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REVIEW ON SOME COMPUTATIONAL ASPECTS OF BORON NEUTRON CAPTURE THERAPY

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Abstract This paper reviews some computational aspects of Boron Neutron Capture Therapy (BNCT) with the emphasis on the BNCT treatment planning system. An example of a computational dosimetry system developed in Japan is discussed, particularly, the need of such system for BNCT which uses epithermal neutron beams for non-craniotomy brain tumors as well as head-&-neck cancers. An example of BNCT dose calculation method is also presented.

Keywords Boron Neutron Capture Therapy, Computational Aspects, Treatment Planning System, Dose Evaluation

1. INTRODUCTION

BNCT is a type of radiation therapy for obstinate cancers such as malignant brain tumors and melanoma. The physical principle of BNCT was presented in 1936 and its medical application for malignant brain tumors had been conducted (Farr 1954). In the BNCT procedure, doctors inject a boron compound that builds up selectively in the cancer cells of a patient at first, and subsequently the affected region of the patient is irradiated by a neutron beam from a reactor core. Alpha particles and lithium atoms, which are generated by interactions between neutrons and boron-10 atoms in the cells, destroy cancer cells selectively. In the last decade, clinical trials of BNCT with epithermal neutron beams have been performed around the world. By using the epithermal neutron beams, the therapeutic range is expanded to deeper regions in the brain more than using thermal neutron beams.

Traditionally, the neutron source for BNCT is generated from a nuclear reactor where neutron beams are used directly or via a fission converter. However, nuclear reactor-based BNCT apparatus requires complicated maintenance, handling, and subjection to nuclear reactor regulations hence it is rather not suitable as a medical device to be installed in a hospital. Particularly in Japan, accelerator-based BNCT apparatus, recently, has been considered more feasible since it is safer, simpler and more compact to be installed in a hospital.

Historically, clinical trials for BNCT in Japan had been performed using thermal neutron beams at several research reactors: Japan Research Reactor No.2 (JRR-2), Musashi Institute of Technology Reactor (MuITR) and Kyoto University Research Reactor (KUR) (Nakagawa and Hatanaka 1997). To deliver thermal neutrons to depth in the brain, the BNCT procedure at that time had included craniotomy such as skin flap reopening and bone removal.

Before the Fukushima Dai-Ichi Nuclear Power Plant accident (March 2011) where all

research reactors in Japan were in operation, the clinical trials for BNCT were performed using mainly epithermal neutron beams at JRR-4 and at KUR. The BNCT clinical trial at JRR-4 has started since 1999 (Yamamoto et al. 2004). First, the BNCT trials in JRR-4, Intra-Operative BNCT (IOBNCT) including the craniotomy were performed with thermal neutron beams. Based on further developments described below and the experiences obtained from the IOBNCT, since 2003 clinical trials using epithermal neutron beams have been performed at JRR-4 (Matsumura et al. 2004).

At present (2017), research reactors in Japan must submit new licenses for restarting the reactors after fulfilling the new safety standards and regulations imposed after the accident. JRR-4 has submitted a decommissioning plan at the end of 2015 and cannot be used for BNCT any longer. At present, the KUR is applying for a license to restart its reactor and hopefully in near future the reactor can be utilized again for BNCT.
We can conclude that the role of accelerators for BNCT has become more important in Japan. At present, accelerator-based BNCT facilities were installed at Kyoto University Research Reactor Institute (Kyoto) and at the Southern Tohoku General Hospital of the Southern Tohoku Research Institute for Neuroscience (Koriyama City in Fukushima Prefecture). Another accelerator-based BNCT facility is being constructed in the Ibaraki Neutron Research Center (Tokaimura, Ibaraki Prefecture).

The computational aspects of BNCT apparatus or system cover the following: (1) Neutron source (fission reactor, fission converter, accelerator, target, shielding etc.), (2) Neutron beam transport (filter, collimator, shutter, shielding etc.) and (3) Treatment planning system. In this paper, a review on the computational aspects of BNCT treatment planning system is given by taking an example of a system developed in Japan.

