

Simulation Study of Alpha Range in Boron Neutron Capture Therapy

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Abstract. Boron neutron capture therapy trials, BNCT trials, took place in the United States firstly, BNCT was still far from mainstream medicine at that time [1]. However, in recent years, BNCT has already been applied in the therapy of many major diseases, including cancer, and recurrent glioma for example. BNCT is an extremely effective cancer treatment, which has a unique property of tumor-cell-selective heavy-particle irradiation. BNCT can form large dose gradients between cancer cells and normal cells, even if the two types of cells are mingled at the tumor margin [2]. Through BNCT, the difficulty of treating these major diseases has been solved piecemeal. Therefore, patients can see glimmers of hope and the future of BNCT has been given some optimism. This article mainly introduces the advantages of BNCT over others and the Physical Mechanism of BNCT. It supports my view of applying BNCT according to the simulated experimental data.

Keywords: BNCT (Boron Neutron Capture Therapy), TRIM (the Transport of Ions in Matter), Bragg Peak, tumor cells.

1. Introduction

According to the latest data released by the World Health Organization, 8.8 million people die from cancer every year, accounting for nearly one in six of the world's annual deaths. Among the 184 countries and regions, the incidence of malignant tumors in China is generally at the upper-medium level, accounting for about 21.8% of the global incidence. With the acceleration of population aging and social and economic development, the process of industrialization and urbanization is accelerating, and the situation of environmental factors and lifestyle changes is becoming more and more serious.

Some traditional cancer treatments—chemotherapy, hormone therapy, radiation, surgery for example—will bring many negative effects on patients' physical health and patients' mental health. To resolve the problem, in recent years, scientists have come up with many new therapy approach—gamma knife therapy, heavy ion radiotherapy, and BNCT—which can greatly relieve the adverse symptoms in patients.

As these new therapy approaches, some concepts in physics and medicine are becoming more and more important, which helps us understand the principles of these technologies and make better use of them. We will mainly focus on Bragg Peak. Bragg Peak plays an important role in particle research. The Bragg Peak is pronounced on the Bragg curve, showing the maximum value of stopping power and the amount of energy emitted by the particle [3]. Different kinds of particles in different energy have different Bragg Peaks. Especially, Bragg Peaks of some certain particles approach the point where the particles stop. The exact position of the Bragg Peak relates to the Bethe formula:

$$-\left\langle \frac{dE}{dx} \right\rangle = \frac{4\pi}{m_e c^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\epsilon_0} \right)^2 \cdot \left[\ln \left(\frac{2m_e c^2 \beta^2}{I \cdot (1 - \beta^2)} \right) - \beta^2 \right]$$

c : the speed of light

e : the electron charge

ϵ_0 : the vacuum permittivity

m_e : rest mass

β : the proportional coefficient of particle velocity to the speed of light in vacuum

This equation suggests that because electric particles ionize atoms of the material and the interaction areas increase, energy lost by charged particles is inversely proportional to the square of their velocity [4].

We will return to the new therapy approach. The University of California in Berkeley had done the pioneering work in 1977. As time goes on, heavy ion radiotherapy has been of increasing interest recently [5]. There is no cut in the heavy ion radiotherapy. Heavy ion radiotherapy has some remarkable advantages over others, which are reflected in that all heavy ion beam therapies exhibit a defined Bragg Peak in the body so they deliver their maximum lethal dosage at or near the tumor, which means these therapies are more efficient without any heavy adverse reactions (see Fig. 1) [6]. Also, the high energy carried by heavy ions, which are delivered to the tumor, will cause many double-strand DNA breaks which are very difficult for the tumor to repair [7].

