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A Brief Review on Features, Capabilities, and Limitations of Different Treatment Planning System (TPS) for Boron Neutron Capture Therapy

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Abstract

Background: Boron Neutron Capture Therapy (BNCT) generally comprises of four dose components. The primary one which directly deals damage to the tumor is called the boron-dose, as it originates from the nuclear reaction of boron-10. While the, the other three came from the nuclear reaction of hydrogen and nitrogen atoms in the tissues and called the non-boron dose. These nuclear reaction produces secondary particles which stochastically behave when interacts with the tissue. As such, these occurrences pose a great challenge for determining/calculating accurate dose due to their stochastic nature and could deal damage to the healthy tissues. So, a Treatment Planning System (TPS) is utilized to help in determining an effective BNCT treatment. Such that, TPS helps to evaluate dose distributions and therapeutic effect which consequently helps to determine adequate treatment parameters to a successful BNCT treatment. However, TPS are not always compatible to any treatment and some TPS has particular conditions on when can it be utilizing into its full potential and when will it not be efficient for BNCT treatment planning/treatment. Therefore, this study briefly reviews some of the features, capabilities, and limitations of each major TPS's namely, NCTPlan, SERA, JCDS, THORPlan, NeuCure, and Tsukuba Plan.

Conclusion: This study highlighted the strength and shortcomings of the major TPS's in treatment planning for BNCT application. This paper gives insights on the future research to be undertaken of the development of TPS for the advancement of BNCT.

Keywords: Boron Neutron Capture Therapy (BNCT); Treatment Planning System (TPS); Development; MCNP

Abbreviations: BNCT: Boron Neutron Capture Therapy; DICOM: Digital Imaging and Communication in Medicine; ENDF: Evaluated Nuclear Data File; JCDS: JAEA Computational Dosimetry System; JENDL: Japan Evaluated Nuclear Data Library; NCT Plan: Neutron Capture Therapy Plan; MC: Monte Carlo; MCNP: Monte Carlo N-Particle; PHITS: Particle and Heavy Ion Transport Code System; THOR Plan: Therapeutic and Hypothetical Optimized Radiation Planning; TPS: Treatment Planning System; SERA: Simulation Environment for Radiotherapy Applications

Introduction

Radiation therapy has been a crucial tool in treating cancers and one of its modalities is called the Boron Neutron Capture Therapy (BNCT). Unlike other modalities BNCT is known for its unique property of damaging the tumor selectively while greatly sparing the healthy tissues [1]. BNCT is based on nuclear fission reaction when a boron-10 (^{10}B) captures neutron and resulted into an excited boron-11 (^{11}B) which rapidly decays and produces secondary particles: the alpha particle (α) and lithium-7 (^{7}Li) nuclei, henceforth called the boron-dose components [2,3]. The produced secondary particles are high-linear energy transfer (high-LET) particles, such that their energy dissipates faster as they traverse through the medium (e.g., tumor tissue). Consequently, their travel path ranges to 5-9 μm which is comparable to a cell diameter and in return influences the damage to be at targeted tumor cells while sparing the healthy tissue cells [3,4].

Materials and Methods

However, there are some considerations to be taken in BNCT in the aspect of dose calculations which is the occurrence of the non-boron dose components namely the proton dose, nitrogen dose, and gamma dose [5]. These doses occur due to neutrons as it traverses through the healthy tissues and interacts with H (Hydrogen) and N (Nitrogen) which are abundant in tissues. Their interactions are represented as $^{1}H(n,n)p$ "proton dose", $^{14}N(n,p)^{14}C$ "nitrogen dose", $^{1}H(n,\gamma)^{2}H$ "gamma dose" [5-7], and graphically presented. In addition, these non-boron dose can act as an indirect ionization sources which induces indirect ionizing radiation that can highly damage the healthy tissues [8]. Thus

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due to these occurrence of different radiation fields it is challenging for dose calculations in BNCT, and as a precaution to avoid unnecessary damage it is imperative to determine the biological effects of each dose component (*i.e.*, boron and non-boron dose) for evaluation of the doses as to determine and guarantee a successful treatment [9].

Hence, a method of various steps is developed to aid in this problem. One of which is a Treatment Planning System (TPS), which must be utilized before the physical application of BNCT to the patient. TPS is used in determining treatment parameters such as injected dose, timing of the treatment, neutron flux and neutron energy, boron distribution, and also helps to calculate dose distributions, dose-volume histograms, determine cumulative dose, and biological effects that a patient may undergo. This is necessary so that the probability of healthy tissue damage can be minimized and such increasing the effectivity and efficiency of BNCT treatment. Therefore, this study reviews the features, capabilities, and limitations of the major TPS's for BNCT treatment planning.