2. JAEA COMPUTATIONAL DOSIMETRY SYSTEM

Japan Atomic Energy Agency (JAEA, former name JAERI) Computational Dosimetry System (JCDS) was developed by JAEA (Kumada et al. 2005) to carry out the clinical trials based on an optimum treatment plan determined by accurate dose calculations. The BNCT clinical trial based on the treatment planning with JCDS was started in 2003. JCDS was employed to every BNCT procedure in JRR-4.

Clinical trial for head-&-neck cancer was also performed in JRR-4 since 2005 (Morita et al. 2006). In the treatment planning for the head-&-neck cancer BNCT, the geometry involved in the dose calculations is more complex since it includes oral, nasal cavity and lung. Therefore, there is a strong need to develop a precise calculation model in order to determine an optimum treatment plan.

Under these development efforts, JCDS is being improved to deal with the treatment planning for head-&-neck cancer as well as malignant brain tumor.

2.1. System Configuration of JCDS

In neutron irradiation in the BNCT procedure, to evaluate properly the prescribed doses given to a patient, JCDS has been developed by JAEA. Fig. 1 shows the scheme of dosimetry computation process using JCDS. JCDS creates a patient's 3D model based on patient's

medical images such as CT (Computer Tomography) and MRI (Magnetic Resonance Imaging). By using the CT image data, compositions of the human body are automatically differentiated from bone, soft tissues and air according to CT values (See Chapter 3 for detail explanation). On the other hand, the MRI image data are used for defining several regions such as tumor region, target region and critical organs called "Region Of Interest (ROI)" as important information for the dosimetry.

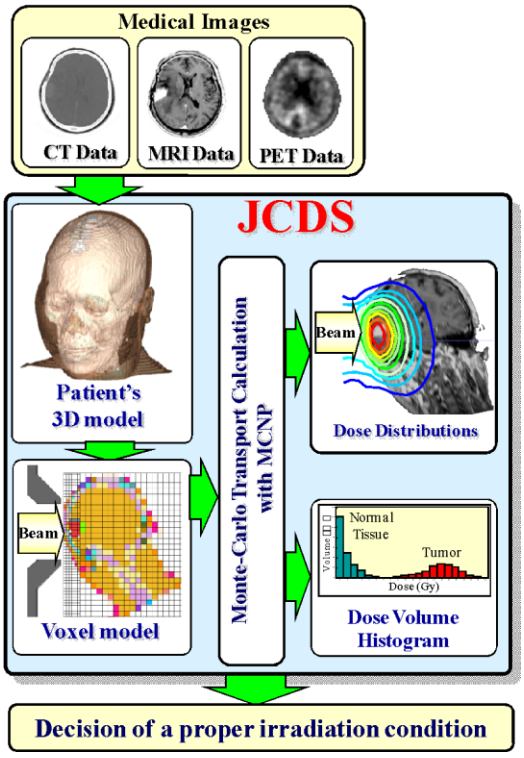


Fig. 1. Process of computational dosimetry with JCDS

By superimposing the MRI images onto the CT images, a detailed 3D model including the compositions information and the ROI information is created. To effectively compute distributions of several dose components and neutron fluxes in the body, JCDS converts the detailed 3D model into a voxel calculation model. The voxel model consists of 10×10×10 mm^3 voxel (10mm voxel) cells that contain proper material data in each voxel cell (See Chapter 3 for detail explanation). The distributions of the dose components and fluxes in the voxel model are determined by MCNP-4 which is a general Monte-Carlo neutron and photon particle transport code (Briesmeister 2000). Finally, JCDS evaluates the detailed distributions of the dose components in the original detailed 3D model by interpolating the voxel calculation results. The development of JCDS enables determination of the optimum conditions for irradiation of BNCT.

