PET and MRI based treatment planning systems: a methodology for a realistic evaluation of the dose and fluence distributions in BNCT and in GdNCT

N Cerullo\textsuperscript{1,2}, G G Daquino\textsuperscript{3} and D Bufalino\textsuperscript{1}

\textsuperscript{1}DIMNP, University of Pisa, Via Diotisalvi 2, 56126 Pisa (Italy)

Email: d,bufalino@tiscali.it

\textsuperscript{2}DITEC, University of Genova, Via All'Opera Pia

Email: cerullo@docenti.ing.unipi.it

\textsuperscript{3}JRC (European Commission), PO Box 2, Westerduinweg 3, 1755 ZG Petten (NL)

Email: giuseppe.daquino@jrc.nl

Abstract. The article focuses on the methodology for a realistic evaluation of the dose and fluence distributions in Neutron Capture Therapy (NCT), based on the Treatment Planning System (TPS) that takes into account the real macroscopic distribution of the neutron capturer. The neutron capturers considered in the present study are \textsuperscript{10}B and \textsuperscript{157}Gd, used in BNCT and GdNCT respectively.

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1. Introduction
Neutron Capture Therapy (NCT) is based on the idea to use a specific element characterized by a high neutron capture cross section. This property gives the chance to destroy selectively the tumour target as long as the element is located exactly in the proximity to the tumour cells. Therefore, NCT is a bimodal therapy because two parameters should perfectly match: a suitable neutron spectrum and a selective neutron capturer carrier, able to bring the element just near the tumour region.

Shortly after the discovery of the neutron by J. Chadwick [1] and the description of the \textsuperscript{10}B (n,\alpha)\textsuperscript{7}Li-reaction by Taylor and Goldhaber [2], the basic idea to use neutron capture reactions in cancer treatment was published by Locher [3].

The neutron capturer is often an element with a high cross section in correspondence of the thermal energies (about 0.025 eV). It is often associated to specific drug, able to arrive till the tumour region preventing huge concentrations in the healthy tissue. The essential experimental work and all clinical approaches in NCT are based on \textsuperscript{10}B (BNCT), mostly on glioblastoma multiforme. However, during the last years an increasing attention has been focused also on \textsuperscript{157}Gd (GdNCT).

Unfortunately, the present tested drugs used in the therapy cannot provide a very high distribution ratio between the tumour and healthy tissue. Therefore, the expected benefit from the NCT is dramatically limited by this drawback, because the dose due to the neutron capture is delivered also to the healthy tissue in remarkable amount.
The neutron spectrum depends on the type of tumour: an epithermal spectrum is more adequate for deep tumours because the neutrons are able to penetrate more in the surrounding healthy tissue leaving a limited energy. On the other hand, swallow tumours require the use of thermal neutrons that are captured immediately on the surface of the organ to be treated.

The main doses involved in NCT are due to:

1. the neutron slowing down process; this is associated to the $^1\text{H}(n,n')$, that is due to the inelastic scattering produced by the high quantity of hydrogen present in the human body;
2. the neutron capture reaction of the nitrogen, that is $^{14}\text{N}(n,p)^{14}\text{C}$;
3. the neutron capture reaction of the hydrogen at the neutron thermal energy, i.e. $^1\text{H}(n,\gamma)^2\text{H}$;
4. the neutron capture reaction of the element chosen for the therapy (therapeutic dose).

Since the first proposal of Locher [3] and following his suggestions, several studies have been performed to analyze the best neutron capturer for NCT. Most of the isotopes proposed are characterized by high toxicity of the fission products.

At first, the most suitable element for such studies appears to be the $^{10}\text{B}$, for several reasons:

1. It is not radioactive and it represents the 20% of the natural boron composition.
2. The secondary particles emitted by $^{10}\text{B}(n,\gamma)^7\text{Li}$ have high Linear Energy Transfer (LET), therefore they deliver their energy in a very short range (of the order of the cellular diameter).
3. The boron chemistry is well known and this permits an easier link of the element to the carrier.

