Production of the PET isotope ^{11}C in hadron therapy via neutron knockout

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Abstract

Purpose: Positron emitting isotopes such as ^{11}C and ^{10}C can be used for vital dose verification in hadron therapy. These isotopes are produced when the high energy ^{12}C primary beam particles undergo nuclear reactions within the patient.

Methods: We discuss a model for calculating cross sections for the production ^{11}C in $^{12}\text{C}+^{12}\text{C}$ collisions, applicable at hadron therapy energies.

Results: Good agreement with the available cross section measurements is found for $^{12}\text{C}(-1n)$, though more detailed, systematic measurements would be very valuable.

Conclusions: Nuclear structure plays a crucial role in the reactions of light nuclei, particularly when those reactions are peripheral and involve only a few nucleons. For such reactions, nuclear structure has a strong influence on the energy and angular distribution of the cross section, and is an important consideration for reliable dose verification using ^{11}C in hadron therapy.

Keywords: Hadron therapy, Nuclear reactions

1. Introduction

Ion beams have significant advantages over conventional radiotherapy in the treatment of cancerous tumours. Unlike photons, ions deposit the majority of their energy near the end of their trajectory, at the Bragg peak, with Carbon ions generating a sharper peak than protons. As a result, Carbon-beam therapy can more effectively spare tissue both before and after the tumour [1].

Depending on the depth of the tumour, ^{12}C beam energies of up to 400 MeV/nucleon are required [2]. Hadron therapy applications therefore encompass a wide range of ion-beam energies, from hundreds of MeV per nucleon down to zero. Over this energy range a remarkable variety of nuclear reaction phenomena occur. Indeed, in hadron therapy applications, nuclear reactions are very common — for beams of 400 MeV/nucleon, only 30% of the primary ^{12}C reaches the Bragg peak intact, the remaining 70% having undergone some nuclear reaction [3, 4]. These reactions produce both fast projectile-like nuclei and slower target-like nuclei, in addition to showers of protons, neutrons and α particles. These secondary particles broaden the Bragg peak and potentially harm healthy tissue beyond it [5]. Understanding these reactions is thus crucial to clinical treatment planning.

Only comparatively recently have dedicated systematic measurements of been made using thin targets at energies directly relevant to hadron therapy [6, 7, 8, 9, 10]. These studies have pointed to deficiencies in the modelling of the reactions of ^{12}C , highlighted by a recent Nuclear Physics European Collaboration Committee (NuPECC) report on Nuclear

Physics for Medicine [11]. The fragmentation models implemented in existing Monte Carlo codes such as GEANT4, which are used in treatment planning, struggle to describe peripheral reaction channels where only a few nucleons are involved [8, 12, 13].

Some of these peripheral reactions do, however, have a beneficial side effect. ^{11}C and ^{10}C have more protons than neutrons and, as a result, are β^+ emitters. Peripheral nuclear reactions in the patient produce these isotopes, with half-lives $t_{1/2} = 20.3$ m and $t_{1/2} = 19.3$ s, respectively. The annihilation photons following the β^+ emission can be used for range verification of the beam via positron emission tomography (PET) [14, 15]. The position emission activity distribution generated show a flat background, arising from target-like β^+ emitters, and a sharp peak near the expected Bragg-peak from projectile-like ^{11}C and ^{10}C [16]. Accurate dose verification using PET requires a precise knowledge of the production cross sections for these isotopes, which is currently insufficient [15].

Here we will discuss a class of few-body models that are applicable to peripheral knockout reactions, where one or two nucleons are removed from the projectile via an interaction with a nuclear target. We first give a brief overview of nuclear reactions relevant to ^{12}C beam therapy, and discuss how the structure of ^{12}C influences reaction outcomes. We then discuss a model for calculating the cross sections for the β^+ decaying isotope ^{11}C produced in collisions of the ^{12}C projectile with ^{12}C target nuclei.

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2. Reactions and structure of ^{12}C

In carbon beam therapy treatment planning, dose distributions are typically modelled using Monte Carlo methods, commonly using the GEANT4 toolkit [17]. Nuclear reaction models are an integral part of this approach, and must provide double differential cross sections $d^2\sigma/d\Omega dE$ for the enormous range of reaction phenomena that may occur — a significant challenge.