2.2. Improvement of JCDS

JCDS in the initial version employed a voxel calculation method by dividing geometry into 10mm voxel cells in order to calculate the dose distributions effectively. In the second version of JCDS, it became possible to create a multi-voxel model combined with 5×5×5 mm^3 voxel cells (Kumada et al. 2004a). Each dose value in each voxel cell was determined by the "cell tally" function in MCNP-4. The calculation accuracy of JCDS was verified by comparing with measurements obtained from cylindrical water phantom experiments (Kumada et al. 2004b). Verification results proved that JCDS had sufficient performance for dose evaluation in BNCT, except for the evaluation near the phantom's surface. The results also indicated that JCDS produced discrepancy at boundary regions between air and soft tissues.

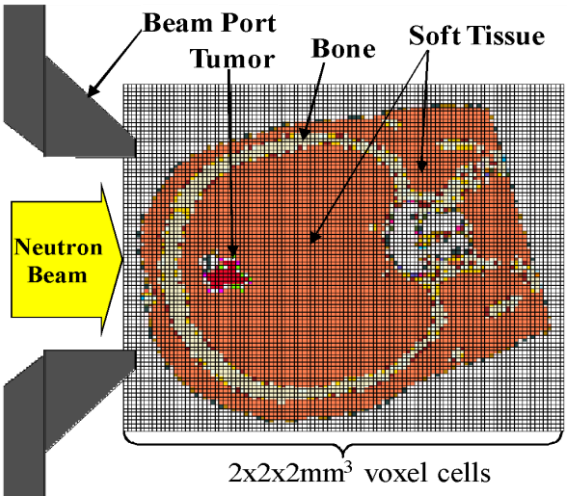


Fig. 2. Voxel model consisting of 2mm voxel cells

In the dose evaluations for head-&-neck cancer BNCT, skin, oral mucosa and nasal mucosa are regarded as important regions which shall be treated cautiously to limit the dose of those regions, and therefore they should be evaluated with higher accuracy to perform dose evaluation with higher accuracies, JCDS was improved to include the capability of creating a detailed voxel model consisting of 1×1×1 mm^3 voxel cells or 2×2×2 mm^3 voxel cells (2 mm voxel). Fig. 2 shows a patient's voxel model consisting of the 2 mm voxel cells. JCDS was also modified such that mesh tally function installed in MCNP-5 can be applied to dose evaluations. The mesh tally function allows effective computing of detail dose distributions.

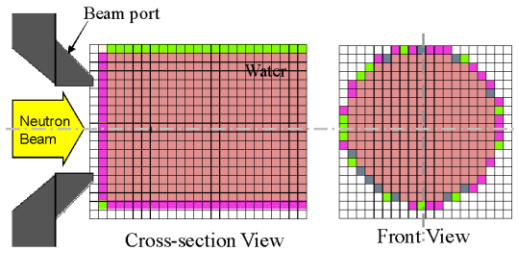
Recently, along with the adoption of accelerator as the neutron source for BNCT, the JCDS solver, MCNP-5, was replaced by PHITS (Particle and Heavy Ion Transport Code System) (Sato et al. 2013). By using PHITS, the treatment planning system can also be used for proton therapy, heavy ion therapy, that is, combined modality therapy beside accelerator-based BNCT.

2.3. Verification of JCDS

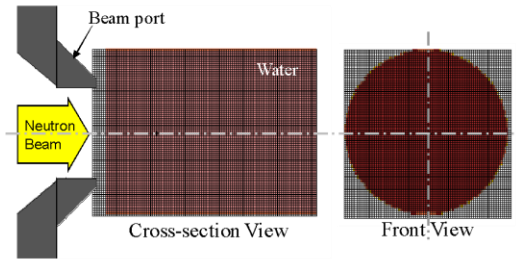
To demonstrate the calculation performance of the modified JCDS applying a detailed voxel calculation, verifications were performed. Fig.3-(a) shows a phantom's voxel model consisted of 10mm voxel cells, while Fig. 3-(b) shows the one for 2 mm voxel cells. In the verification, as for the irradiation beam to the phantom, epithermal neutron beam mode which will be applied to BNCT clinical trials was selected. The beam outlet was shaped to form a circular geometry with 10 cm diameter. Distributions of thermal neutron flux in the phantom were determined with the mesh tally and the cell tally respectively, and finally the calculation results were compared with the experimental values.

