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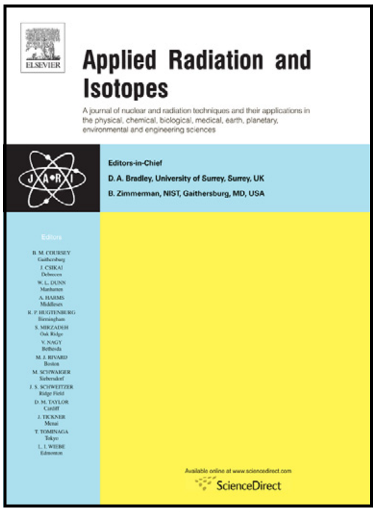

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Dependence of simulated positron emitter yields in ion beam cancer therapy on modeling nuclear fragmentation

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Abstract

In ion beam cancer therapy, range verification in patients using positron emission tomography (PET) requires the comparison of measured with simulated positron emitter yields. We found that 1) changes in modeling nuclear interactions strongly affected the positron emitter yields and that 2) Monte Carlo simulations with SHIELD-HIT10A reasonably matched the most abundant PET isotopes ^{11}C and ^{15}O. We observed an ion-energy (i.e., depth) dependence of the agreement between SHIELD-HIT10A and measurement. Improved modeling requires more accurate measurements of cross section values.

Keywords:
PET nuclides, nuclear fragmentation, ion beam cancer therapy, Monte Carlo simulation, SHIELD-HIT10A

1. Introduction

Ion beam cancer therapy has the potential to advance radiotherapy due to its improved spatial dose distribution (sparing healthy tissue) and increased radiobiological effect (killing cells more efficiently). In ion beam therapy, several quantities depend on nuclear fragmentation: e.g. physical dose distribution, relative biological effectiveness (RBE), dosimetric correction factors, as well as the positron emitter distribution relevant for treatment plan verification by means of positron emission tomography.

Lühr et al. (2012a) studied the effect of differences in modeling nuclear interaction for the first three quantities in clinically relevant situations. They observed that physical dose distributions depended substantially on how nuclear interactions were modeled while the RBE and the dosimetric correction factors did not.

The principle of treatment plan verification by means of positron emission tomography (PET) is to determine the positron emitter activity distribution inside the patient—induced by the ion beam—using a PET device (Enghardt et al., 2004). The measured data serve as input for the range verification of an irradiated ion treatment field (Fiedler et al., 2010, 2011). However, the positron-activity distribution measured by PET does not directly relate to the achieved dose

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distribution. Instead, the PET approach requires a comparison of the measured distribution to a simulated positron emitter distribution in the patient (based on the specific treatment plan). This simulated distribution depends on the modeling of nuclear interaction. España et al. (2011) discussed the reliability of nuclear cross section data for protons by comparing simulated results to measured PET images. They concluded that for proton beams *in vivo* range verification with millimeter precision required more accurate experimental nuclear cross section data.

In this study, we addressed two questions related to range verification in ion beam therapy using PET:

1. How do changes in modeling nuclear interactions impact on simulated positron emitter distributions?
2. How well does the Monte Carlo program SHIELD-HIT simulate relevant positron emitter yields?

We considered lithium and carbon ion beams with energies relevant for ion beam therapy and varied the modeling of nuclear interaction in the same way as was done by Lühr et al. (2012a).

2. Materials and Methods

2.1. Setup of simulations

Monte Carlo simulations were performed with SHIELD-HIT10A (Hansen et al., 2012a), revision number 370 (Bassler et al., 2012). We simulated beams of 10×10^6 monoenergetic 299.9 AMeV carbon ions in PMMA and 5×10^6 monoenergetic 205.3 AMeV lithium ions in water and graphite. The densities in g/cm^3 of the three materials were 1.18, 1.0, and 1.64, respectively. The computer library libdEdx (Toftegaard et al., 2010; Lühr et al., 2012b) provided stopping power data that are based on the tables recommended by the International Commission on Radiation Units and Measurements (ICRU) (ICRU Reports 1993; 2005; 2009). The target extensions were 300 mm parallel to the beam axis and 90 mm $\times$ 90 mm perpendicular.

