

Evaluating the Efficacy of Carborane-Monoclonal Antibody Conjugates in Boron Neutron Capture Therapy Using Particle and Heavy Ion Transport Code System (PHITS)

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Abstract

Boron Neutron Capture Therapy (BNCT) offers a promising avenue for treating aggressive cancers by selectively targeting malignant cells while sparing healthy tissue. A key determinant of BNCT efficacy is the precise and sufficient accumulation of boron-10 (¹⁰B) atoms at the tumor site, a challenge that remains a major obstacle in BNCT. To address this, this study employs the Particle and Heavy Ion Transport Code System (PHITS) to investigate the feasibility of using a carborane-monooclonal antibody conjugate (CMAC) as a boron-delivery agent. This study integrates a carborane-based monoclonal antibody construct with Monte Carlo particle transport modeling to characterize secondary particle production and penetration behavior relevant to BNCT micro-dosimetry. In the simulation, a soft tissue phantom containing 25 ppm of ¹⁰B was irradiated with an epithermal neutron beam at 1.0×10^{-2} MeV, yielding a neutron flux of 1.2×10^9 cm⁻² s⁻¹. Monte Carlo analysis of the secondary particle fluence showed the production of α particles and ⁷Li ions with high linear energy transfer and subcellular penetration ranges, along with lower-energy photons with broader dispersion. These results suggest that CMAC may induce sufficient ¹⁰B(n, α)⁷Li reactions to achieve localized cytotoxic effects, indicating its potential viability as an effective boron-delivery agent for BNCT.

Keywords: alpha particles, epithermal neutron beam, Monte Carlo simulation, neutron flux, secondary particle fluence

1. Introduction

Boron Neutron Capture Therapy (BNCT) is a unique approach to treating malignant and complex cancers. This therapy uses the energy from fission reactions between boron and neutrons to specifically damage targeted cells, as stated by Barth *et al.* (2018). This approach ensures a high therapeutic ratio by selectively targeting cancerous cells, minimizing risk to a patient's overall well-being. BNCT aims to induce biological damage solely in its targeted cells without affecting surrounding normal cells. Thus, effective BNCT requires precise localization and a high accumulation of boron-enriched delivery agents (BDAs) in the target, according to Nedunchezian *et al.* (2016).

Studies have been conducted to develop a suitable BDA that will ensure the success of BNCT. However, to date, boronophenylalanine (BPA) and sodium borocaptate (BSH) remain the predominant BDAs used clinically, despite their limitations, including variable uptake and low tumor selectivity, as demonstrated by Cheng *et al.* (2022) and similarly observed by Järvinen *et al.* (2023) and Flieger *et al.* (2023) in their respective studies.

A study by Jin *et al.* (2022) also highlights the inadequacy of currently used BDAs, which has led to increased research into targeted molecules, such as amino acids, liposomal conjugates, and porphyrin derivatives, to enhance the selectivity of BDAs for cancerous cells. This underscores that one of the primary challenges still confronting BNCT is acquiring a BDA with improved cell-targeting capabilities, as shown by Malouff *et al.* (2021), while also ensuring that it will provide a sufficient amount of lethal $^{10}\text{B} + \text{n} \rightarrow ^7\text{Li} + ^4\text{He}$ reaction needed to induce damage in the target cell.

Carborane and monoclonal antibodies (mAbs) have been extensively studied for their potential as boron delivery agents in BNCT. Carborane, a boron-carbon compound, is stable and rich in boron, making it ideal for BNCT, as stated by Zargham *et al.* (2019). Meanwhile, monoclonal antibodies provide antigen-specific binding to cancer cells, enabling highly selective delivery, as reported by Zahavi and Weiner (2020). The carborane-monoclonal antibody conjugate investigated in this study combines these two advantages, providing a dual-targeting strategy that enhances tumor specificity while maximizing boron payload per molecule. This approach positions CMAC as a promising next-generation alternative to conventional BDAs.

Dicarba-closo-dodecaborane, a distinct compound within the boron–carbon cluster family (carboranes), was utilized in this simulation owing to its exceptional structural stability and broad applicability. Its unique characteristics distinguish it from other carborane derivatives. This preference is supported by Zargham *et al.* (2019) and agreed upon by Marforio *et al.* (2023).

To evaluate this potential, the Particle and Heavy Ion Transport Code System (PHITS), a well-established Monte Carlo particle transport simulation tool widely used in radiation research and BNCT studies, was employed. PHITS enables controlled, risk-free modeling of particle interactions, geometric measurements, and tally functions, among other simulation features (Sato *et al.*, 2024). Due to its versatility and reliability, PHITS continues to gain recognition and popularity in medical physics applications such as BNCT.