In the calculations with the 10 mm voxel model, 3D distributions in the phantom were determined by using both cell tally and mesh tally. In the benchmark for the 2 mm voxel model, only mesh tally calculation was performed. Particle histories for each condition are 800 million.

Accuracy of mesh tally calculation was confirmed by comparing with results of cell tally calculation which has been already applied to clinical trials. With cell tally values, the mesh tally values at each corresponding point in the phantom were in good agreement within the error of less than 3%. The discrepancy is within statistical uncertainty of the Monte-Carlo calculations. The results demonstrated that dose evaluation with MCNP-5 allows to switch from cell tally to mesh tally.



(a) 10mm voxel phantom model



(b) 2mm voxel phantom model

Fig. 3. Voxel model for the cylindrical water phantom

Influences of miniaturization of voxel model were confirmed continuously. Thermal neutron flux profiles on beam's central axis in the phantom for experimental data, calculated values for 10 mm and 2 mm voxel models. Both calculated values were obtained by mesh tally. The detailed distributions on the axis for both calculation profiles were determined by interpolating the calculated values of each voxel cell using JCDS function. Comparing with the experimental values showed that both calculations in phantom deeper than 1 cm produced errors of less than 5%. The value of the 2 mm voxel model on the phantom's surface was also in agreement with the experimental value within experimental error. However, the value of the 10 mm voxel model was overestimated by approximately 40%. These results proved that the miniaturization of the voxel model enhanced the accuracy of the dose calculation in the BNCT's dosimetry. The results demonstrated that detailed voxel model with 2 mm voxel cells combined with mesh tally option can be employed to treatment planning in actual BNCT trials.

The verification results show that calculation methodology adopting the 2 mm voxel model is practical and efficient. Based on the results, for the treatment planning in BNCT procedure, dose calculation using 2 mm voxel model with mesh tally has been applied. The same accuracy was achieved by the PHITS code and practically now PHITS code has become the solver module for BNCT treatment planning systems in Japan.

3. DETAIL COMPUTATIONAL ASPECTS

In this chapter, a more detail explanation on some computational aspects of JCDS is given.

In JCDS, the preferred patient's image data format is DICOM. DICOM stands for Digital Imaging and Communications in Medicine, and it is a standard format for handling, storing, printing, and transmitting information in medical imaging. It includes a file format definition and a network communications protocol.

The tissue material composition definition adopted in JCDS is based on ICRU-46 (White 1992) which includes H, C, N, O, Na, P, S, Cl, K, Mg and Ca elements.

In JCDS, a user can use built-in materials (1) soft tissue, (2) tumor, (3) bone, (4) air, and (5) lithium helmet. Lithium helmet is needed especially for brain tumor BNCT protocol.

Based on the patient's CT data the voxel based material data is determined as illustrated From the CT data, the type of material is determined automatically by

using prescribed ranges of mass density as shown in the upper part of the figure. The air containing pixel can be easily detected since its mass density is very different from human parts. The next denser material is the soft tissue (which may be normal tissue or tumor tissue). The soft tissue has a certain range of mass density which is used to detect the soft tissue region. The densest material is bone, and similarly it has a certain range of mass density.

Since a voxel dimension is usually larger than a pixel dimension, a voxel may contain more than one type of material as shown in the lower part of the figure. In JCDS, a limited number of available material mixing sets (amongst types of materials) can be used to define the final voxel composition which will be used by the MCNP-5 or PHITS code.