Later on it was decided to test also the use of gadolinium, that, in fact, offers several advantages; in particular, the extremely high neutron capture cross section at thermal energy that implies a huge dose delivery in proximity to the tumour region.

The spectrum of the secondary particles emitted by the gadolinium is quite complex and, among others, the presence of strong $\gamma$ spreads out the dose delivery to a broad region (also in the healthy tissue), loosing the selectivity of the therapy.

However, Auger and IC electrons are also emitted after the Gd neutron capture and are characterized by a short range and high LET. Therefore, they contribute consistently to the local dose (tumour dose) delivery in GdNCT.

The transport of epithermal neutrons is most sensitive to the shape and composition of the patient's body and involves a complex assortment of radiation components having different biological weighting factors which therefore need to be considered separately. $^{10}\text{B}$ and especially $^{157}\text{Gd}$ in tissues may cause significant thermal neutron flux depression which in turn influences most of the other radiation components. Finally, because the $^{10}\text{B}$ carrier has a concentration/time profile that is different in each patient, in those facilities which have relatively weak epithermal beams (where irradiation times are long) on-line monitoring of the $^{10}\text{B}$ concentration in blood is necessary. For these and other reasons, most practitioners have decided to utilize the Monte Carlo simulation technique for BNCT computed treatment planning.

By simulating the interactions of radiation with tissues, Treatment Planning Systems (TPS’s) provide physicians with precious quantitative data that are used to fix the relevant parameters prior to irradiation (e.g. optimal irradiation time and patient positioning). These systems are therefore essential to perform appropriate therapeutic treatment, ensuring that the dose to healthy tissues will remain within the right limits. Particularly, all TPS’s currently employed in BNCT trials are based on the reconstruction (by CT and/or MRI) of a 3D model of the patient head. This model, with the introduction of data on the boron distribution, is implemented in a computer code, which then simulates the interaction of radiation with tissues, computing the spatial distribution of the dose delivered to each anatomical structure.

The standard approach in the TPS foresees the definition of the tumour and the healthy tissue regions on the CT or MRI images. A Monte Carlo model is automatically set up in order to perform the simulation of the treatment. At the moment, there are several TPS’s in use in BNCT. Most of them make use of a Monte Carlo engine for the simulation of the nuclear reactions during the irradiation. For example, NCTPlan [4] uses MCNP [5], SERA [6] has rtMC [7] in the background. Because the added value of these therapies consists of the use of a neutron capturer, the knowledge of the isotope ($^{10}\text{B}$ or $^{157}\text{Gd}$) distribution in the simulation is a key element to reproduce faithfully the real dose delivery. It is important to note that in this approach only two values of boron concentration (estimated mainly on the basis of blood sample analysis) are assumed to be uniformly distributed in tumour and healthy tissue, respectively [8]. This situation was
dictated by the absence of any other information on the real *in vivo* distribution of the boron in the patient head.

2. Ideas, materials and methods

Positron Emission Tomography (PET) is a functional imaging technique that allows the *in vivo* investigation of metabolic processes. This is made possible by linking a positron-emitting nucleus to the molecule of the substance (labelling) whose biological kinetics must be investigated.

The synthesis of the $^{18}$F-BPA has induced several scientists to put their attention on a PET-based BNCT. In particular, at the Kyoto Prefectural University of Medicine [9] (Japan) and contemporarily at the Departments of Radiobiology and Neurosurgery [10], University of Tennessee Medical Centre (USA) two groups of scientists have independently labelled boronophenylalanine (BPA) with $^{18}$F atom (a positron emitter). They developed a model to estimate the $^{10}$B concentration value from the counts associated to each voxel by the PET tomographer [9].

The $^{18}$F-BPA is infused into the patient, who later undergoes scanning. The PET scanner can detect the radiation emitted when a positron-electron annihilation reaction occurs and ascertains the location of this reaction.