The simulated detector had the same dimensions as the target. It was divided into 10 mm slices in depths which covered laterally the whole target, i.e. produced laterally integrated depth profiles. The number of positron emitters per slice was counted resolved by isotope. The obtained target yields are presented per 10^6 primary ions (PI).

2.2. Modeling of nuclear fragmentation

The default nuclear fragmentation cross sections in SHIELD-HIT10A were optimized for carbon ion cancer therapy (Hansen et al., 2012b) and considered as a reference setting for this study. Additionally, four different cases of modeling nuclear fragmentation were used with selective changes relative to the default settings as listed in table 1.

In the cases 080 and 120 the total inelastic nuclear cross sections were multiplied with 0.8 and 1.2, respectively, for *all* ions. They describe the energy-dependent probability that an inelastic nuclear event occurs. In the cases *few* and *many* two model Fermi-Breakup parameters were modified which influence the size and number of the produced fragments: the relative free volume, V_{fr}/V_0, and the relative free Coulomb volume, $V_{\mathrm{fr}}^{\mathrm{C}}/V_0$. Compared to the references case 100, *few* leads to few large fragments while *many* leads to many small fragments. To ensure consistency, we chose these five cases to be the same as in (Lühr et al., 2012a) where they were motivated and explained in more detail.

2.3. Literature data

The results for positron emitter yields obtained with SHIELD-HIT10A were compared to experimental data and recently published simulations based on two other programs. Measurements for ^{7}Li irradiation on water and graphite as well as for ^{12}C irradiation on PMMA were performed at the former medical beam line at the GSI Helmholtzzentrum für Schwerionenforschung, Darmstad, Germany by Priegnitz et al. (2008, 2012).

Priegnitz (2012) simulated the positron emitter yields for carbon ion beams with Posgen (Hasch, 1996; Pönisch et al., 2004). The description of the nuclear cross sections in Posgen simulations was based on work by Sihver et al. (1996). The simulations for lithium ion beams were performed with Geant4 (Agostinelli et al., 2003), since Posgen is not optimized for ion species other than carbon, using the physics list recommended for medical applications (Geant4 Collaboration, 2011). Both programs simulated 10×10^6 primary ions.

The Posgen code was frequently considered for calculating positron emitter activity distributions, e.g., from real treatments to evaluate the quality of PET images for different camera settings in real therapeutic situations. Posgen has, however, only been optimized for carbon ions. Therefore, the simulations for the lithium ions were performed with Geant4.

3. Results

Changes in modeling the nuclear interaction (compared to the default in SHIELD-HIT10A, cf. table 1) substantially influenced the simulated positron emitter distributions (cf. figure 1). A decrease (080) or increase (120) of all inelastic nuclear cross sections by 20% resulted in a 20%-35% decrease and 25%-40% increase in yield, respectively. The relative deviations increased with depth except for ^{11}C and ^{10}C at a depth close to the Bragg peak where the differences reduced to about 10%. Simulations with the case *few* changed the yields less than 10%, except for ^{10}C where they increased by about 40%-50%. In the case *many* the yields decreased for all isotopes: about 10% for ^{11}C and ^{15}O and in the order of 30% for ^{10}C and ^{13}N. The use of the case *many* improved the agreement with experiment for carbon ion irradiation on PMMA for all four isotopes (cf. figure 2) and to some smaller extend also for irradiation with lithium ions (cf. figures 3 and 4).

SHIELD-HIT10A tended to overestimate measured data (cf. figures 2 – 5). It reproduced measured data better for irradiation with carbon than with lithium ions. SHIELD-HIT10A agreed

Table 1: The five cases of modeling nuclear interaction are listed: modifications relative to the default settings (100) in SHIELD-HIT10A and the Fermi-Breakup parameters. Further description and motivation can be found elsewhere (Lühr et al., 2012a).