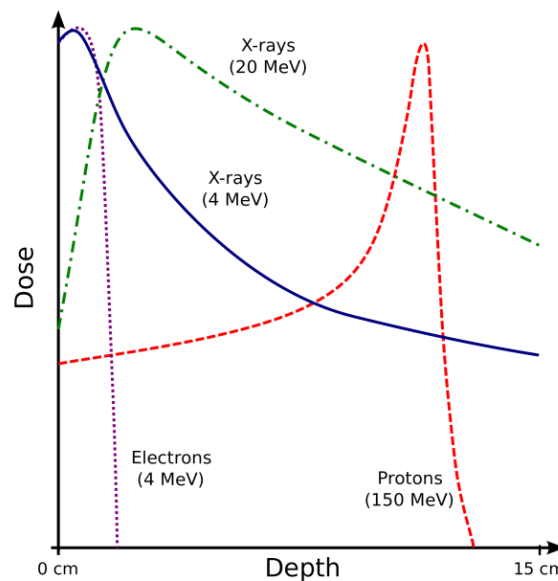


Fig. 1. Bragg Peak of X-rays, electrons, and protons

Gamma Knife radiotherapy is used to treat tumors and veins that have developed differently in the brain. Like heavy ion radiotherapy, there are also no incisions in the therapy. Different beams are dispersed at different angles, and each beam has very little effect on the brain tissue it passes through. Depending on the extreme accuracy, all beams meet at the location of tumors and the energy of radiation delivered to the place where all the beams meet is so high that can eliminate the tumors effectively [8].

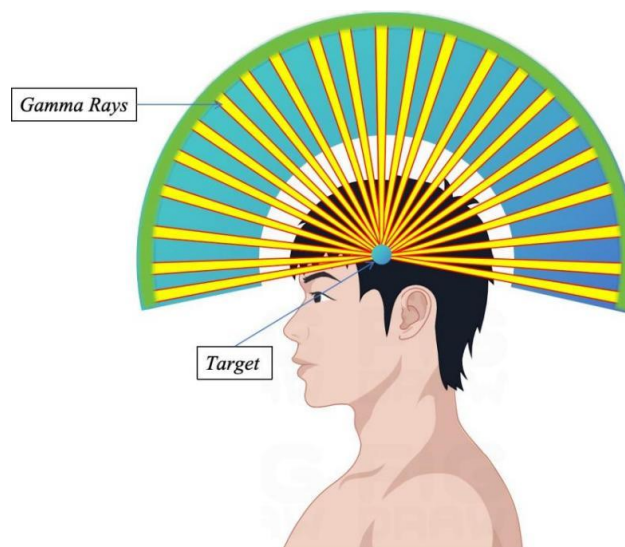


Fig. 2. Device structure and gamma-ray distribution in Gamma Knife radiotherapy

These two therapies, heavy ion radiotherapy, and gamma knife radiotherapy, however, also have some negative effects on patients, which include some side effects including fatigue, swelling, diarrhea, and so on, the duration of radiotherapy, and the costs. BNCT is the better therapy that can avoid these problems. BNCT is based on the nuclear capture and decay reactions that occur with non-radioactive boron-10 which can produce high-energy alpha particles [9].

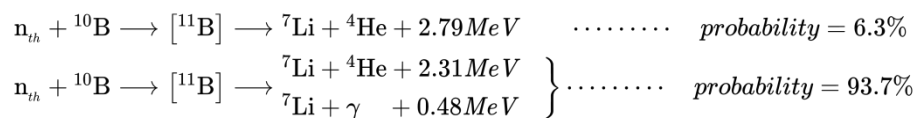
Scientists have synthesized a wide variety of boron delivery agents, which will be injected intravenously into the patient. These boron delivery agents can bring the selective delivery of sufficient amounts of ^{10}B to the tumor with only small amounts localized in the surrounding normal tissues, which is also the key factor of success [10]. When the neutron beam produced by neutron accelerators enters the patients, the neutron will react with boron in the tumor and produce high-energy alpha particles. These alpha particles can eliminate the tumor without harming any of the surrounding normal cells.