In hadron therapy, reactions can occur at collision energies ranging from the primary beam energy downwards. However, because the rate of energy loss by the beam increases as the energy falls, larger distances are covered when the beam has high energies. As a result, high energy collisions (> 100 MeV/nucleon) should be most common. At these energies a variety of nuclear reaction phenomena occur, ranging from peripheral collisions of a few nucleons to central collisions that destroy the projectile and target creating an array of light, highly excited fragments.

Nuclear fragmentation is often modelled within a two-stage abrasion-ablation picture. In the first stage, some fraction of the projectile and target overlap, abrading nucleons and creating a highly excited “fireball”, along with projectile-like and target-like “spectator” nuclei. All the resulting nuclei are energetically excited, and subsequently de-excite in the ablation stage by emitting nucleons and light nuclei.

Numerous attempts have been made to benchmark the nuclear reaction models provided by Monte Carlo codes in the context of particle beam therapy [18, 19, 20, 8]. One example is Quantum Molecular Dynamics (QMD). Here the nuclear structure description is schematic. Within the model the colliding nuclei are constructed by randomly placing nucleons, represented by Gaussian wave packets, so as to reproduce the expected density distribution of the nucleus in question. If the binding energy calculated with the appropriate effective interaction is unacceptable, the state is rejected [21]. The effect of the Pauli principle can be simulated by introducing a minimum allowed distance and momentum difference between the nucleons. After the collision nucleons of small relative distances are assumed to coalesce, and restructure into spherical clusters. The resulting excited fragments are then passed to a statistical decay model.

The initial state within QMD models is constructed to optimally approximate some of the characteristics of the true ground state [22]. However, some aspects cannot be described. Light nuclei are known to have distinctive cluster structures, generated by the strong binding of the α particle [23]. This is particularly true for ^{12}C , which is known to have 3α cluster structures [24]. The neglect of this aspect of nuclear structure in the QMD initial state may be the reason that ^4He production cross sections are underestimated by the model [8, 11].

A further deficiency in the QMD initial state is its stability: the ground states generated are stable on the time scales of interest ($\sim 10^{-21}$ s), but may spontaneously emit nucleons for longer times [22]. Whilst for central collisions this may not be a significant problem, in peripheral grazing col-

lisions the instability results in a discrepancy [22]. Here the subtleties of nuclear structure become very important to the reaction outcomes [25], with shell structure of ^{12}C having a strong influence when the collisions involve the interactions of only a few nucleons. One such process is nucleon knockout, where one or two nucleons are removed from the projectile via an interaction with the target nucleus [26, 27]. In the case of ^{12}C , these reactions create the projectile-like reaction products ^{11}C , ^{11}B , ^{10}C , ^{10}B and ^{10}Be . These peripheral reactions constitute around $\sim 20\%$ of the total reaction cross section. However, the reaction models available within GEANT4 perform poorly for these channels, failing to describe measured angular distributions for ^{11}C and ^{10}B [7].

3. Nucleon knockout reactions

We now discuss a model for calculating the ^{11}C production cross sections, highlighting the importance of nuclear structure in determining the reaction outcomes. The production of these isotopes must come from a direct interaction of a single neutron from the projectile with the target nucleus. ^{11}C cannot be produced in significant quantities via neutron evaporation, as the neutron separation threshold of ^{12}C ($S_n = 18.722$ MeV) is significantly larger than either the one-proton ($S_p = 15.956$ MeV) or α -particle ($S_\alpha = 7.367$ MeV) thresholds.

3.1. Single particle cross sections

Here we focus on the production of ^{11}C via an interaction of a ^{12}C projectile with a ^{12}C target nucleus. For the energies of most relevance to carbon beam therapy (> 100 MeV/nucleon) we may reasonably assume that the deflection by Coulomb repulsion is negligible and that the projectile follows a straight line trajectory past the target. The ^{12}C projectile is described as a ^{11}C core plus a single valence neutron. Their centre of mass has impact parameter $\mathbf{b}$, with the core and neutron impact parameters being $\mathbf{b}_c$ and $\mathbf{b}_n$ respectively. The relative coordinate between the core and neutron is denoted by $\mathbf{r}$. As the interaction between the projectile and target is fast, it is reasonable to assume that the core-neutron coordinate $\mathbf{r}$ does not change for the duration of the collision. Furthermore, as core must (at most) elastically scatter from the target, it is assumed that it spectates, and that the interaction with the target does not couple any of its internal states.