Results and Discussion

Present day TPS uses Monte Carlo simulation modeling to calculate and determine adequate parameters during BNCT application, moreover many TPS has been developed over the years based on accelerator-based neutron source and nuclear-reactors neutron source as show in Table 1. TPS is very crucial for BNCT treatment in computing the doses and determine the dose distributions, and suitable irradiation parameters for the best outcomes of BNCT treatments. Basically, TPS is a system use as a tool in radiation therapy for optimizing the effects of different radiation fields that occurs in BNCT and such TPS development is very essential for the application and advancement of BNCT. In light of development of BNCT TPS, unlike the other conventional therapy such as X-ray and particle therapy where TPS's are spread and used, BNCT's TPS are still in clinical trials application. As seen in Table 1, the tallied major TPS's are the oldest systems that is developed, yet until now they are still non-commercial and none of them have been approved as medical device. This can be linked to the diverse behaviors of different radiation fields present in BNCT that influences the dose delivered and makes it more complicated for dose calculations. To address this, TPS's for BNCT are equipped with Monte Carlo transport code software (e.g., PHITS, MCNP).

Table 1: Major treatment planning system designed for BNCT, with respective facility developer and type of Monte-Carlo code based software.

TPS	MC transport code
NCTPlan	MCNP
SERA	Sera MC
JCDS	MCNP transitioned to PHITS
THORPlan	MCNP
NeuCure	PHITS
Tsukuba-Plan	PHITS

Monte Carlo simulation

Monte Carlo (MC) simulation approach is very useful to determine results such as dose distribution, energy deposition, absorbed dose calculation, etc., by interpreting statistical data using repeated random sampling of which greatly assists in determining the effect of the different radiation fields present in BNCT. Basically, MC method has a repetitive pattern. First, is to specify acceptable inputs; second, is to produce random histories from a set of distribution of probabilities; third, is to perform computation, and lastly it combines the outcome of each iteration which are usually we used in analyzing and interpretating BNCT treatment evaluation. MC method is particularly suitable for BNCT due to its capability to handle and model complex particle interactions such as interaction of neutron and produced secondary particles of each dose components with matter, which allows an accurate dosimetry calculation for evaluation of BNCT efficacy even with varying and complex geometries (*i.e.*, target phantom) such as human head or tissues. Thus, Monte Carlo transport code are indispensable in treatment planning in BNCT, and most commonly used MC transport code are Monte Carlo N-Particle (MCNP) and Particle and Heavy Ion Transport Code System (PHITS).

Treatment Planning System (TPS)

TPS has an important role in assisting the efficacy and effectiveness of BNCT treatment, as such to execute its role TPS's should have the following:

- Capable of translating medical images such as CT and MRI images into 3D geometric voxel model.
- 3D voxel model should include material volume and densities.
- Equipped with an interface that which allows manual input of irradiation parameters such as neutron beam intensity, neutron source, beam directions, etc.
- Generally, equipped with MC transport code for particle simulation and dosimetry calculation (particle fluences, radiation transport).

- Capable of producing visual presentation of calculated results such as two dimensional dose distribution (e.g., graphs).

Accordingly, the features are placed in order to generalized the workflow of TPS in BNCT. With these, we review some features of major TPS listed in Table 1. and see how these different TPS implement these features and know their limitations. In Table 2 it shows the comparison of features of the major TPS. Here, we see the list of developers for each individual TPS. We also can see in Table 2 the type of image format that works for a particular TPS, together with the cross section libraries that is installed in the TPS and also the sizes of their voxels which help us to determine their accuracy.

Table 2: Comparison and lists of features of the major TPS, along with their developer and cross-section library.

TPS	Developer	Image format	Image fusion	Voxel size (cm^3)	Cross section library
NCTPlan	Harvard/MIT/CNEA	TIFF	NO	1	ENDF/B-VI
SERA	INEEL/Montana State University	QSH	NO	1	ENDF/B-VI
JCDS	JAEA	DICOM	NO	1	ENDF/B-VI
THORPlan	Tsing Hua University	DICOM	PET/CT	8 px to 1 homogenized	ENDF/B-VI
NeuCure	Sumitomo Heavy Industries	DICOM	NO	0.003	JENDL 4.0
Tsukuba Plan.	Tsukuba University	DICOM	NO	2 px to 1 homogenized	ENDF/B-VII.1