Compared with heavy ion radiotherapy and gamma-ray radiotherapy, BNCT has some obvious advantages. First, through the development of more ideal boron delivery agents, scientists can selectively gather in tumor cells, to make the treatment more accurate. Second, neither heavy ion radiotherapy nor gamma-ray radiotherapy can overcome the negative effects caused by respiratory movement and position. When patients are breathing, with the inflow and outflow of gas, regular volume changes will occur in the chest, resulting in changes in the depth of the diseased tissue, which is hard for radiotherapy. However, BNCT occurs inside the tumor cells, which means BNCT does not care about the depth of the tumor cells. Third, in radiotherapy, heavy ions or rays need to traverse the normal cells, which can have a negative effect or even kill the cells. However, BNCT which occurs inside the tumor cells can protect the normal cells completely [11].

2. The Physical Mechanism of BNCT and Simulation Software

2.1. The Physical Mechanism of BNCT

The physical principle of BNCT is a kind of decay nuclear reaction involving boron and neutrons. Actually, these reactions are composed of three different sets of reactions, each with a certain probability of occurring.



Source of Nuclear Reactants. Getting these reactants is an important task scientists should do. The principle of the reaction is known, so the key to the degree of recovery of a patient is the applicability of boron delivery agents to tumor cells and the quality of neutron sources, which have been studied by scientists all over the world for a long time.

Source of boron. A successful boron delivery agents need to meet the following requirements [12].

- A. Tumor has high uptake compared to normal cells;
- B. Low systemic toxicity;
- C. Tumor to brain (T:Br) and tumor to blood (T:Bl) concentration ratios greater than 3:1 or 4:1;
- D. Tumor concentration in 20-50 $\mu\text{g/g}$.
- E. Rapid tumor clearance during BNCT

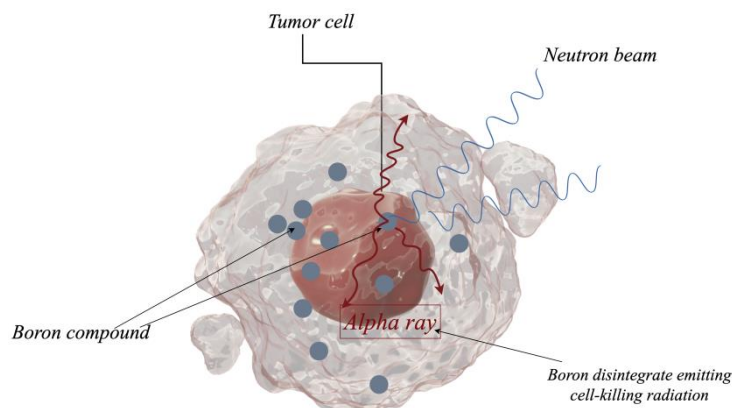
Until now, the boron delivery agents that can fulfill all the requirements have not been developed yet, but we already have some agents performing better on organisms, boronophenylalanine (BPA) and sodium borocaptate (BSH) [13].

Source of neutron. In the past, scientists have built many neutron reactors all over the world, such as MITR in MIT, KURRI in Japan, and IHNI in Beijing, and used these neutron reactors to produce neutrons for a long time. However, there are some disadvantages to using neutron reactors [14]:

- A. The reactivity is not determined by the reactors themselves but by the quality of the neutron.
- B. Sodium which is often used as a coolant in fast reactors will burn and foam in air.
- C. It is costly to build and operate these neutron reactors.
- D. It is difficult to refuel, and some optical tools cannot be used.

In this way, scientists always use neutron accelerators to provide neutrons, which truly have advantages over neutron reactors.

Principles of Physics. To understand the principles of physics clearly, we should divide the process into three subprocesses, A, B, and C.



Boron Delivery Agents Affect Tumor Cells

Fig. 3. BNCT process diagram (Principles of Physics)

A. Injecting Boron Delivery Agents

Before the therapy, patients will be injected with boron delivery agents, which can reach the cells through the circulatory system like the blood, and then will enter into the tumor cells (see “Boron compound” in Fig. 3). The amount of boron element in the tumor cells is greater than the normal cells. In this way, the normal cells will not participate in the decay reactions. In some certain cases, however, some normal cells can also participate in the reactions caused by the amount of boron element, which is the biggest drawback in BNCT. Therefore, we can see that the greater the ratio of the amount of boron in the tumor cell to that in the normal cell, the better the therapy effect. The real cases will be more complex.