The relevant coordinates are illustrated in Fig. 1. The target can be thought of as boring a cylindrical hole through the projectile, with the neutron removed from the projectile either by an elastic or inelastic interaction with the target. The cross sections for the latter process (referred to as neutron stripping) are larger than the former (diffractive disassociation), and so we concentrate on their contribution.

The probability for removing a neutron from the projectile depends on three factors: (i) the probability that at an impact parameter $\mathbf{b}_c$ the core will survive the interaction with the target intact, (ii) the probability that the neutron at impact parameter $\mathbf{b}_n$ will be stripped by the target, and (iii)

Figure 1: Illustration of the knockout reactions, showing the core (green), neutron (red) and target (blue). The z -axis is defined to be parallel to the beam direction. The impact parameter for the centre of the mass of the projectile is $\mathbf{b}$, and the relative co-ordinate of the core and valence neutron is $\mathbf{r}$. The respective impact parameters of the core and neutron are then $\mathbf{b}_c = \mathbf{b} - \mathbf{r}/(A_c + 1)$ and $\mathbf{b}_n = \mathbf{b} + \mathbf{r} A_c/(A_c + 1)$ where A_c is the mass of the projectile core.

the probability for finding the projectile core and neutron at relative separation $\mathbf{r}$.

The survival and absorption probabilities (i) and (ii) are typically calculated using density folding models, using the $t\rho\rho$ approximation [28, 29]. Within this scheme, the survival probability depends exponentially on the density overlap integrated over the assumed straight line trajectory — the greater the overlap, the smaller the survival probability. Assuming zero-range nucleon-nucleon interaction, the survival probability can be written as

$$P_{ct}(\mathbf{b}_c) = \exp \left[-\bar{\sigma}_{NN} \int_{-\infty}^{\infty} dz \int d\mathbf{R} \rho_c(\mathbf{b}_c + \mathbf{z} - \mathbf{R}) \rho_t(\mathbf{R}) \right]. \quad (1)$$

The target and core centres are separated by $\mathbf{b}_c + \mathbf{z}$. For each separation the density overlap (integral over $\mathbf{R}$) is made, and then all points along the core trajectory are integrated over (integral over z). The isospin averaged nucleon-nucleon cross section $\bar{\sigma}_{NN}$ sets the strength of the effective nucleon-nucleon interaction, and is taken from experiment. The density distributions of the target ρ_t and core ρ_c are either calculated using nuclear structure models (e.g. Hartree-Fock), or, where the data is available, taken from experiment. P_{ct} can also be directly used to calculate total reaction cross sections, and very good agreement has been found when Hartree-Fock densities are used [30].

For central collisions — small impact parameters b — the density overlap is large and the survival probability is zero. Conversely peripheral collisions, where the impact parameter is large, the density overlap is negligible and the survival probability tends to 1. In between, where the impact parameter is such that the surfaces of the two nuclei graze one another, P_{ct} makes the transition between these two limits. The size of the density distributions determines the impact parameters corresponding to the transition region.

The neutron absorption probability (ii) can be thought of as the non-survival probability for the neutron, $[1 - P_{nt}(b_n)]$. The neutron is typically assumed to be point-like, or to have a Gaussian shaped density distribution. The present model

is inclusive with respect to the final states of the neutron and target nucleus. Given that a violent collision between the two will have occurred, a large number of reaction outcomes are possible. Studies of proton knockout from ^9C and ^8B have identified protons, deuterons, and tritons with energies from that of the beam, ~ 90 MeV/nucleon, down to the detection limit at ~ 20 MeV/nucleon [31]. Such high-energy light fragments may contribute to dose deposition after the Bragg peak.