We can see that JCDS, THORPLAN, Tsukuba Plan, and Neu Cure supports DICOM which is typically used in radiology and makes it easier to integrate in clinical work since it is widely adopted in medical fields. On the other hand, NCT Plan who supports TIFF image format may limit clinical integration such that DICOM images need to be converted to TIFF. Table 2, also explicitly shows us that some voxel model of the scanned medical images can be adjusted due to the range capability of the voxel sizes in some TPS. To be specific, it can be seen that NCT Plan, SERA, and JCDS share the same value of voxel sizes. Voxel sizes in SERA can be adjusted to any size and JCDS voxel size can be adjusted from 8 mm^3 (0.8) to 1 cm^3, and Tsukuba Plan voxel size range to 2 mm^3 to 1 cm^3. As shown, NeuCure has the smallest voxel size at 0.003 cm^3 which greatly implies that NeuCure is more accurate in dose calculation due to its smaller voxel size, smaller voxel size enhances voxel model accuracy, however it negatively affects computational time. With strong concerns for accuracy in dose calculations, some TPS adopts a special method like THORPlan which utilizes grouping model. This model groups each cell together to reduce materials in calculation model which improves calculation accuracy. With regards to the image fusion column, it indicates whether the system supports combining data from multiple imaging modalities such as MRI, CT, and PET. As shown in Table 2 only THORPlan supports PET/CT image fusion while the other five TPS do not, this emphasizes the capability of THORPlan to be accurate and effective in mapping boron distribution which enhances dosimetry accuracy that is crucial for optimizing treatment planning for efficient BNCT application. In addition, PET/CT provides a better visualization of the arrangement and connections between tumors and healthy tissues which greatly aids in the accuracy of delivering sufficient dose in the tumor during therapy.

Other feature of TPS such nuclear cross section library is very crucial as it defines the accuracy in modeling of neutron interactions in BNCT, specially for evaluating neutron flux. The nuclear cross-section library as shown in Table 2 used by the major TPS for simulation accuracy of neutron interactions. These libraries are Evaluated Nuclear Data File (ENDF) and Japan Evaluated Nuclear Data Library (JENDL). All major TPS utilizes ENDF respectively ENDF/B-VI and VII.1 except Neu Cure which uses JENDL 4.0. The choice of cross-section library ultimately affects the simulation accuracy, modern libraries (updated version of old libraries) are preferred than of the standard ones (old version libraries) such as ENDF/B-VIII is much more accurate than ENDF/B-1, and likewise JENDL 3.3 to JENDL 4.0. The choice between the two libraries (*i.e.*, ENDF, JENDL) depends on the application with respect to their capabilities such like in flux spectrum ENDF/B-VIII underestimate flux levels below 111 keV which greatly influences the neutron capture and scattering results, on the other hand JENDL 4.0 overestimate total flux levels, particularly in the energy range (60 keV to 20 MeV) which imply higher predicted reaction rates in a specific system. However, by modern standards ENDF/B-VI has limited datasets, and is a general purpose nuclear data for reactors and shielding while JENDL-4.0 includes high-resolution thermal scattering and neutron interaction data employed for medical application making it more advantageous for BNCT making NeuCure more advantageous than other TPS.

Now with all these features to assist in BNCT application, there are still limitations that these TPS's faced. Firstly, NCTPlan limitations is that it relies in a simple modeling for dose

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calculations which the system struggles to deal with complex geometries often encountered in head and neck tumors, along with the incompatibility of the system with more developed dose calculation formalism such as photon-isoeffective formalism which limits the accuracy of dose calculation and evaluation. As for SERA, its limitation is in regards to memory usage due to large voxel size (10 mm) which also hinders producing accurate voxel model that include the complicated definition of region of interest and tissue information, due to SERA can't process DICOM such it has poor input-output usability. For JAEA Computational Dosimetry Sytem (JCDS) its calculation accuracy is determined by water phantom experiments, which shows that at 10 mm^3 voxel size it overestimates the value of thermal neutron flux by 40% and it also shows discrepancies at boundary between the soft tissue and air. THOR Plan is challenge by its inability to produce in homogenous dose distribution which may lead to induce insufficient dose delivered to some areas (cold spots) that can cause head and neck cancers recurrence. Unlike others Tsukuba Plan can handle dose calculations even at cellular level and simultaneously calculate RBE-weighted dose and physical dose, however the issue with Tsukuba Plan is the computational time that takes a long time which is a typical concern for Monte Carlo calculations. Coming in last, is the TPS NeuCure has issues with treatment homogeneity especially in dealing with deep seated tumors, thus producing cold spots the same as THOR Plan which reduces the treatments efficacy.

Conclusion

Capabilities and limitations of different Treatment Planning System (TPS) are being reviewed in this study highlighting their own strength and shortcomings, which gives insights on the possible future works in developing TPS for better treatment outcomes in BNCT application. This study suggests an integration between different TPS, such as an integration between the capability of THOR Plan to support image fusion could help to assist the JCDS issue in showing discrepancies between boundaries of materials (*i.e.*, tissue, air). On that note, even though these major TPS produces satisfactory outcomes, still a thorough evaluation needs to be done for their efficiency in BNCT treatment specially in complex phantom model treatment.

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