Case	$\Delta\,\sigma_{\mathrm{nuc,in}}$ [a]	V_{fr}/V_0 [b]	$V_{\mathrm{fr}}^{\mathrm{C}}/V_0$ [c]
100	0%	0.65	18.0
080	−20%	0.65	18.0
120	+20%	0.65	18.0
few	0%	1.00	1.0
many	0%	30.00	30.0

[a] $\sigma_{\mathrm{nuc,in}}$: inelastic nuclear cross sections;
[b] V_{fr}/V_0: free volume;
[c] $V_{\mathrm{fr}}^{\mathrm{C}}/V_0$: free Coulomb volume.

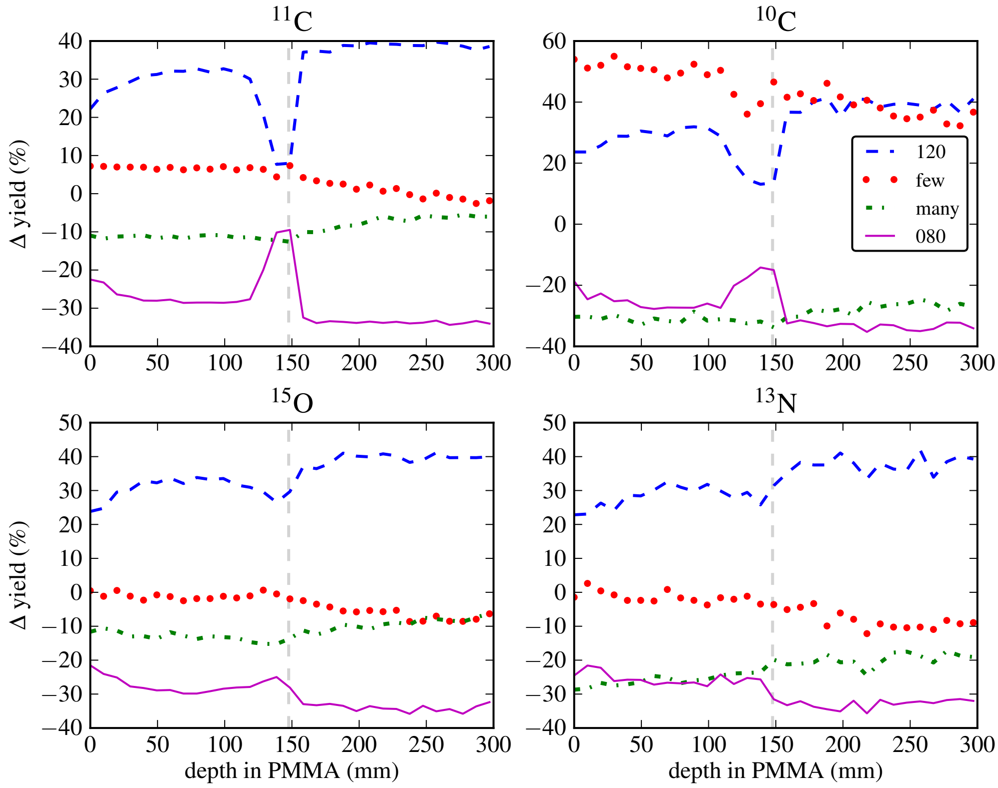

Figure 1: Relative differences in positron emitter yields in PMMA after ^{12}C irradiation with an initial energy of 299.9 AMeV: ^{11}C, ^{10}C, ^{15}O, and ^{13}N. Four different settings of modeling nuclear interaction are compared to the default of SHIELD-HIT10A: 080, 120, *few*, and *many* (cf. table 1). The dashed vertical line indicates the depth at 50% dose fall-off.

better with experiment for high—i.e., for small depths—than for low ion energies and better for ^{11}C and ^{15}O than for the other two isotopes. With default settings (100), a substantial overestimation occurred toward the depth close to the Bragg peak—i.e., low primary ion energies—for the isotope ^{10}C as well as partially for other isotopes. In particular, a spiky behavior occurred for ^{10}C, ^{15}O, and ^{13}N produced by carbon ion beams in PMMA; ^{15}O produced by lithium ion beams in water; and ^{11}C and ^{10}C produced by lithium ion beams in graphite. Other isotope depth distributions for lithium ions in water were dominated by an overall quantitative offset.