Furthermore, comprehensive descriptions of PHITS and its recent developments are available (Sato *et al.*, 2018; 2024), and detailed implementation instructions can be found in the PHITS User’s Manual issued by the Japan Atomic Energy Agency (JAEA, 2023).

Thus, the objective of this study is to use PHITS to investigate the efficacy of a carborane-monoclonal antibody conjugate in enhancing the selectivity of BNCT towards cancerous cells and to assess its impact on treatment outcomes. In essence, the careful consideration of the distribution of secondary particles produced by irradiating the carborane-monoclonal antibody conjugate, the chosen boron delivery agent, with 1.0×10^{-2} MeV epithermal neutrons is pivotal to the success of Boron Neutron Capture Therapy.

2. Methodology

The Particle and Heavy Ion Transport Code System (PHITS) software version 3.29, developed by the Japan Atomic Energy Agency (JAEA), was used to simulate the entire experimental setup. The simulation was conducted on a laptop equipped with an 11th Gen Intel Core i3 processor and running Windows 11. The neutron source used in the simulations was precisely modeled to match the BNCT irradiation setup. For this experiment, the target material is soft tissue, modeled as a single circular geometry with a radius

extending from -10 cm to 10 cm along both the x - and z -axes. Figure 1 illustrates the target configuration as implemented in PHITS.

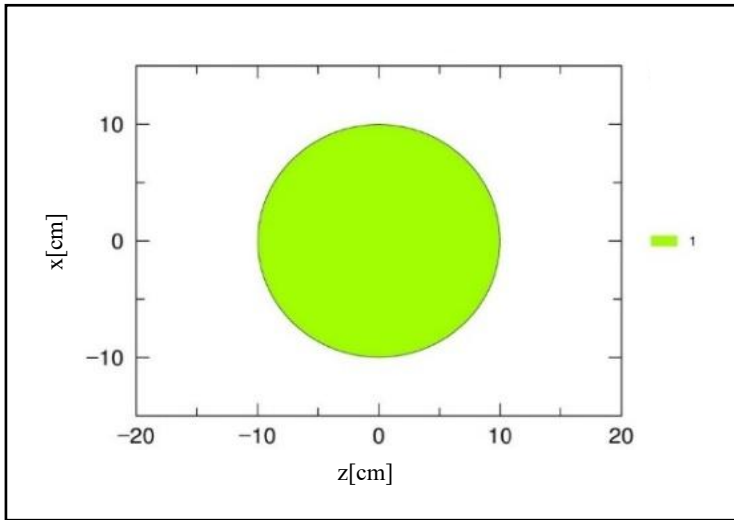


Figure 1. Target material (soft tissue) visualization

Considering the complexity of actual soft-tissue structures and the study’s focus on examining the fluence track of secondary particles and the neutron flux arising from the presence of CMAC delivering 25 ppm of ^{10}B , a simplified geometry was adopted. Therefore, a single circular model was selected to represent the tissue (Figure 1).

The use of PHITS codes was selected as the approach due to its reputation as a valuable tool for simulating neutron radiation intensity in tissue during Boron Neutron Capture Therapy (BNCT), using experimental data. The molecular formula for the soft tissue was attained from the International Commission on Radiation Units and Measurements, ICRU report 44 (ICRU, 1989), as shown in Table 1.

Table 1. Soft tissue composition

| ICRU soft tissue | H | C | N | O |
|------------------------|-------|-------|-------|-------|
| Mass fraction per gram | 0.101 | 0.111 | 0.026 | 0.762 |

Chemical compositions of carborane and monoclonal antibodies were obtained from the National Center for Biotechnology Information, as shown in Tables 2 and 3, respectively.

Table 2. Chemical composition of carborane

| Dicarba-closo-dodecaboranes | C ₂ B ₁₀ H ₁₂ | | |
|-----------------------------|--|---------|--------|
| | C | B | H |
| Atomic weight | 12.0107 | 10.8110 | 1.0078 |
| Mass fraction per gram | 0.167 | 0.750 | 0.084 |

Table 3. Chemical composition of monoclonal antibody

| Monoclonal antibody | C ₆₄₉₄ H ₁₀₀₆₀ N ₁₇₂₂ O ₂₀₃₂ S ₄₄ | | | | |
|------------------------|--|--------|---------|---------|--------|
| | C | H | N | O | S |
| Atomic weight | 12.0107 | 1.0078 | 14.0067 | 15.9994 | 32.065 |
| Mass fraction per gram | 0.541 | 0.070 | 0.167 | 0.226 | 0.009 |

In PHITS, there are T-track and T-deposit tallies, which are integral features within the software. These tallies are utilized for Monte Carlo simulations of particle transport. The T-track tally captures comprehensive data on particle trajectories, whereas the T-deposit tally calculates the spatial distribution and intensity of energy deposition resulting from particle interactions within the simulation. These tallies were generated to evaluate the neutron spectra and quantify the fluence track, as well as the energy range of secondary particles generated within the target material, respectively.