B. Radiating Neutron

After injecting the boron delivery agents, doctors will take the patients close to the neutron source and expose them to neutron radiation. Neutrons will pass through the patient’s body and react with the boron delivery agents (see “Neutron beam” in Fig. 3). In the therapy, instead of using other types of neutrons, doctors use higher energy types such as thermal, hyperthermal, epithermal, and so on, in that the higher energy types of neutrons can make a lower negative influence on normal cells, compared with other neutron [15].

C. The Decay Reactions

The decay reactions are the key subprocess in the process of BNCT.

We will pay attention to the decay reaction which produces ${}^7\text{Li}$, ${}^4\text{He}$, and the energy of 2.31MeV (precisely, the energy of ${}^7\text{Li}$ is 0.84MeV and the energy of alpha ray (${}^4\text{He}$) is 1.47MeV), and we can name it as reaction-A. Fig. 4 preserve reaction-A.

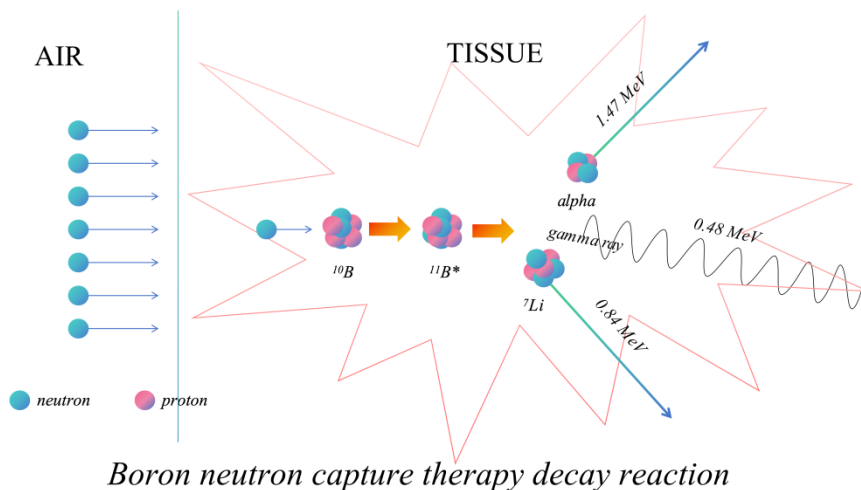


Fig. 4. Detailed illustration of boron agents decay reactions (reaction-A) with neutrons in BNCT (Principles of Physics)

As we see, reaction-A can produce high-energetic alpha rays inside the tumor cells. These alpha rays can kill the tumor cells without harming other normal cells, in that these alpha rays only have a range of 5–9 μm . Both the ${}^7\text{Li}$ and the gamma-rays cannot harm normal cells yet. Such a small-scale centralized energy again confirms the advantage of BNCT compared with other methods.

2.2. Introduction to SRIM Software

SRIM is a group of programs that calculate the stopping and range of ions into matter, and it uses a full quantum mechanical treatment of ion-atom collisions to calculate. SRIM consists of two main programs, Tables of Stopping and Ranges of ions in simple targets (SR) and the Transport of Ions in Matter (TRIM), and several special-purpose programs (see Fig. 5). We only use TRIM in calculation, so the introduction to SRIM is specific to TRIM.

TRIM is a Monte-Carlo calculation that follows the ion into the target, making detailed calculations of the energy transferred to every target atom collision (multi-layer complex targets).