These studies showed that the $^{10}$B, used in BNCT, diffuses heterogeneously throughout the whole brain, without a clear distinction between tumour and healthy tissue. This consideration leads to a PET-based approach, that differs from the actual protocol based on the hypothesis of uniform two-zones boron distribution. In these studies important parameters for treatment planning have been achieved, such as the optimisation of the treatment time, the optimisation of the infusion protocol and the determination of the cellular-level distribution of boron.

Consequently, the idea to couple the treatment planning system with the boron distribution data acquired through PET scanning has been circulating in the BNCT scientific community. In particular, the BNCT Group at DIMNP of Pisa University (Italy) has collaborated with the Joint Research Centre (JRC) of Petten (The Netherlands) in order to design and implement this different approach to the TPS. Our idea was to link the PET data, related to the *in vivo* boron distribution, to the 3D modelling to make a realistic Monte Carlo (MC) simulation. This idea led to the development of the original prototype software CARONTE [11]. This code contained a pre-processing module that received in input the PET images and prepared the input file for the MC simulation. Then a post-processing module provided some simple visualization tools for the analysis of the results. CARONTE was employed to carry out a comparative study between the standard and the PET-based approach [12].

However CARONTE built a simplified geometrical model of the patient’s head for the MC simulation (a Snyder phantom, widely used in this field since early NCT TPS studies), in which the appropriate boron concentration value was computed at the location of each voxel. A natural follow up of the CARONTE experience was the improvement of the PET-based TPS methodology and the development of a real TPS, which contains both the standard tools and the connection to the boron data acquired through the PET scanning. The new TPS is called Boron Distribution Treatment Planning System (BDTPS) [13,14] and is written in Visual C++. Among other features, a 3D modelling module is added, devoted to the geometrical 3D representation of the patient head starting from the CT slices, more realistic than the simpler Snyder phantom.

BDTPS is a software package whose task is to simulate the BNCT irradiation of the patient’s organ, assuming a given set of positioning and beam parameters, and to compute the three-dimensional spatial distribution of the dose delivered to tumour and healthy tissue. The procedure through which this is accomplished includes several steps:

- acquisition of a 3D data set describing the anatomy of the region to be irradiated, by CT or MRI;
- processing of the aforementioned data set to automatically build a 3D (*geometric*) model of the region’s anatomy. In this model the user defines different regions, i.e. volumes identifying anatomical structures (e.g. target, organs at risk, etc.) which are of special interest in the assessment of the irradiation efficacy. In this step a description of the materials of each structure (mass density and nuclear composition) is also given.
- Acquisition of a 3D data set describing the *in vivo* spatial distribution of the boron carrier in the region to be irradiated.
- Processing of the aforementioned data set to automatically build a boron model which will be used to compute the dose at a later stage.
• Processing of all the above mentioned data structures to define a Monte Carlo model, i.e. a description (in MCNP or MCNPX syntax) of all the relevant information that the radiation transport code will need in order to perform the simulation. This model, in analogy with the medical imaging data sets it is derived from, describes the region of space physically containing the patient’s organs as a 3D matrix of cells (voxels), each filled with a given material.

• Simulation of the irradiation and computation of the dose delivered to each cell on the basis of the real spatial distribution of the boron-carrier, stored in the boron model described above.

• Display of the spatial distribution of the computed dose values as 2D maps (on the plane corresponding to each CT/MRI slice) or 1D profiles along a line of arbitrary orientation, but parallel to the CR/MRI scanning planes.

Figure 1 shows the main components of the PET-based approach to TPS. The default BDTPS calculations are referred to the main doses and fluences to take into account in BNCT:

• neutron fluence (thermal, epithermal, fast and total),
• photon fluence;
• boron dose;
• hydrogen neutron capture dose (or gamma dose);
• proton recoil dose;
• nitrogen dose.

The nitrogen dose is always calculated, due to the presence of air all around the 3D model voxels.

The kerma factors used for the photon dose calculations are reported in ICRU-46 [15], while the kerma factors used for the proton recoil and nitrogen doses are taken from ICRU-63 [16]. Finally, the boron dose is calculated through the kerma factors reported in [17].