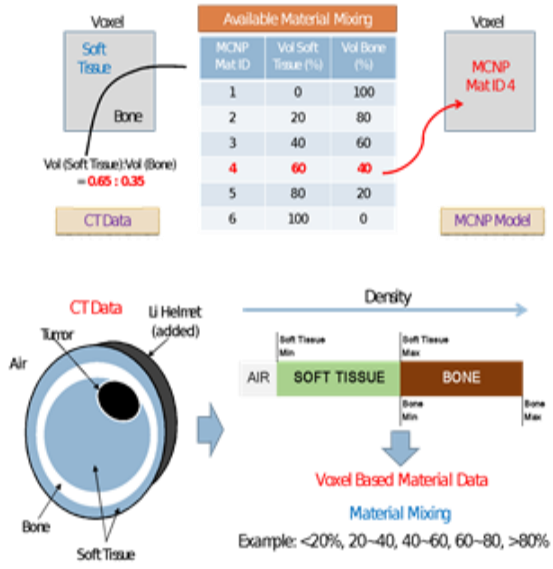


Fig. 4. Voxel-based material data for MCNP/PHITS code calculation

In this example, a voxel is composed of 65% volume of soft tissue and the rest is bone (based on the CT data). There are six sets of material mixing available and the nearest one is set number 4 (60%:40% of soft tissue and bone volume fractions, respectively) and it is automatically assigned to the voxel.

4. COMPUTATIONAL BNCT DOSE

The BNCT dose computation conducted in a treatment planning system is an important part of the system. Unfortunately, there is still no global standard procedure for BNCT dose computation, that is, each institution has its own procedure which is not necessarily identical with other institution.

Here, an example of BNCT dose calculation procedure is given (JSNCT 2011). The absorbed dose components of BNCT are illustrated in Fig. 5, namely, (1) boron-10 dose from $^{10}B(n,\alpha)^{7}Li$ reaction (D_B), (2) hydrogen dose from $^{1}H(n,n')p$ reaction (D_H), (3) nitrogen dose from $^{14}N(n,p)^{14}C$ reaction (D_N) and gamma dose (D_G). The gamma dose can be further divided into two components, the one from the primary beam source and the one (secondary) from $^{1}H(n,\gamma)^{2}H$ reaction.

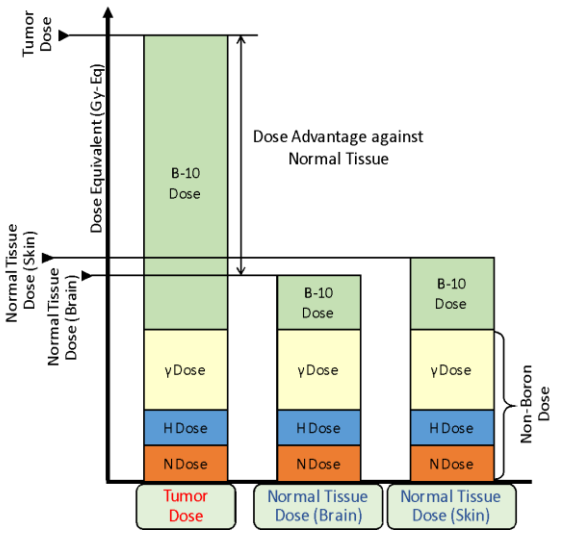


Fig. 5. BNCT dose components

As shown in Fig. 5, during BNCT we expect that the tumor dose should be much

higher than the one of the normal tissue dose. In other words, the treatment planning system should obtain the maximum dose advantage shown in the figure.

Fig. 6 shows the BNCT equivalent dose (Gy-Eq) equation and the recommended weighting factors. The boron-10 dose depends on the compound biological effect (CBE) for tumor, normal and skin tissues. Furthermore, the CBE depends also on the boron delivery agent (drug) type. At present, there are two choices of delivery agent, namely, sodium borocaptate (BSH) and boronophenyl-alanine (BPA). The other doses components use relative biological effectiveness (RBE) which does not depend on the delivering agent.

$$C_B \times D_{Bppm} \times CBE_B + D_N \times RBE_N + D_H \times RBE_H + D_G \times W_G$$

RBE, CBE		BPA	BSH
Boron	Tumor	3.8	2.5
	Normal	1.35	0.37
	Skin	2.5	0.8
Hydrogen (Fast)		2.5	
Nitrogen (Thermal)		2.5	
Gamma		1	

C_B: B-10 Concentration(ppm)
RBE: Relative Biological Effect
CBE: Compound Biological Effect
BPA, BSH: Boron Delivery Agents

Fig. 6. BNCT absorbed dose equivalent calculation

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