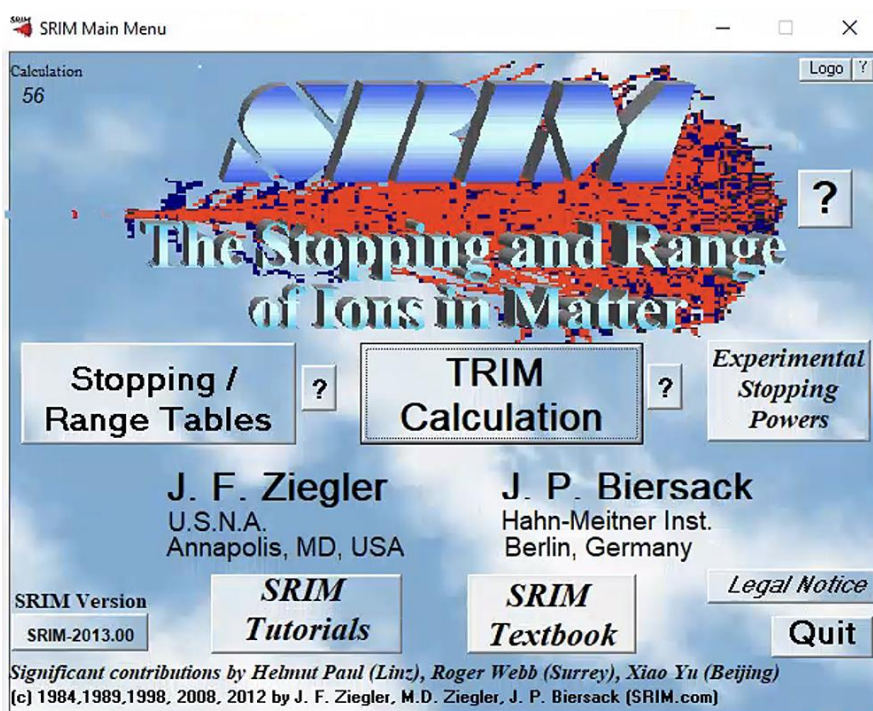


Fig. 5. SRIM software (version 2013)

the Basic Method used in TRIM. TRIM tracks a large number of incident particles through computer simulation, stores the particle position, energy loss, and various parameters of secondary particles in the whole tracking process, and finally obtains the expected value of various required physical quantities and corresponding statistical errors. In TRIM, the collision between incident ions and the target nucleus of the material is described as a two-body collision, and the energy loss comes from the elastic energy loss part, and it is considered that the interaction between incident ions and electrons in the material continuously and uniformly loses energy between two two-body collisions. When incident ions are heavy ions, it is considered that the incident ions move in a straight line during this period, and the energy loss comes from the inelastic energy loss part.

Advantages. TRIM has many advantages over other software:

Firstly, the scale of TRIM is large. It has a large ion energies range (from 10 eV to 2 GeV/amu), large numbers of layers (up to eight layers, made up of twelve different elements), and great varieties of substances that can be involved in simulation experiments (human skin, human blood, human skeleton, human cells, variety of gases, variety of liquids, ...).

Secondly, TRIM has a variety of functions. TRIM can provide a wide variety of functions: Ion/Recoil Distribution, Lateral Range, Ionization, Phonons, Energy to Recoils, Damage Events, Backscattered Ions, Transmitted Ions, and Collision Details (both 2-D Plots and 3-D Plots). Also, each function can provide satisfactory data to our simulation experiment.

Finally, TRIM has a high accuracy of calculation.

3. Simulation of Interaction between Alpha Particles and Cells

3.1. Simulation Study Preparation

Before the simulation study, we need to use TRIM to do some preparation work. TRIM is divided into some parts, and some of them need to be manually adjusted and entered some values.

