BDTPS: THE BNCT TREATMENT PLANNING SYSTEM JOINTLY DEVELOPED AT DIMNP AND JRC/IE

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SUMMARY

The idea to couple the Treatment Planning System (TPS) to the information on the real boron distribution in the patient is the main added value of the new methodology set-up at DIMNP of University of Pisa, in collaboration with the JRC of Petten (NL). The methodology has been implemented in the new TPS, called BDTPS (Boron Distribution Treatment Planning System), which takes into account the actual boron distribution in the patient brain, while the standard TPS assumes a uniform boron distribution, absolutely far from the reality. Nowadays, Positron Emission Tomography (PET) is able to provide this *in vivo* information.

The new TPS, based on the Monte Carlo technique, has been validated comparing the main BNCT parameters (thermal flux, boron dose, etc.) as measured during the irradiation of a special heterogeneous boron phantom (HEBOM), *ad hoc* designed, as calculated by the BDTPS and by the standard TPS SERA. An evident SERA overestimation of the thermal neutron flux, as well as the boron dose, has been detected. On the other hand, BDTPS response is in good agreement with the calculation results obtained using a MCNP analytical model.

Hopefully, this study is the starting point for future improvements in the TPS research and will be followed by similar works, with the aim to confirm that PET-based TPS methodology represents the next frontier in the BNCT applications.

Introduction

The success of Boron Neutron Capture Therapy (BNCT) of inoperable cancers, such as gliomas and astrocytomas (III and IV grade) will be a milestone in the fight against tumours. This success is strictly related to the proper combination of several research aspects: nuclear physics and engineering, medicine, pharmacology, dosimetry, informatics and molecular imaging.

In the last twenty years several improvements have been achieved in BNCT, which permitted to start patient trials, after encouraging *in vivo* and *in vitro* tests. In particular, the synthesis of new boron carriers, the developments in clinical tolerance studies of the healthy tissue, the application of neutron transport calculation codes to the patient's organ geometry and the definition of the real macroscopic boron distribution in the tumour and healthy tissue are only the main items of a long list of improvements.

Nevertheless, one of the problems, which still needs a solution, is the proper definition of the ^{10}B distribution in the cancerous, as well as in the healthy, tissues. Recent excellent research studies demonstrated the possibility to acquire information on the boron distribution *in vivo*, making use of sophisticated diagnostic machines, such as the Positron Emission Tomography (PET). Several scientists have been involved also in trying to apply Magnetic Resonance Imaging to the ^{10}B localization, but the small magnetogyric ratio of both ^{10}B and ^{11}B compared to hydrogen makes them much less sensitive to magnetic resonance detection [1].

In particular, the synthesis of the ^{18}F-^{10}B-FBPA, performed independently at the Prefectural University of Medicine in Kyoto [2] and at the University of Tennessee [3] in 1996, should be really considered a milestone in BNCT research. It allowed the starting of a new field of research: **the development of the BNCT Treatment Planning System (TPS) based on the PET boron distribution data**.

The BNCT group of DIMNP has been involved in this activity since 1996, firstly demonstrating the feasibility of the PET-based TPS. That work led to the development of a new software, whose main feature was to provide a pre- and post-processing suite for managing the Monte Carlo calculations necessary in a BNCT-dedicated treatment planning. This system, named CARONTE [4], has been referenced in scientific articles as "an interesting approach to space-dependent boron quantification

and modelling, that is based on labelling of the administered boron compound with a suitable positron-emitting radionuclide" [5].

Actually, the idea of linking the treatment planning system with the boron data acquired through the PET scanning was also developed by other scientists at the University of Tennessee, as a natural consequence of the research related to the synthesis of the ^{18}F targeted BPA. They used SERA, the most used TPS, developed at INEEL [6]. However, it is not clear the procedure followed by these scientists for linking the output of SERA results with the PET boron data [7]. Two possible ways can be followed in that work:

- The first uses the thresholding technique available in SERA package, which permits to define semi-automatically several macro-regions grouping the pixel values in user-defined intervals. The more the intervals that are chosen by the user, the longer is the process. Therefore, this approach should be completely inadequate in case of intervals definition at the pixel level.
- In the second way, the output of SERA is simply multiplied to the PET boron data, which should be prepared in a way compatible to the SERA outcome. In this case the post-processing of the SERA data should be done by an auxiliary software, external to the SERA package. The main drawback of this approach is the difficult use of co-registration between the PET and CT images stack, which is fundamental if a precise overlapping is required. However, recent updating work has been done in order to solve this co-registration problem, making use of the Statistical Parametric Mapping Algorithm (SPM99) developed by the Welcome Department of Cognitive Neurology in London, UK [8].