The third factor, $P_\beta(\mathbf{r})$, describes how probable it is to find the core and neutron at relative position $\mathbf{r}$ in a particular quantum shell $\beta \equiv (n\ell j)$. The radial dependence is determined by the square of the core-neutron relative wavefunction $u_\beta(r)$ [32], which is unit normalised, and usually calculated in a Woods-Saxon potential. The depth of the potential is varied to give the state with the desired quantum numbers at the appropriate effective binding energy. The radial extent of $u_\beta(r)$ is primarily determined by this effective binding energy. It is equal to the neutron separation energy in the projectile S_n plus any residual (core) excitation energy E_x . Strongly bound neutrons have smaller radial extent, resulting in a smaller probability for finding the neutron far from the core. As a result the cross sections are proportional to the root-mean-square radius of $[u_\beta(r)]^2$ [33].

The total single-neutron stripping (str) cross section is just the integral over all projectile-target impact parameters $\mathbf{b}$ and core-neutron coordinates $\mathbf{r}$,

$$\sigma_{str}^\beta = \int d\mathbf{b} \int d\mathbf{r} P_{ct}(\mathbf{b}_c) [1 - P_{nt}(\mathbf{b}_n)] P_\beta(\mathbf{r}). \quad (2)$$

The knockout cross section is then a balance: core survival favours large impact parameters $\mathbf{b}_c = \mathbf{b} - \mathbf{r}/(A_c + 1)$, whereas neutron absorption favours small $\mathbf{b}_n = \mathbf{b} + \mathbf{r} A_c/(A_c + 1)$. Though both would be favoured by large core-neutron distances, the core and neutron are bound together, with their relative position probability determined by $u_\beta(r)$ which decays exponentially for large r . These requirements naturally restrict neutron knockout to surface grazing collisions, as illustrated by $d\sigma/db$ in Fig. 2.

In addition to this stripping cross section, where the neutron is absorbed by the target, the neutron may also be removed via an elastic interaction with the target. Here the target remains in its ground state, but energy is imparted to relative motion of the neutron and core such that it breaks up. This is termed *diffractive dissociation* (dif). The total *single-particle* (sp) removal cross section is then the sum of these two components $\sigma_{sp}^\beta = \sigma_{str}^\beta + \sigma_{dif}^\beta$. At the energies relevant here, this diffractive dissociation component contributes approximately 20% of the total single-particle cross section.

3.2. Nuclear structure

We have already seen one aspect of the influence of nuclear structure, namely the neutron binding energy, which determines the radial extent of the core-neutron separation. A further aspect arises from the fact that nuclei exhibit shell structure. The shell which the nucleon initially inhabits will

Figure 2: Calculated core survival probability $P_{ct}(b_c)$ (blue dotted line), and neutron stripping probability $[1 - P_{nt}(b_n)]$ (red dashed line). These two create a window of impact parameters where neutron stripping is favourable. The cross section $d\sigma/db$ is also shown (black solid line). Note that the three quantities are plotted for different impact parameters — core b_c , neutron b_n , and centre-of-mass b , respectively — resulting in an apparent shift between the survival probabilities and cross section.

Figure 3: Illustration of the shell structure of ^{12}C . Different nucleon partitions are mixed with amplitudes c_n . Typically only the lowest order configurations (c_1 and c_2 , labelled 0p-shell) are taken into account. In reality, higher order configurations (e.g., c_3 – c_5) are mixed into the ^{12}C ground state.

determine which states in the final residue may be populated by its removal, with cross sections loosely scaling with the number of nucleons in that shell. In the simplest independent particle model of ^{12}C , two neutrons will sit in the deeply bound $0s_{1/2}$ shell, and four in $0p_{3/2}$, as illustrated in Fig. 3. The nucleon removal cross section for the latter will be larger for two reasons: (i) there are twice as many neutrons to remove, and (ii) the binding energy of $0p_{3/2}$ is much less than $0s_{1/2}$, so the root-mean-square radius of $[u_\beta(r)]^2$ much larger. Removal of a $0p_{3/2}$ neutron will populate the ground state of ^{11}C , whose simplest neutron configuration is $[0s_{1/2}]^2[0p_{3/2}]^3$. The single-particle cross section σ_{sp} must be multiplied by a factor to account for the number of neutrons initially in $p_{3/2}$. This factor is called the spectroscopic factor S_f and depends on the final state f populated in ^{11}C .