Figure 1. Main components of the PET-based approach to TPS.

We are also working around a new version of BDTPS© with the view to apply it at GdNCT, taking into account the metabolic model of the Gd compound. In this approach, MRI scanning provides the necessary information on Gd real distribution in order to be used by BDTPS©, properly modifying the code to this purpose.

As previously mentioned, in the pre-processing module of BDTPS© the boron concentration \([B^{\text{th}}]_{ij} \, \mu g/g\) in the voxel at the location \(ij\) of image \(k\) at time \(T\) is evaluated proportionally to the count value \(C_{ij}^{th}\) associated to the voxel:
where $K(T)$ is a parameter whose value is computed through a semi-empirical model, taking into account the total quantity of injected BPA, metabolic processes and measured blood activity [9].

In the future BDTP5© application to GdNCT, the gadolinium distribution is acquired through Magnetic Resonance Imaging (MRI). However it is very difficult to carry out quantitative measurements with Nuclear Magnetic Resonance (NMR). In fact the NMR signal does not depend only on the amount of resonant spins in the voxel, but on many other parameters such as relaxation times, spin-spin interactions and so on. Gd is characterized by different relaxation times related to the biological environment where it is located. The Gd relaxation time in the blood is different from that in the tumour. It is however possible to measure all this parameters to recover a reliable quantitative value. This requires many experimental tests.

As a first guess we have assumed a logarithmic correspondence, according to the Fechner-Weber law:

$$\left[ B_{ijk}^{10} \right] (T) = K(T) \cdot C_{ijk} (T)$$

$$\left[ Gd^{158} \right]_{ijk} (T) = K(T) \cdot \log \left( \frac{S_{ijk} (T)}{S_0} \right)$$

where:

- $[Gd^{158}]_{ijk}$ is the gadolinium concentration ($\mu$g/g) in the voxel located at row $i$ and line $j$ in the $k$-th image of the array of MRI slices;
- $K(T)$ is a parameter whose value is determined experimentally, taking into account the relaxation times, the used impulse sequence, the internal and external magnetic field strength, the total quantity of injected substance and metabolic processes;
- $S_{ijk} (T)$ is the signal strength of MRI image;
- $S_0$ is the base signal strength.

A preliminary validation of the methodology has been performed [18] using a special phantom (HEBOM [19]) able to reproduce as much as possible the heterogeneous boron distribution. In this way, the validation exercise can be considered as close as possible to the real situation, which appears from the PET scanning.

On the other hand, the experimental requirements impose the monitoring of the main parameters during the irradiation, which in turn limits somehow the freedom in the choice of the phantom geometry. For example, the necessity to have inter-space for the insertion of detectors prevents from disposing different boron concentrations very close each other.

HEBOM’s final design allows up to 64 vials to be placed in four layers, containing 8 different boron concentrations. Each vial has different colour depending on its boron content. The decision to colour the vials has been taken in order to facilitate quick vial recognition during the PET loading phase. The vials are located in the centre of the phantom.

All the slabs contain clearance holes (15 mm diameter), between the vials, to host neutron and gamma detectors. Figure 2 shows HEBOM demounted (a) and mounted (b).

Figure 2. HEBOM demounted (a) and mounted (b) in front of the HB11 aperture.
To provide the information necessary to reconstruct the 3D and the boron model in BDTPS, HEBOM had to be scanned with a CT and a PET tomographer.

The measurements have been performed at the JRC, where the 45MW HFR nuclear reactor is present. HEBOM has been irradiated at HB11 Petten and the main parameters (neutron flux, gamma, fast neutron dose) have been monitored using the standard techniques utilized also in the BNCT clinical routine. The positioning of HEBOM has been performed using the standard laser technique, also adopted for the patient’s head positioning. P/N diodes were used for measuring the thermal neutron fluence, while paired Ar(Mg) and TE(TE) ionization chambers measured the fast neutron fluence. The Ar/Mg chambers were used also for the gamma dose evaluation.