The second solution, having the unavoidable drawback to be an external patch to the main program SERA, is similar to the work presented in this paper. However, every future upgrade of SERA can cause problems in code applications.

Materials and Methods

After the feasibility study [9], it was clear that the natural follow-up of that activity would have been the development of clinically oriented treatment planning system based on the PET boron data. The main goal of this work was exactly focusing on this development, taking into account the most important specifications associated to a TPS designed for clinical use. Inheriting the CARONTE experience, a new treatment planning system has been developed, tested and validated: **BDTPS** or **B**oron **D**istribution **T**reatment **P**lanning **S**ystem [10].

The main advantage of BDTPS is that it constitutes a stand-alone integrated system, which does not depend on the upgrade of other programs, still in developing phase, such as SERA. It is true that BDTPS makes use of the well-experienced Monte Carlo code MCNP, developed at Los Alamos National Laboratory, but this code has demonstrated in the past a perfect inheritance passing from one release to another.

During BDTPS development a great care has been taken in order to include the main parameters necessary in a complete clinical treatment planning. The definition of the fiducial markers and the organs at risk represents an example: the fiducial markers, together with the beam centreline entry and exit points, define uniquely the position of the patient during the treatment, according to what previously optimised through the TPS calculations. The evaluation of the dose released to the organs at risk is another important step in the TPS: an irradiation plan should release as much energy as possible to the tumour region, saving at the same time as much as possible the surrounding healthy tissue. This compromise should be monitored, especially in some radiosensitive organs, called *organs at risk*. Some of them are the inner ears, the eyes, the salivary glands, the pituitary glands, the optic chiasm and the thalamus vessels.

Apart from these features, which are almost standard and comprised in all the clinically oriented treatment planning systems, BDTPS has been thought out in order to deal with the proper ^{10}B localization into the Monte Carlo neutron transport and dose evaluation.

The main BDTPS added value is the implementation of a software architecture based on three strictly dependent models, named the *3D*, the *Monte Carlo (MC)* and the *Boron (B) models*.

The 3D model is constructed through the CT slice of the patient's organ (for example, the head in the present Petten "glioblastoma multiforme" trials). The pixel-based *3D model* contains the regions to be evaluated during the Monte Carlo simulations. Each region is assigned its own unique identifier (ID), which serves as reference for the automatic reconstruction of the Monte Carlo model. Therefore the *MC model* is also pixel-based. The big advantage of this approach is the best achievable preciseness. On the other hand, it creates some problems from the calculation time point of view.

The speed of the TPS is a very important issue. A clinical TPS is expected to perform the calculation in less than one hour. This is quite easy in the case of photon therapy, because the interactions of the photon in matter are regulated by physics definitely simpler than the neutron ones. In particular, in BNCT four main nuclear reactions have to be considered during the irradiation: the boron, the hydrogen and the nitrogen thermal neutron capture reactions and the proton recoil reaction, due to the neutron slowing down process.

However, several improvements have been achieved in the recent period in the acceleration of the Monte Carlo neutron transport. For example, a speed-patch-tally has been developed by MIT and LANL scientists [11], in order to upgrade the tracking speed with MCNP-4B. Moreover, MCNPX, the extended version of MCNP, contains a special type of tally, called *mesh tally*, which enables an acceleration up to 10000 times in comparison to the standard lattice tally [12]. It seems that the next version of MCNP and MCNPX will contain a further tracking speed acceleration in the *standard lattice tally* of an order of magnitude compared to the mesh tally. For this reason, as the MCNP as the MCNPX input structure have been maintained in BDTPS version 1.0.

In both cases, the geometry is defined using a lattice grid, based on the region IDs assignment, independently from the PET boron distribution. In fact, it has been demonstrated in previous works [13] and also during the validation of BDTPS, that the boron concentration does not influence the neutron transport, even though sharp spatial differences of the boron concentrations are present in small volumes. Presumably, the situation could change if relatively big volumes of different boron concentrations are evaluated. On the other hand, this situation seems quite unrealistic, at least taking into account the dynamic biodistribution studies performed through PET scanning [2].