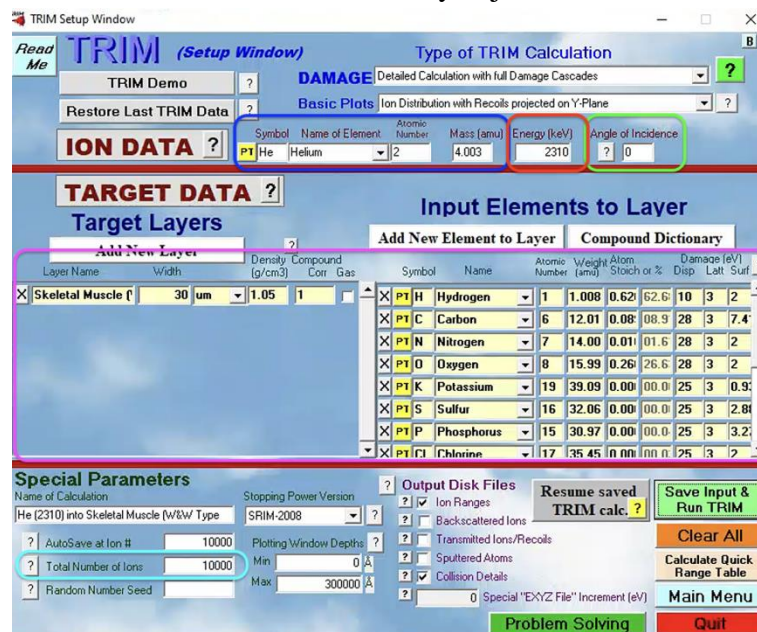


Fig. 6. the setup window of TRIM and the areas we need to modify

Five kinds of values should be adjusted: element (ions), energy of the ion, angle of incidence of ions, target layers, and total number of ions.

We need to do the simulation study inside the tumor cells, so we can obtain the following values:

1. Element [blue]: Helium (alpha ray) [Atomic Number: 2, Mass: 4.003]
2. Energy (KeV) [red]: 2310 KeV

3. the Angle of Incidence: 0 degree/ 30 degrees/ 60 degrees

[We will simulate different influences of different angles in the same target layers]

4. Target Layers: tumor cells

Table 1. Detailed information about target layers --- tumor cells.

<i>Element</i>	<i>Stoich</i>	<i>DE</i> (eV) ⁽¹⁾	<i>LBE</i> (eV) ⁽²⁾	<i>SBE</i> (eV) ⁽³⁾	<i>Target Layers</i>
<i>H(1)</i>	<i>0.598927</i>	<i>10</i>	<i>3</i>	<i>2</i>	
<i>C(6)</i>	<i>0.307357</i>	<i>28</i>	<i>3</i>	<i>7.41</i>	<i>Cell Membrane_1</i>
<i>N(7)</i>	<i>0.086037</i>	<i>28</i>	<i>3</i>	<i>2</i>	<i>[75 Ang; 0.9 g/cm³]</i>
<i>O(8)</i>	<i>0.007679</i>	<i>28</i>	<i>3</i>	<i>2</i>	
<i>H(1)</i>	<i>0.666667</i>	<i>10</i>	<i>3</i>	<i>2</i>	<i>Cell Plasma_1</i>
<i>O(8)</i>	<i>0.333333</i>	<i>28</i>	<i>3</i>	<i>2</i>	<i>[19925 Ang; 1.0 g/cm³]</i>
<i>H(1)</i>	<i>0.648017</i>	<i>10</i>	<i>3</i>	<i>2</i>	
<i>C(6)</i>	<i>0.04617</i>	<i>28</i>	<i>3</i>	<i>7.41</i>	
<i>N(7)</i>	<i>0.01408</i>	<i>28</i>	<i>3</i>	<i>2</i>	<i>Cell Nucleus</i>
<i>O(8)</i>	<i>0.285793</i>	<i>28</i>	<i>3</i>	<i>2</i>	<i>[90000 Ang; 1.0 g/cm³]</i>
<i>P(15)</i>	<i>0.00517</i>	<i>25</i>	<i>3</i>	<i>3.27</i>	
<i>S(16)</i>	<i>0.00077</i>	<i>25</i>	<i>3</i>	<i>2.88</i>	
<i>H(1)</i>	<i>0.666667</i>	<i>10</i>	<i>3</i>	<i>2</i>	<i>Cell Plasma_2</i>
<i>O(8)</i>	<i>0.333333</i>	<i>28</i>	<i>3</i>	<i>2</i>	<i>[19925 Ang; 1.0 g/cm³]</i>
<i>H(1)</i>	<i>0.615386</i>	<i>10</i>	<i>3</i>	<i>2</i>	
<i>C(6)</i>	<i>0.315383</i>	<i>28</i>	<i>3</i>	<i>7.41</i>	<i>Cell Membrane_2</i>
<i>O(8)</i>	<i>0.061541</i>	<i>28</i>	<i>3</i>	<i>2</i>	<i>[75 Ang; 0.9 g/cm³]</i>
<i>P(15)</i>	<i>0.00769</i>	<i>25</i>	<i>3</i>	<i>3.27</i>	