Non of the three simulations codes was able to equally well describe the measured data for all isotopes. SHIELD-HIT10A reproduced quantitatively the experimental ^{11}C yields better than PosGen for carbon ions and better than Geant4 for lithium ions. For lithium irradiation on water, Geant4 simulated the ^{15}O distribution well. PosGen produced too large yields for all isotopes at small depths—i.e., for high ion energies ($\gtrsim$ 100 AMeV).

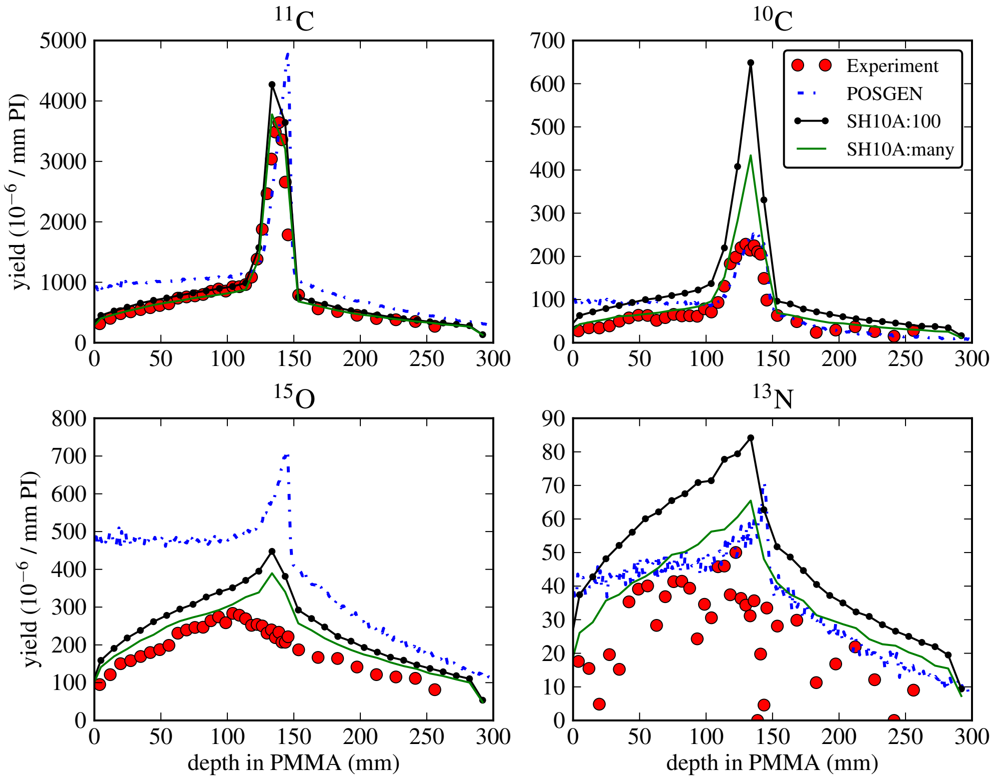

Figure 2: Positron emitter yields in PMMA after ^{12}C irradiation with an initial energy of 299.9 AMeV: ^{11}C, ^{10}C, ^{15}O, and ^{13}N. Results obtained with SHIELD-HIT10A (cases: 100 and *many*, cf. table 1) are compared to experimental data (Priegnitz et al., 2012) and POSGEN simulations (Priegnitz, 2012).