For this reason, the previous CARONTE approach, based on the ^{10}B-dependent Monte Carlo modelling [4], has been changed. This reduced the number of materials to be used during the Monte Carlo simulation and, consequently, the calculation time. Besides, using that boron-dependent structure, it would have been impossible to achieve the huge amount of calculation cells, required by the pixel-based 3D reconstruction method; in fact, not more than 999 independent transformed "universe" cells can be defined in MCNP geometry.

However, the option to assign a boron concentration to each macro-region is maintained in BDTPS, in order to take into account the boron affection on the neutron transport in case of very large region definition.

The PET boron data is collected in a data structure, called *B model*, which should be perfectly coupled to the MC model, because the combination of these two models provides in the post-processing the proper evaluation of the boron dose distribution. The idea of using three completely correlated models should be considered one of the main BDTPS improvements.

Results

As said, the development, test and validation of BDTPS constituted the main goal of this work. The test and the validation of such system required the use of an *ad hoc* phantom, characterised by a "stressed" heterogeneous boron distribution. This new phantom, called **HEBOM** (**HE**terogeneous **BO**ron phanto**M**), was designed taking into account the measurements space requirements and the heterogeneous boron distribution definition. Due to these conflicting issues, HEBOM is to be considered a compromise solution, which worked, however, properly to the purpose.

HEBOM is filled with four PMMA layers, which house several vials, containing sharply different boron concentrations. The phantom model was thought for:

1. Monitoring the effect of a heterogeneous boron distribution on thermal neutron flux and boron dose.
2. Monitoring the effect of the heterogeneous boron distribution on the beam penumbra.
3. Offering measurement points for validating BDTPS.

The first issue has confirmed the results of previous calculations: the boron heterogeneity in small volumes does not influence the neutron flux and, therefore, it can be neglected during the neutron transport. Figure 1 shows the thermal neutron flux along the top PMMA layer centreline, which contains the maximum boron concentration (100 ppm). Flux measurements indicate that the behaviour is independent from the boron presence in the vials.

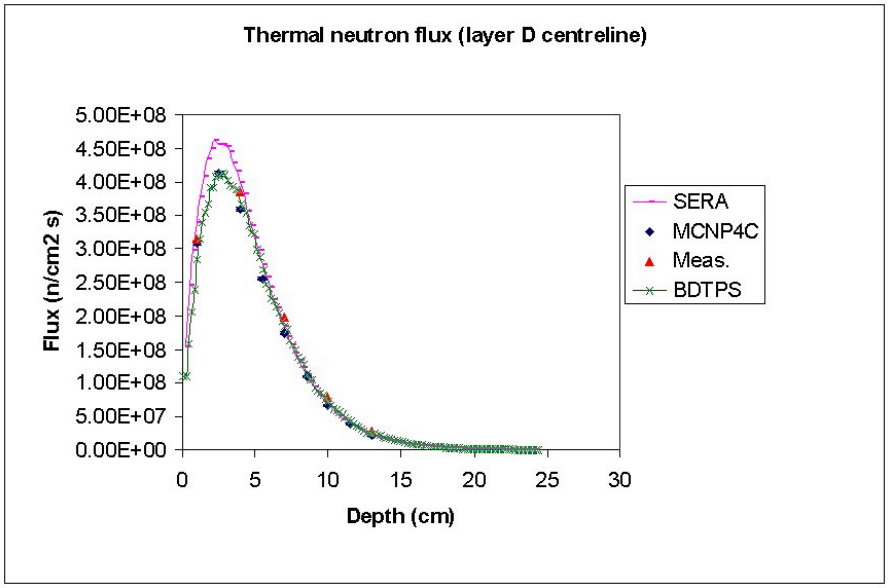

Fig.1. Thermal neutron flux along the HEBOM top layer centreline. Calculations have been made using SERA, MCNP-4C3 and BDTPS. Measurements checked the calculation results in specific points

The second issue has shown the same results of the first one, as the lateral behaviour of the neutron flux seemed not to be influenced by any boron difference.

Finally the third item needed the CT and PET scanning of HEBOM. Both have been performed in Pisa (Italy), while the HEBOM irradiation was done in High Flux Reactor (HB11 beam) at Petten.

The HEBOM CT images served for the *3D model* reconstruction, while the PET images constituted the basis for the *B model*. Figure 2 shows the BDTPS *3D Model* of the HEBOM vials and its positioning with respect to the beam centreline.

The BDTPS validation through the HEBOM measurement campaign was integrated with calculations made using SERA and MCNP-4C3.