(1): DE: Individual Target Atom Displacement Energies (eV)

(2): LBE: Individual Target Atom Lattice Binding Energies (eV)

(3): SBE: Individual Target Atom Surface Binding Energies (eV)

5. Total number of ions: 10000 [the greater the number, the higher the accuracy]

After adjusting these values, we will do some other steps: Choosing “Detailed Calculation with full Damage Cascades” and Checking “Ion Ranges” and “Collision Details”.

3.2. Simulating Ray Range in All Cases

According to the Bragg Peak, we talked about above, in BNCT, we need to keep the Bragg Peak of the alpha particle within the tumor cell so that it can effectively kill the tumor cell without harming other normal cells, and this is the main topic of our simulate study using TRIM. We will use TRIM to simulate alpha rays in tumor cells with different angles and alpha rays in other materials.

Alpha Rays in Tumor Cells with Different Angles. To simulate the real clinical situation of alpha particles, and to ensure that alpha particles do not harm other healthy cells, we use different particle incidence angles. Due to the large number of angles, we will be represented by 0 degrees, 30 degrees, and 60 degrees.

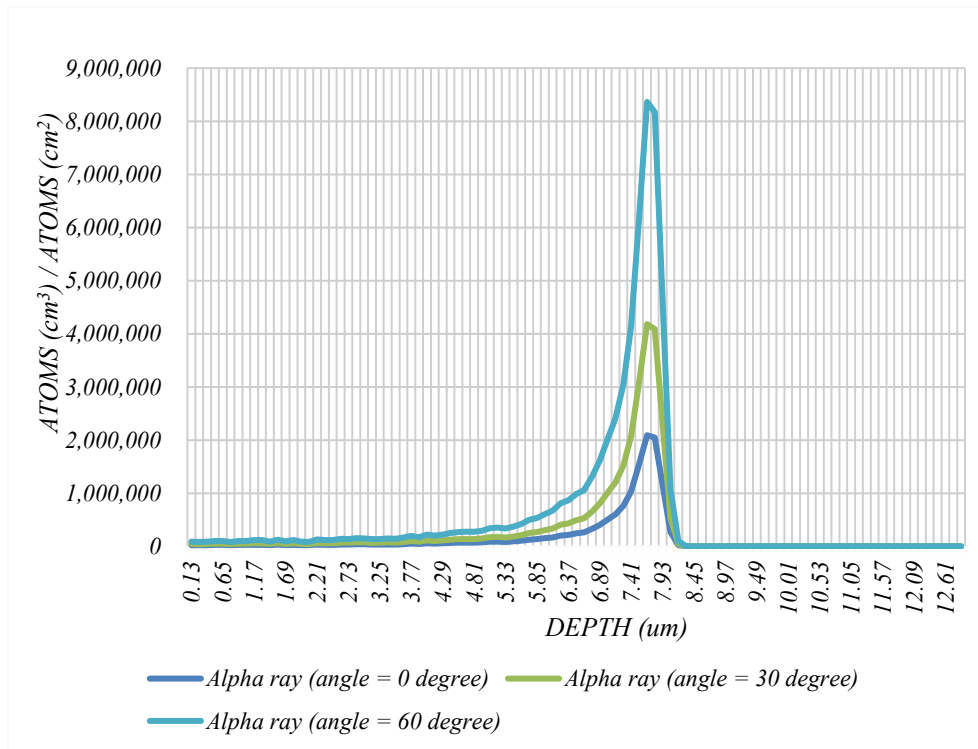


Fig. 7. The quantity loss of alpha particles with incidence angles of 0 degrees, 30 degrees, and 60 degrees respectively in tumor cells with depth

In Fig. 7, according to the raw data table, we can find that regardless of the incidence Angle, the Bragg Peak of the alpha ray is located at a depth of 7.80 microns. The average diameter of tumor cells is 20um, and the diameter of hepatocellular carcinoma cells selected for our simulation study is 13um. Compared to the depth of the Bragg Peak of the alpha ray, 7.80um, we can be sure that the Bragg Peak of alpha particles is inside these cells and will not harm other cells. Also, the maximum energy is concentrated at the Bragg Peak of alpha particles, so it kills tumor cells more effectively.