3. Results
The BDTPS experimental validation, performed through the HEBOM measurement campaign, was integrated with computational tests made using SERA, MCNP-4C3 and BDTPS©.

SERA was used as reference treatment planning system, because it is pixel-based like BDTPS: However, due to the uncertainties related to the application of a standard TPS to the heterogeneous boron phantom, a confirmation of the results was checked through an analytical model, using MCNP-4C3.

In this paper we present only the results related to the neutron flux and the boron dose on the top vials layer. The results of the comparison between the measurements and the calculations show an overestimation of the thermal neutron flux, calculated by SERA, especially at the entrance of the neutron beam in the phantom. Consequently, also the boron dose rate is overestimated. On the other hand BDTPS calculations are close to the MCNP analytical results in a ±10% range. This confirms the correct operation of the new TPS, taking into account that the MC calculations are performed in BDTPS using the MCNP [5] Monte Carlo engine.

Figure 3 shows the thermal neutron flux along the centre-line of the top layer. SERA overestimates the peak immediately after the boundary face of the phantom. Probably this is due to the method used by SERA to take into account the geometric differences between two adjacent regions. On the other hand, the measurement points and the BDTPS simulation values are quite close.

Figure 4 shows the corresponding boron dose rate; SERA shows a visible overestimation in the 100ppm boron vial, whose centre is positioned at 5.5 cm depth. However, the main reason of this validation was to confirm the correct operation of the new TPS. In particular, BDTPS makes use of MCNP as Monte Carlo engine; therefore, the similar behavior (concerning the thermal neutron flux) of the BDTPS modeling and the analytical model, which is indicated in figure 3 and figure 4 as “MCNP4C3”, demonstrates that the construction of the 3D, Monte Carlo and Boron models in BDTPS works properly.

The differences between BDTPS and MCNP4C3 calculations in figure 4 are due to the assumption on the boron distribution in each single vial. In fact, BDTPS takes into account also the boron micro-distribution in the vial through the PET data, while only a single averaged value per vial can be assigned using MCNP4C3 (and SERA).
4. Conclusions and further developments

The real macroscopic distribution of $^{10}$B in the patient’s organ can be evaluated using the PET technology and a boron compound labelled with $^{18}$F ($^{18}$F-BPA).

The incorporation of this information in a treatment planning system allows the simulation of the treatment in a more realistic manner. The standard approach, based on the assumption that the $^{10}$B diffuses homogeneously in the target and the surrounding healthy tissue, cannot provide results close to the reality. In fact, the comparison between the two approaches has shown an overestimation of the boron dose in the tissues surrounding the tumour [12]. Consequently the treatment planning based on the standard approach calculates a treatment time, which must avoid an over-irradiation of the healthy tissue. But this constraint
could have been overcome because in reality the dose delivered to the healthy tissue is still below the acceptable level. And at the same time this preserves some tumour cells from death.

The PET-based approach to TPS has been applied in BDTPS and a preliminary evaluation of the correct operation has been performed using a heterogeneous boron phantom, called HEBOM. This experimental validation has been accompanied by calculations done with SERA, following the standard approach.

The measurements of the thermal neutron fluence in HEBOM have shown an overestimation of the calculation results, obtained with the standard approach. Besides, the differences are more evident in the regions of HEBOM where the heterogeneous boron concentration is more emphasized. For example this is visible near the vial containing the biggest \(^{10}\)B concentration, that is 100 ppm, surrounded by absence of boron.

This result is in line with the previous comparison [12], based only on a computational exercise. However the geometry of HEBOM is quite different from the real cellular situation. This suggests that the possibility to use more realistic boron distribution maps acquired by means of PET imaging in BNCT treatment planning deserves more consideration and further investigation. BDTPS needs further in vivo experimental validations. These studies are already planned in Pisa making use of implanted cancer cells in rats. After the infusion of \(^{18}\)F-BPA (and Gd-DTPA), the animals will be PET (and MRI) scanned. The modelling will be performed with both BDTPS and SERA.

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