compared to $^{12}$C. Finally, our results are summarized in table 2, where the best two projectiles are listed for each combination of the radiosensitivity of the tumor and surrounding healthy tissues.

Finally, we would like to note that several fields are typically applied at various directions with their overlap in the target volume in order to alleviate the damage to healthy tissues. This treatment technique used with a proper fractionation scheme improves the contrast between the cell survival fractions outside and inside the tumor volume. However, the superiority of certain projectiles with respect to other species in terms of the reduced damage to healthy tissues can be demonstrated already in the case of a single treatment field, as shown in figures 7 and 8. Further studies are needed to confirm our results for treatment protocols with multiple fields.

### 4. Conclusions

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In order to reduce side effects of ion therapy the damage to surrounding healthy tissues should be minimized. We have used the combined MCHIT + MK model to investigate the severity of this damage by calculating the cell survival fractions in healthy tissues for
therapeutic $^1$H, $^4$He, $^{12}$C and $^{16}$O beams. We have considered several combinations of normal (HSG cells), high and low radiosensitivity of healthy tissues and tumor and calculated the depth distributions of survival fractions for such cells after irradiation with $^1$H, $^4$He, $^{12}$C and $^{16}$O ions. In all cases the characteristics of SOBP distributions of the biological dose were adjusted to ensure the survival of 10% or 50% of the tumor cells. The comparison of the impact of $^1$H, $^4$He, $^{12}$C and $^{16}$O SOBP beams on healthy tissues in front of and behind the tumor in all these cases led us to the following conclusions:

- In the case of a radioresistant tumor surrounded by radiosensitive healthy tissues all four ion beams induce severe damage not only to the target volume, but also around it. In this case, in order to reduce the damage to the healthy tissues, the treatment planning should use several fields (beam directions). Nevertheless, such sensitive healthy tissues are better spared by $^{12}$C and $^{16}$O ions, but more damaged by $^1$H.
- In the case of healthy tissues with normal radiosensitivity (HSG cells) they are less damaged by $^4$He ions compared to $^1$H, $^{12}$C and $^{16}$O beams, in both considered tumor locations centered at 130 and 240 mm. Due to the reduced nuclear fragmentation of $^4$He with respect to $^{12}$C and $^{16}$O, $^4$He ions can be recommended, especially when sparing healthy tissues behind the distal edge of the SOBP is crucial.
- Radioresistant healthy tissues are better spared with $^1$H and $^4$He compared to $^{12}$C and $^{16}$O in the case of radiosensitive tumors.
- No definitive advantages of $^{16}$O with respect to $^{12}$C in terms of the impact on healthy tissues were found because of the similarity of the depth distributions of cell survival fractions calculated for these projectiles. Nevertheless, due to their higher LET $^{16}$O can be prospective to treat highly resistant hypoxic tumors surrounded by radiosensitive healthy tissues.
- The shapes of depth distributions of cell survival fractions after irradiation with light ($^1$H and $^4$He) and heavy ($^{12}$C and $^{16}$O) ions are different for the deeply-seated tumor centered at 240 mm. Due to higher fragmentation cross sections of $^{12}$C and $^{16}$O the fraction of primary ions which reach the target volume is considerably reduced compared to $^1$H and $^4$He. This means that a larger number of projectiles is required at the beam entrance compared to the case of a shallow tumor to obtain the same level of tumor cells survival. This is reflected in a higher damage at the entrance and makes $^{12}$C and $^{16}$O less advantageous with respect to $^4$He in this case.
- As follows from our simulations, the optimization with respect to the ion type may result in the reduction of the biological dose delivered to the healthy tissues at the level of 10–30%. Therefore, one can think about including such an optimization in the treatment planning. With modern diagnostic methods and computational capabilities this task may become realistic in the near future.

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