SERA was used as reference treatment planning system, being pixel-based like BDTPS. However, due to the uncertainties related to the application of a standard TPS to the heterogeneous boron

phantom, we decided to find a confirmation of the results through an analytical model, using a well-experienced Monte Carlo code (namely MCNP-4C3).

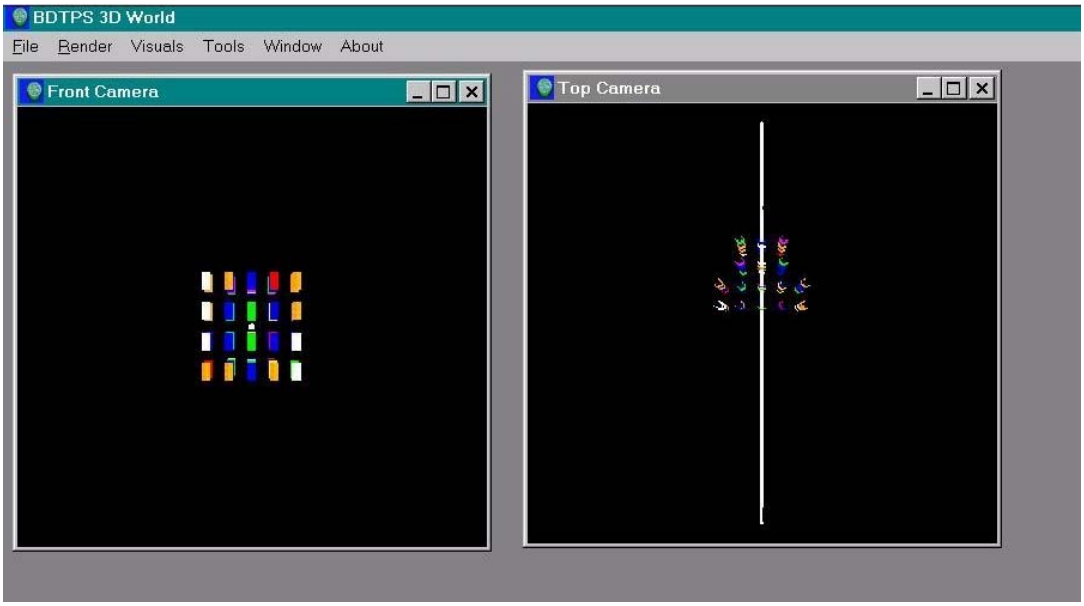

Fig.2. BDTPS 3D Model of HEBOM vials and its positioning with respect to the beam centreline

The outcome of this validation exercise is extremely interesting, because it has demonstrated the difficulty for a standard TPS to follow the boron dose distribution as more boron heterogeneity is approached. In fact, SERA overestimates the thermal neutron flux on the first HEBOM surface (see Fig. 1). Consequently, it overestimates also the boron dose along the same layer D centreline (see Fig. 3)

In addition, a definitely wrong approach to the boron heterogeneity was encountered in the SERA algorithm of the isocontours generation. This algorithm creates the isocontours before the plan definition, which is the step when SERA assigns different boron concentrations to each region. This means that the isocontours are represented on the grounds of the unprocessed data, which are calculated with the hypothesis that a uniform 1 ppm ^{10}B is distributed everywhere. Boron isodose contours have been generated even when there was no boron. For example, this happened on the beam centreline HEBOM layer, which is only made by PMMA and no boron vials are present.

This evident bug was not reported until now because, at least, in the Petten BNCT protocol, there is no different boron concentration between the various regions (tumour and normal tissue) at the beginning of the calculation. Afterwards, using the T/B ratio, the tumour and normal tissues are differentiated, supposing that the boron is present in both of them. On the other hand, this bug does not affect the remaining isodose and isoflux contours.

Taking into account the difficulty to rely completely on the SERA outcomes, an analytical model of HEBOM was manually built. This model was also constructed in order to check the proper operation of BDTPS. In fact, both models use the same Monte Carlo engine and it is expected a very similar behaviour for the main BNCT parameters, if BDTPS works properly in the three models preparation. A complete agreement was found between the results of BDTPS and the analytical model in all HEBOM layers and in all the monitored parameters, such as the boron dose, the thermal neutron flux, the proton recoil dose and the total gamma dose.