In reality, things are more complicated. Different nucleon configurations are mixed in the ground state of ^{12}C

by the residual two-body interaction. In the simplest 0p-shell structure model, this mixes $[0s_{1/2}]^2[0p_{3/2}]^4$ (c_1) and $[0s_{1/2}]^2[0p_{3/2}]^2[0p_{1/2}]^2$ (c_2) configurations, as illustrated in Fig. 3. Though the former configuration is still dominant, the latter allows population of excited $1/2^-$ and $3/2^-$ states in ^{11}C , which then decay via γ emission, contributing to the prompt γ yield. The states will have different spectroscopic factors: for the ground state, and first excited $1/2^-$ and $3/2^-$ states of ^{11}C , the calculated spectroscopic factors are 3.16, 0.58 and 0.19 [34]. These spectroscopic factors also require a small centre-of-mass correction factor $(A_c + 1)/A_c$ for the 0p-shell [35]. The total cross section for a particular final state f in ^{11}C is then a sum over all the different neutron configurations β that may contribute to its population,

$$\sigma_{1n}^f = \sum_{\beta} S_{f\beta} \sigma_{sp}^{\beta}. \quad (3)$$

For the present calculations, we note that as we must conserve angular momentum — specifically, because our projectile is spin-zero — only a single β will contribute to each final state f . In general however, more than one β will contribute to each final state f . The total neutron removal cross section is summed over the final states

$$\sigma_{1n} = \sum_f \sigma_{1n}^f. \quad (4)$$

Nuclear configurations beyond the 0p-shell are also possible, as shown in Fig. 3 (c_3, c_4, c_5). These configurations are typically not included in structure calculations as the model spaces rapidly become too large. However, their neglect means that the spectroscopic factors are overestimated. This has long been known from electron scattering and $(d, ^3\text{He})$ experiments [36, 37], and more recent nuclear-induced knockout [33], that indicate the actual spectroscopic factors are 50% to 70% of the simple particle shell model limits discussed above. This must be taken into account when making calculations with a more limited structure model space.

4. Results for ^{11}C production

4.1. Cross sections energy dependence

Here we make calculations for single neutron knockout from ^{12}C from energies of 100–2200 MeV/nucleon. The density distributions for the ^{12}C target and ^{11}C core are assumed to be Gaussian, with root-mean-square radius taken from reaction cross sections measurements [38]. Three states in ^{11}C are expected to be populated, and are appropriately weighted by the shell model spectroscopic factors given above. For consistency across the energy range, we have used a zero-range nucleon-nucleon interaction, as was done in Ref. [34]. Inclusion of a finite-range interaction would increase the cross section by around 5%.

The results are shown in Fig. 4, along with available experimental measurements. The calculations have been renormalised to include the quenching factor discussed above, $R_s =$

Figure 4: Calculated one neutron knockout cross section $^{12}\text{C}(-1n)$ with a ^{12}C target (solid line). The dashed lines illustrate the cross sections obtained with the upper (bottom) and lower (top) limits of the ^{11}C root-mean-square radius that enters the core-survival factor from Ref. [38]. Full symbols indicate measured cross sections for neutron knockout from ^{12}C producing ^{11}C , whereas open symbols indicate cross sections for the isobaric analog reaction, proton knockout from ^{12}C , producing ^{11}B . The data points are from Dudouet *et al.*[7] (red squares), Kidd *et al.*[39] (blue circles), Webber *et al.*[40] (green upward triangles), Lindstrom *et al.*[25] (purple downward triangles), Ogawa *et al.*[10] (orange diamonds), and Thies *et al.* (black pentagon).

$\sigma_{\text{exp}}/\sigma_{\text{th}} = 0.49 \pm 0.02$, found in Ref. [34] from the data points at 1050 and 2100 MeV/nucleon. The plot also includes data for the isobaric analog reaction, proton knockout from ^{12}C , producing ^{11}B . In terms of the underlying nuclear structure, the two reactions are essentially identical. Differences arise from the somewhat weaker binding of the proton in ^{12}C . As the primary ^{12}C slows from 400 MeV/nucleon to 100 MeV/nucleon, it is predicted that the ^{11}C production cross section will increase modestly by around 10%. Broadly, the calculations agree with the available data well, though there is considerable variation between the data sets, particularly at lower energies. Further detailed measurements across the 100-400 MeV/nucleon range would clearly be enormously valuable.