3. Results and Discussion

In response to the interaction between neutrons and boron delivered by the carborane-monoclonal antibody conjugate within the material, we were able to attain our secondary particles: alpha, lithium-7, and photon, as shown in Figure 2.

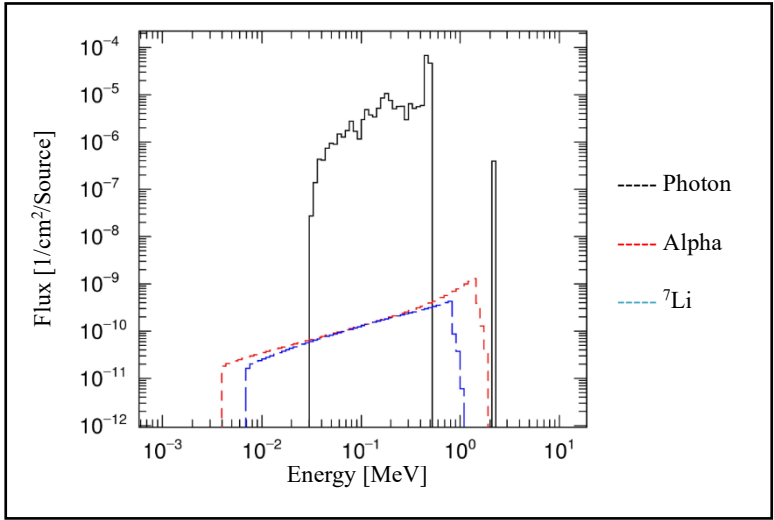


Figure 2. Secondary particle fluence track in BNCT utilizing carborane-monoclonal antibody as BDA

The fluence track of secondary particles revealed distinct peaks at specific energy levels for each generated particle. Notably, there is a correlation between alpha particles and lithium-7, where an increase in their tracks is accompanied by a corresponding increase in energy. The graphical representation illustrates that both alpha particles and lithium-7 exhibit high energy and short travel distances, traveling approximately the size of a typical human cell ($\approx 10 \mu\text{m}$). This observation aligns with findings from a related study by Marforio *et al.* (2023), which state that BNCT depends on the high energy and short travel distance of the generated lithium-7 and alpha particles. In a biological context, this ensures that cytotoxic damage is highly localized, with lethal interactions confined to cellular dimensions, consistent with observations reported by Horiguchi *et al.* (2015) and Xiang *et al.* (2023).

In contrast, photons, as depicted in the graph, exhibit a high flux but a smaller energy range compared to other secondary particles. This suggests that photons, with lower energy and longer trajectories, may distribute their energy over a larger volume rather than concentrating it within a small area. Consequently, ionization events caused by photons are dispersed over a wider area, resulting in a lower density of ionization events compared to particles with higher energy and Linear Energy Transfer (LET) such as alpha particles and lithium-7 (He *et al.*, 2021). A lower density of ionization events in healthy tissue surrounding a tumor could suggest a decreased likelihood of radiation-

induced harm to normal cells. Thus, the fluence track of secondary particles exhibits characteristics that increase the probability of damaging the targeted material.

Table 4. Measured Flux and Energy Range of Secondary Particles generated using Carborane-Monoclonal Antibody Conjugate as BDA

| Secondary particles | Flux (1/cm ² /source) | Energy Range (MeV) |
|---------------------|----------------------------------|---|
| Alpha | 1.5204E-08 | 4.3652E-03 – 1.9055E+00 |
| Lithium-7 | 7.5590E-09 | 7.5858E-03 – 1.0965E+00 |
| Photon | 2.1850E-04 | 3.3113E-02 – 5.2481E-01 → 2.2909E+00 |

Essential information regarding the measured flux and energy spectrum of secondary particles is presented in Table 4, which provides valuable understanding into the behavior and traits of radiation generated in BNCT employing CMAC as the boron delivery agent. Notably, the simulated α -particle flux ($1.52 \times 10^{-8} \text{ cm}^{-2} \text{ source}^{-1}$) is approximately 7.0×10^{-5} of the accompanying photon component ($2.19 \times 10^{-4} \text{ cm}^{-2} \text{ source}^{-1}$), equivalent to a ratio of roughly 1:14 000. Despite this markedly lower flux, the high-LET α -particles remain the primary drivers of localized cytotoxicity in BNCT, underscoring that therapeutic efficacy arises not from particle abundance but from the concentrated energy deposition of boron-induced reaction products.