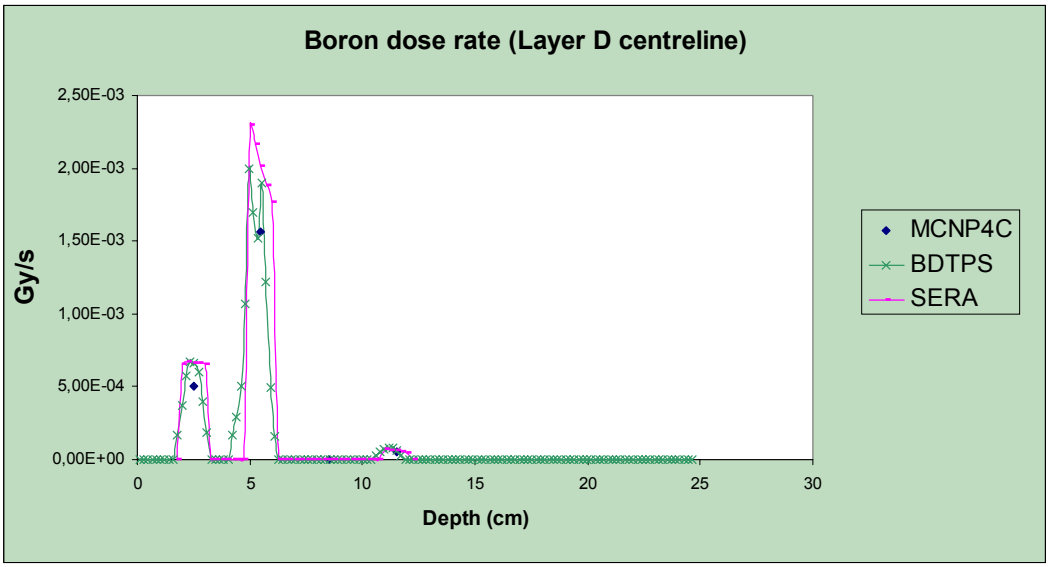

Fig.3. Boron dose rate along the HEBOM top layer centreline

Conclusions

The development, test and validation of BDTPS, this PET-based treatment planning system, required a burdensome informatics and programming effort in the last years. It is worth to mention, just for comparison, that the SERA project was started in 1996, with the first introduction to the community in 1998, at the La Jolla BNCT Symposium. There have been four full-time people at INEEL working on it, either for development, validation, or both. Approximately 8 MSU graduate students worked on it at various times. In addition there were many people in the BNCT community who helped with benchmarking and QA.

Taking into account the huge difference between the resources devoted to BDTPS and SERA projects, it should be comprehensible why improvements still need to be added to BDTPS version 1.0. However, BDTPS is up to now the only *integrated TPS package* able to evaluate the boron dose, based on the real macroscopic boron distribution acquired through PET scanning.

In any case, the presence of another important University Institute working on this subject is a tangible signal of the increasing interest towards the PET-based treatment planning systems in the last period. This could be seen as a demonstration that the initial idea of coupling PET and TPS [4] was scientifically valuable and it constitutes another impulse to proceed in this direction.

The main goal of this work was focused on the demonstration of the correct operation of the system and its validation through measurements and reference calculations. It can be stated for sure that this goal was achieved. Hopefully, this new tool will be applied and further validated in the Italian BNCT research project [14], this work being part of it.

A relatively good agreement was found between BDTPS and the measurements, although some discrepancies appeared due to an improper neutron and photon source definition. Actually, this problem is already well known at Petten and several calculations and measurements are in progress. In particular, a measurement campaign will be organized in the near future in order to check the fast neutron tail of HB11 spectrum, using the superheated drop detectors [15].

Apart from small discrepancies, BDTPS has successfully passed the HEBOM test. In some cases, like the boron dose evaluation, it has demonstrated a more precise behaviour in comparison to the standard SERA TPS.

At the moment, the calculation speed seems still an issue, but great improvements are expected using a proper powerful machine and the standard speed-patch tally already declared for the next MCNP version.

Starting from this work, future BNCT protocols based on PET data (or another similar boron detection technique) can definitely help in reducing the errors associated to the treatment planning. Actually, the main added value of this work is the demonstration of the feasibility of PET-based BNCT as a new methodology for affording the complex boron heterogeneity and its correlation to the treatment planning evaluation. The development of new fast Monte Carlo algorithms and the production of more and more powerful calculation machine, as well as the optimization of the 3D reconstruction algorithm, should offer also the possibility to make very fast calculations at the same level of the standard radiotherapy.

Hopefully, this will be followed by similar works, which will confirm that PET-based treatment planning systems represent the next frontier in the BNCT applications. A TPS able to respond properly to the heterogeneity of the boron distribution is the key for successful Boron Neutron Capture Therapy.

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