4. Discussion

We found that 1) changes in modeling nuclear interactions strongly affected the positron emitter yields and that 2) the current version of SHIELD-HIT10A tended to overestimate experimental positron emitter distributions but reasonably reproduced the most abundant isotopes ^{11}C and ^{15}O. We could also observe an energy (i.e., depth) dependence of the agreement between the SHIELD-HIT10A simulations and experimental data: a good agreement for small depths, i.e., high energies and a tendency to peak and overestimate around depths close to distal fall-off of the isotope distribution. The latter overestimation was reduced when changing the Fermi-Breakup model parameters (free Coulomb volume and free volume).

This study demonstrates the sensitivity of positron emitter distributions to nuclear modeling. Changing all inelastic cross sections by 20% (cases 080 and 120, cf. table 1) resulted in a disproportionally increased deviation (20%-40%) relative to the default settings. The available sparse data base on measured nuclear cross sections may well lead to uncertainties in their modeling in the order of 5%-20%. The change of the Fermi-Breakup model parameters (cases *few* and *many*, cf. table 1) yielded relative deviations that considerably differ among the isotopes and range from 0 to 50%. The parameter values for case *many* improved the agreement of SHIELD-

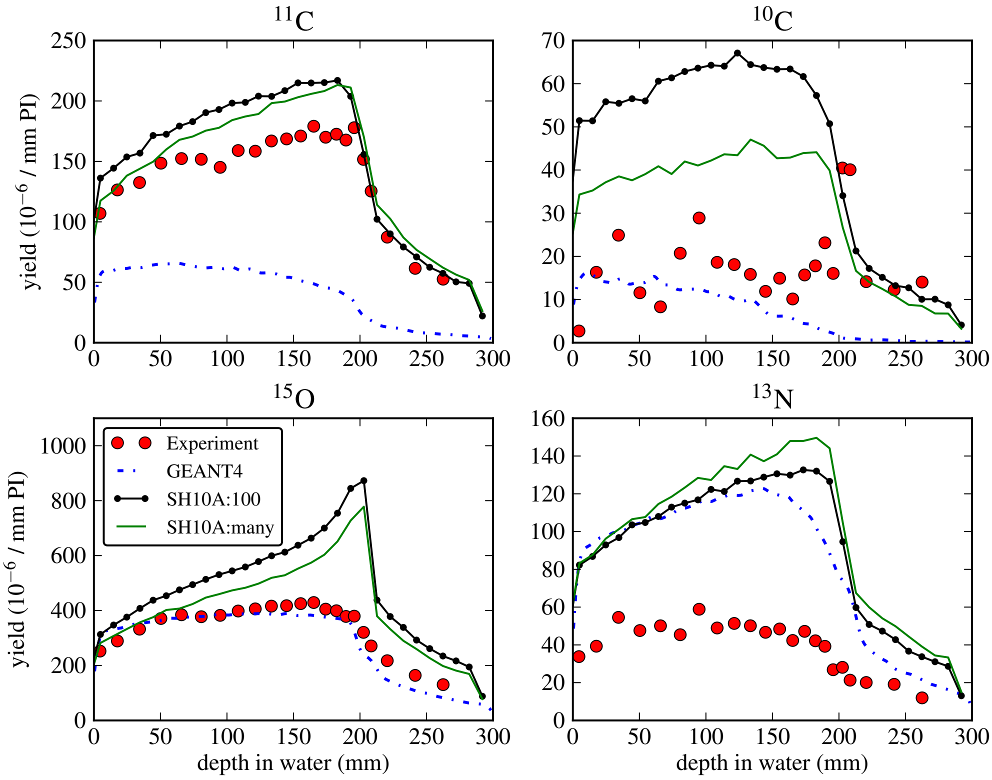

Figure 3: Positron emitter yields in water after ^{7}Li irradiation with an initial energy of 205.3 AMeV: ^{11}C, ^{10}C, ^{15}O, and ^{13}N. Results obtained with SHIELD-HIT10A (cases: 100 and *many*, cf. table 1) are compared to experimental data (Priegnitz et al., 2008) and GEANT4 simulations (Priegnitz, 2012).