Alpha Rays in Other Materials. We will do some simulation studies in other materials just in case some boron delivery agents exist in other places in our body such as blood or skin.

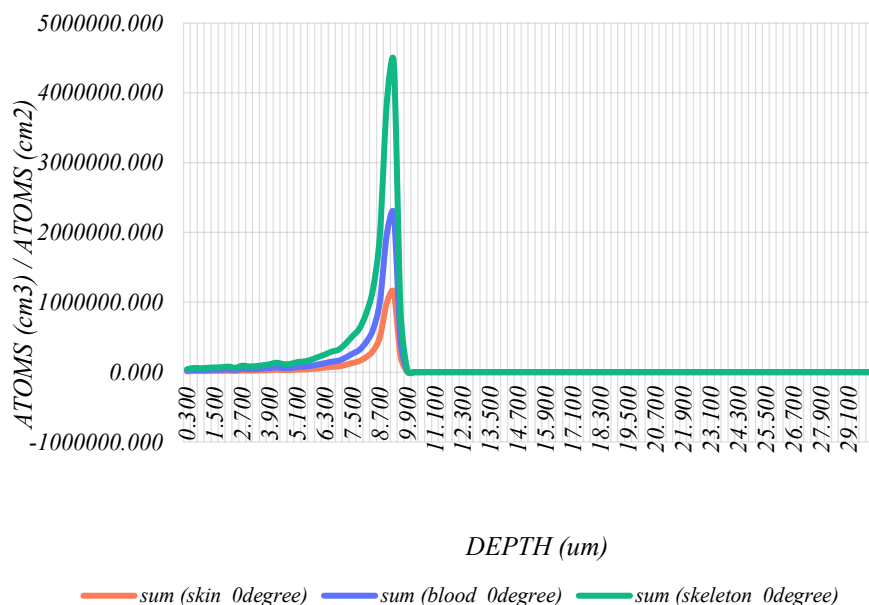


Fig. 8. The quantity loss of alpha particles in skin, blood, and skeleton with depth

In Fig. 8, according to the raw data table, we can find that no matter how the materials are, the Bragg Peak of the alpha ray is located at a depth of 9.30 μ m. Now there is enough data to make sure that alpha rays will not harm normal cells and destroy the tumor cells with maximum energy even though some boron delivery agents do not make it to the inside of the tumor cells.

we can find that no matter whether some boron delivery agents are in the tumor cells or not, alpha rays produced by decay reactions of BNCT can kill the tumor cells effectively without harming other cells, which directly proves the feasibility of BNCT.

4. Conclusion

Throughout the article, we have stated the nature of BNCT and the advantages of BNCT over other therapies. Also, we have used TRIM to prove the feasibility of BNCT. No matter from which aspects of view, BNCT is always the pioneer of the trend, and is also the core method of tumor therapies.

In some certain cases, however, alpha cannot have a positive influence on the tumor cells, such as some cells less than 5 μ m in diameter, which are some drawbacks in BNCT. In these cases, some traditional methods, at least with today's technology, will make a better performance in therapy.

For the future development of BNCT, scientists need to once again break through basic fields to improve the quality and accuracy of boron delivery agents. With the improvement of the accuracy of agents, scientists can cope with different situations and can integrate BNCT into clinical therapy in any case. With the development of BNCT, I believe it can provide all cancer patients in the world with good medical therapies, reduce the death rate of cancer, and make cancer no longer the most feared disease of mankind.

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