Furthermore, the Spatial Distribution of Neutron Flux, as illustrated in Figure 3, provides insight into the spatial variations of the neutron flux within the target material under investigation.

The combination of a neutron energy level of $1.0 \times 10^{-2} \text{ MeV}$ delivered from the epithermal neutron source and a boron concentration of 25 ppm delivered by carborane-monooclonal antibody conjugates to the target material is capable of generating a neutron flux sufficient to cause biological harm to the tissue, as shown in Figure 3.

Figure 3 depicts the dispersed flux distribution in the target area, with the highest flux at the center and decreasing outward. This suggests a greater likelihood of nuclear capture interactions within the material, thereby enhancing the therapeutic ratio. This observation is consistent with findings by Yuan *et al.* (2019), indicating that improved tumor-localization properties resulting from the use of boron-containing agents contribute to an enhanced

therapeutic ratio. Nevertheless, it is important to note that the present model assumes a homogeneous, circular soft-tissue geometry and does not account for patient-specific heterogeneities, such as bone or air cavities. Future work should incorporate voxel-based anatomical phantoms derived from CT data to more accurately evaluate dose distribution and treatment performance in realistic clinical scenarios.

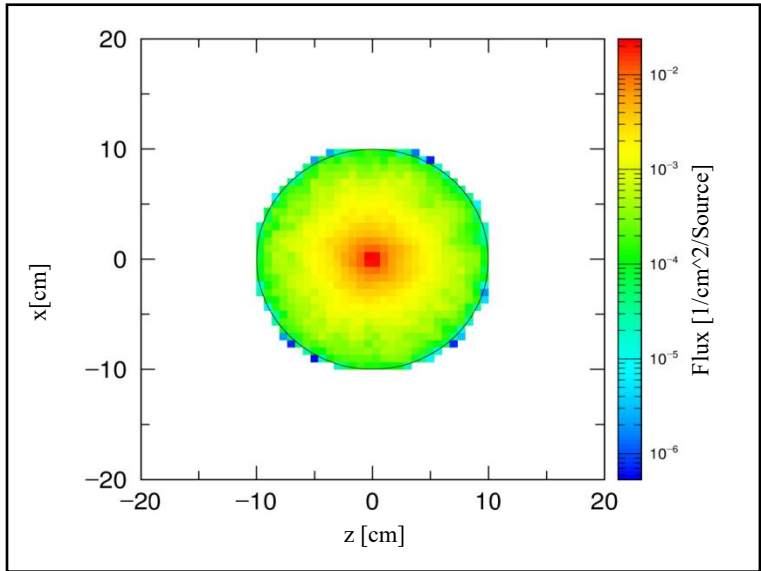


Figure 3. Spatial Distribution of Neutron Flux within the target material

4. Conclusion and Recommendation

The simulation of Boron Neutron Capture Therapy (BNCT) in soft tissue enriched with ^{10}B at a 25-ppm concentration, delivered via a carborane-monooclonal antibody conjugate, demonstrates significant potential. In this study, the target material was irradiated with epithermal neutrons at an energy of 1.0×10^{-2} MeV. The ^{10}B absorbed the neutron, resulting in a reaction that produces a lethal $^{10}\text{B} + n \rightarrow ^7\text{Li} + ^4\text{He}$. Analysis of secondary-particle fluence tracks and neutron flux generated during BNCT is essential for enhancing the therapeutic ratio. The experiment produced secondary particles capable of inducing biological damage within targeted tissues while sparing adjacent tissues. The results validate the promise of carborane-monooclonal-antibody

conjugates as effective boron delivery agents in BNCT, owing to their ability to generate high-LET secondary particles that support therapeutic selectivity. These findings provide valuable insights into the feasibility of CMAC as a next-generation boron delivery agent, establishing a physics-based foundation for future translational research. Future studies should incorporate anatomically realistic voxel-based phantoms, compare performance against established boron delivery agents such as BPA and BSH, and integrate biological response models to progress toward clinical applications. The findings serve as a foundational reference for subsequent investigations.

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