HIT10A simulations with the measured data on positron emitter yields. The values for *many* (as well as for *few*) were not optimized and only chosen to maintain consistency with a recent related study by Lühr et al. (2012a). A further adjustment of these parameters to experimental data is desirable but requires the consideration of a variety of different nuclear reaction channels and lies therefore beyond the scope of this study. Optimization of model parameters based on a single fragmentation process may lead to a biased outcome.

The better agreement of SHIELD-HIT10A simulations for small depths may be caused by the fact that experimental inelastic nuclear cross sections are mostly available for ion energies larger than 100 AMeV. For lower energies (i.e., larger depths) Monte Carlo programs have to extrapolate the cross sections with implemented models. Modeling of cross sections is also necessary for a number of light ions heavier than protons because experimental data concentrate on single ions such as helium and carbon with no data available, e.g., for lithium ions. An enlarged data set of accurate experimental nuclear cross sections, including more ions as well as energies below 100 AMeV, would constrain the nuclear modeling and improve predictions of fragment distributions. España et al. (2011) also pointed out the need for more accurate measurements of cross sections relevant for production of PET isotopes by protons even though

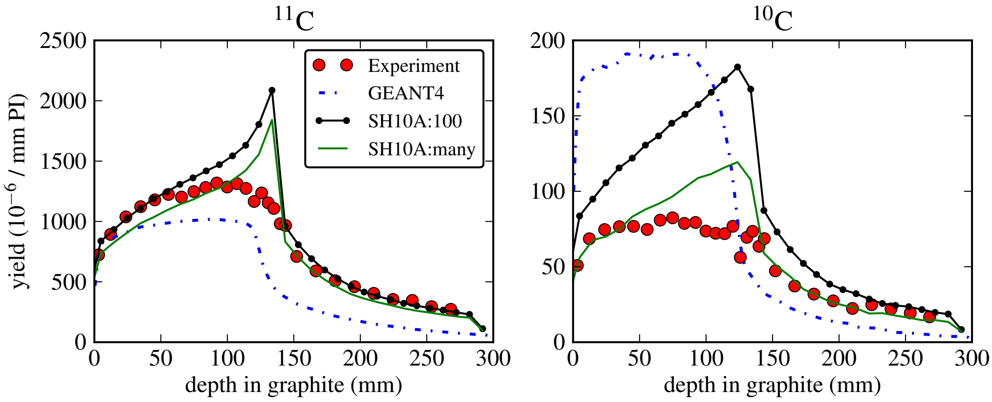

Figure 4: Positron emitter yields in graphite after ^{7}Li irradiation with an initial energy of 205.3 AMeV: ^{11}C, ^{10}C. Results obtained with SHIELD-HIT10A (cases: 100 and *many*, cf. table 1) are compared to experimental data (Priegnitz et al., 2008) and GEANT4 simulations (Priegnitz, 2012).

the experimental data basis for protons is much more comprehensive than for other ions.

In the studied case of carbon ion beams on PMMA, projectile as well as target fragmentation may lead to ^{11}C and ^{10}C isotopes. The target fragments usually have only a short range, in contrast to the projectile fragments, due to the kinematics of the collision process. Therefore, the depth distribution of the target fragments directly reflects the energy dependence of the fragmentation process while the PET signal from the projectile fragments concentrates mostly around the relatively small area of the activity peak.

We may speculate whether the observed decrease (cf. figure 1) of relative deviations for ^{11}C and ^{10}C at a depth close to the Bragg peak for the cases 080 and 120 results from a compensating effect. For the case of increased inelastic cross sections (120) more projectile fragments are produced. On the other hand, less primary ^{12}C ions reach the Bragg peak region where they have low energies and therefore a larger inelastic nuclear cross section. The inverse compensation effect may apply for decreased cross sections (080).