4.2. Momentum and angular distributions

Within the framework discussed above, one may also calculate the momentum distributions of the core following removal of the nucleon. The distribution depends on the motion of the nucleon relative to the core at the point of removal. Distributions parallel and perpendicular to the beam direction are usually considered, which translate into the energy and angular distributions of ^{11}C respectively. The parallel momentum (energy) distributions are highly sensitive to nuclear structure — in particular, the orbital angular momentum quantum number ℓ of the nucleon removed. Perpendicular momentum (angular) distributions are additionally sensitive to target effects, such as the nuclear size, diffuseness, and core-target Coulomb interaction [41]. These momentum distributions have been exploited in fundamental studies of the

Figure 5: Calculated angular distribution of the ^{11}C residues at 95 MeV/nucleon (red line) compared to data points from Refs. [7, 9].

structure of exotic nuclei for the past 20 years. Further details on their calculation may be found in Refs. [42, 41, 43].

In Ref. [44] the measured widths of the parallel momentum distributions are given for each fragmentation product from $^{12}\text{C}+^{12}\text{C}$ reactions at 2100 MeV/nucleon. The agreement between the calculations and data is very good — the Gaussian fitted widths are $\Delta_G^{\text{th}} = 100$ MeV/c and $\Delta_G^{\text{exp}} = 103 \pm 4$ MeV/c respectively [45]. Similarly good agreement is found for the other one- and two-nucleon removal channels, producing ^{11}B , ^{10}C , ^{10}B and ^{10}Be . As the widths arise from the underlying nuclear structure, they should be essentially independent of the beam energy.

The perpendicular momentum distribution can be converted to an angular distribution by using the fact that $d\Omega \approx d^2k_{\perp} k_0^2$ where k_0 is the momentum of the beam, and $k_{\perp} \approx 2 \sin(\theta/2)$ [43]. Calculations were made using the MOMDIS code [43], using the same inputs as discussed above. The general trend is in excellent agreement with the experimental data. The cross section decays exponentially with the scattering angle θ . For this specific channel the agreement is significantly better than the QMD model (see Figure 3(f) of Ref. [8]) commonly used with GEANT4.

Though the calculated integral cross section is close to that given in Ref. [7], the calculations underestimate the data for the measured angles. The data points cover a relatively small fraction of total the cross section: the calculations suggest that 93% of the cross section comes within $\theta < 5^\circ$. If just a small fraction of this is scattered to larger angles, the discrepancy with the experimental data would be ameliorated. Dissipative effects for nucleon stripping that are known to result in low momentum tails on parallel momentum distributions (see e.g., Ref. [46]). Their effect on the angular distributions is not clear, but will certainly result in enhanced large angle yield due to the reduced parallel momentum component. For the smaller diffractive breakup component, target recoil effects will also give more yield at larger angles, and have been investigated with continuum-discretized coupled-

channels models [47].

5. Conclusions

We have discussed models for the production the β^+ emitting isotope ^{11}C in $^{12}\text{C}+^{12}\text{C}$ at energies relevant to hadron therapy applications. Few-body models can give a reasonable description of both the absolute cross sections and the corresponding momentum distributions for the projectile-like residue. Nuclear structure has a significant impact via (a) binding energies, which determine the root-means-square size of the valence nucleon radial wave function, (b) spectroscopic factors, to which the cross section is proportional to, and (c) nucleon quantum numbers, that determine the width of the longitudinal momentum (energy) distribution.

Direct two-nucleon removal cross sections, such as for producing ^{10}C , are typically an order of magnitude smaller than the corresponding one-nucleon removal process. Though we have not discussed them here in detail, related models can be used to calculate two-nucleon removal cross sections [48, 49, 50]. Whilst the nuclear structure description is more complicated, the reaction model assumptions are essentially the same, and a good description can be obtained [45].

Properly accounting for nuclear structure factors can give a good account of peripheral one- and two-nucleon removal reactions from ^{12}C , which more general fragmentation models struggle to describe. These channels contribute a sizable fraction of the total reaction cross section, of the order of 15 – 20%.

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