For lithium ion beams only target fragments can occur. Accordingly, the depth distribution of the isotopes allows for a more direct insight into the energy dependence of the fragmentation process.

Non of the three simulation codes (POSGEN, GEANT4, SHIELD-HIT10A) appeared to be superior in reproducing the experimental data with the employed nuclear modeling settings. Accordingly, this study demonstrates the importance of experimental yield data to constrain simulation programs. SHIELD-HIT10A calculated the isotope production best for ^{11}C and reasonable for ^{15}O by carbon and lithium irradiation. For irradiation with carbon ions POSGEN simulated better the less abundant isotopes ^{10}C and ^{13}N. The observed agreement of SHIELD-HIT10A for ^{11}C may originate from the fact that its modeling of nuclear interactions was recently optimized especially on collisions of carbon ions in the energy range of 50 AMeV to 500 AMeV. This ion-energy combination was chosen because—apart from protons—first, most experimental cross section data were available here and second, it is most relevant for carbon ion therapy. As a result of this optimization (which included the variation of Fermi-Breakup parameters) partial charge changing cross sections matched experimental data for $\Delta Z = 1$ but overestimated them

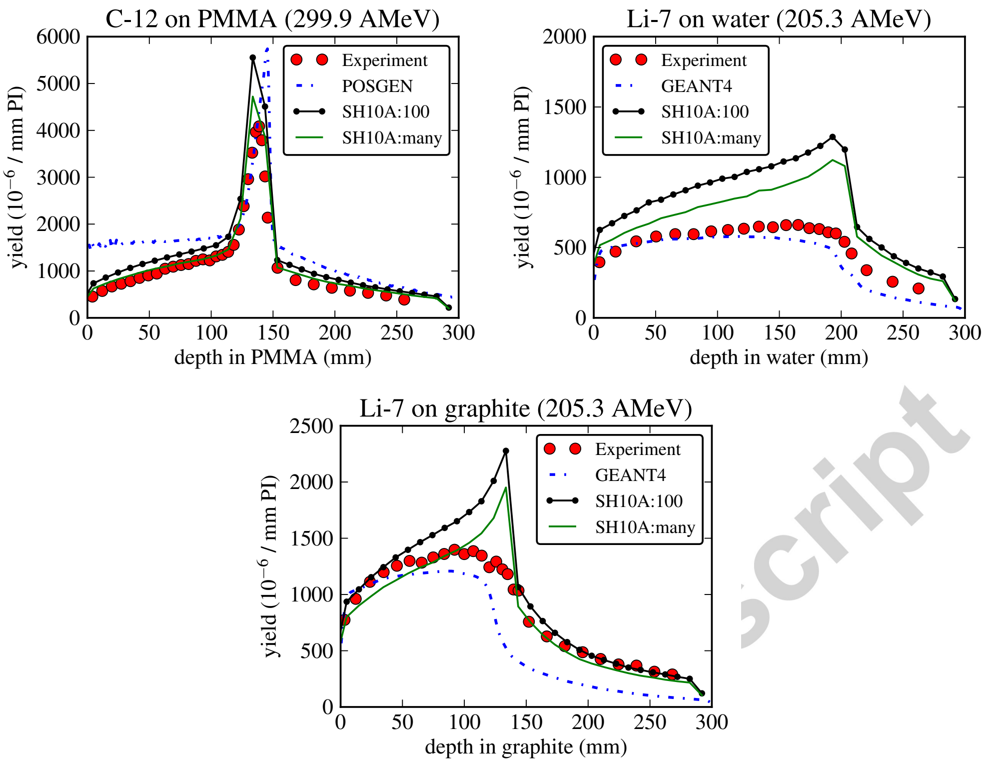

Figure 5: Total positron emitter yields: 299.9 AMeV ^{12}C ions on PMMA, 205.3 AMeV ^{7}Li ions on water, and 205.3 AMeV ^{7}Li ions on graphite. Results obtained with SHIELD-HIT10A (cases: 100 and *many*, cf. table 1) are compared to experimental data (Priegnitz et al., 2008, 2012) and simulations with Posgen and Geant4 (Priegnitz, 2012).

for $\Delta Z = 2$ (Hansen, 2011), where ΔZ denotes the charge change after a nuclear reaction. The overestimation we observed here for ^{10}C production—i.e., for twofold change in the number of neutrons instead of protons—appears to be similar to that for $\Delta Z = 2$.

The agreement of the Geant4 simulations for lithium irradiation (Priegnitz, 2012) was mixed. They were performed with the physics list recommend for medical applications (with the Quark-Gluon String Precompound – Binary Cascade Model with high precision but without the Fermi-Breakup model). These settings could probably be improved to achieve a better matching with experiments for positron emitters.

When applying the same four cases of modifying the modeling of nuclear interactions (cf. table 1) Lühr et al. (2012a) found a weak dependence of the relative biological effectiveness and two dosimetric correction factors: stopping power ratio (Lühr et al., 2011a) and fluence correction factor (Lühr et al., 2011b). Only the physical dose distributions of large and deep-seated target volumes changed significantly inside the target (about +10% and −10% for the cases 080 and 120, respectively). The two studies clearly illustrate large differences in how the accuracy of modeling nuclear interactions affects a number of clinically relevant aspects in ion beam therapy.

The isotope yields for ^{11}C and ^{15}O, which are decisive for range verification based on PET imaging since they are most abundant, were modeled reasonably well, while we found too large yields for the rarely produced ^{10}C and ^{13}N. We omitted to discuss further positron emitters since they are difficult to measure due to their marginal effect for the studied target materials. Other variations of modeling the nuclear interaction (e.g., 10% change or change of parametrization of cross sections) may lead to further insights. We considered the change of all nuclear cross sections by 20% as a kind of worse case scenario. Also, Monte Carlos programs often interpolate cross sections based on analytical models which may lead to a systematic over- or underestimation.

While this study could show the quantitative effect of modeling nuclear fragmentation on positron emitter yields some questions of specific interest for range verification where not addressed here and might be subject of a further study. This may include the impact of the fragmentation modeling on the position of the (projectile) fragment peak and on the shape in the distal activity fall-off.

The current findings encourage to improve nuclear fragmentation modeling in SHIELD-HIT10A provided that necessary experimental data are available. This includes adaption of: the energy dependence of inelastic cross sections (especially below 100 AMeV and for ions other than carbon) and the Fermi-Breakup model parameters. Further simulations may focus on the position of the distal edge of the positron emitter distributions and its variation, which are decisive for range estimation. They may also include irradiation of extended target volumes with a homogeneous dose distribution obtained by treatment planning. The use of more complex targets consisting of several materials is a natural step toward more realistic *in vivo* simulations.

5. Conclusion

This study demonstrated the importance of precisely modeling nuclear interactions to simulate positron emitter yields relevant for range verification by means of positron emission tomography. For carbon ion beams, SHIELD-HIT10A reproduced the dominating ^{11}C yields well but tended to overestimate distributions of other isotopes especially at depths close to the Bragg peak. Improved modeling, relevant for light-ion beam therapy, requires more accurate measurements of cross section values including data for: low ion energies ($<$100 AMeV), a larger variety of ion-target combinations, and partial (charge changing) cross sections.

Acknowledgments

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Ion range verification using PET requires to compare measured with simulated yields.

Changes in modeling nuclear interactions strongly affect positron emitter yields.

Monte Carlo simulations with SHIELD-HIT10A reasonably matched PET isotope experiments.

Non of the employed simulation codes was superior in reproducing all experiments.

Improved modeling requires more accurate measurements of nuclear cross sections.