Monte Carlo based treatment planning systems for Boron Neutron Capture Therapy in Petten, The Netherlands

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Abstract. Boron Neutron Capture Therapy (BNCT) is a bimodal form of radiotherapy for the treatment of tumour lesions. Since the cancer cells in the treatment volume are targeted with 10B, a higher dose is given to these cancer cells due to the 10B(n,α)7Li reaction, in comparison with the surrounding healthy cells. In Petten (The Netherlands), at the High Flux Reactor, a specially tailored neutron beam has been designed and installed. Over 30 patients have been treated with BNCT in 2 clinical protocols: a phase I study for the treatment of glioblastoma multiforme and a phase II study on the treatment of malignant melanoma. Furthermore, activities concerning the extra-corporal treatment of metastasis in the liver (from colorectal cancer) are in progress. The irradiation beam at the HFR contains both neutrons and gammas that, together with the complex geometries of both patient and beam set-up, demands for very detailed treatment planning calculations. A well designed Treatment Planning System (TPS) should obey the following general scheme: (1) a pre-processing phase (CT and/or MRI scans to create the geometric solid model, cross-section files for neutrons and/or gammas); (2) calculations (3D radiation transport, estimation of neutron and gamma fluences, macroscopic and microscopic dose); (3) post-processing phase (displaying of the results, iso-doses and -fluences). Treatment planning in BNCT is performed making use of Monte Carlo codes incorporated in a framework, which includes also the pre- and post-processing phases. In particular, the glioblastoma multiforme protocol used BNCT_rtpe, while the melanoma metastases protocol uses NCTPlan. In addition, an ad hoc Positron Emission Tomography (PET) based treatment planning system (BDTPS) has been implemented in order to integrate the real macroscopic boron distribution obtained from PET scanning. BDTPS is patented and uses MCNP as the calculation engine. The precision obtained by the Monte Carlo based TPSs exploited at Petten is considered sufficient for the scope of the project. In order to accelerate obtaining an optimised treatment plan, a study is performed which uses linear programming. In this way the beam weights of a particular set of calculated beams are obtained mathematically.

1. Introduction
The basic concept of Boron Neutron Capture Therapy (BNCT) is that cancer cells are loaded with the isotope 10B. Afterwards the site containing these cells is irradiated with neutrons. 10B and the neutrons are non-toxic. After 10B has captured a neutron, a nuclear reaction takes place and releases two heavy particles, namely an alpha particle (4He) and lithium (7Li). This so-called (n,α) absorption reaction is illustrated in Figure 1.

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According to the energies, the alpha particle and $^7\text{Li}$ nuclei can be regarded as short ranged particles since they travel less than 10 µm in tissue. This range is similar to the size of a human cell and implies that the heavy particles have a high probability to kill or damage the cancer cell. The cell is killed when the alpha or Li particle causes a double-strand break of the DNA. This occurs when a heavy particle travels through the cell nucleus. In the field of BNCT, often the energy spectrum of the neutrons is classified in three parts: thermal neutrons (below 0.5 eV), epithermal neutrons (between 0.5 eV and 10 keV) and fast neutrons (above 10 keV and below 20 MeV). $^{10}\text{B}$ has a high probability to react with thermal neutrons, indicated with $n_{\text{th}}$ in Figure 1. For thermal neutrons, this probability, known as the microscopic nuclear absorption cross section ($\sigma_a$) of $^{10}\text{B}$, is proportional to $1/v$, where $v$ is the velocity of the incoming neutron. For example, the absorption cross section of $^{10}\text{B}$ for 0.025 eV neutrons is 3837 barn and only 6 barn for 10 keV neutrons. However, the neutrons slow down due to interactions with tissue. This means that the starting neutron energy, coming from the source, has to be epithermal or fast in order to become thermal in a deep seated tumour after slowing down.

BNCT is a disease targeted therapy as the neutrons only kill the cells which are labelled with $^{10}\text{B}$. Unfortunately, with the presently available $^{10}\text{B}$ carrier compounds, also healthy cells contain some $^{10}\text{B}$. Besides, human tissue contains certain isotopes that react with neutrons as well. These reactions result in a dose given to the healthy tissue which should not exceed a certain limit, called the tolerance dose. A lot of literature on BNCT has been published, [1] and [2] are just two examples. Although the concept of BNCT might look quite simple, BNCT is still under investigation seven decades after its first proposal. So far, as a maximum achievement, only phase I/II clinical trials are performed with only a relatively low number (a few hundred) of patients involved. After all these years, researchers of various disciplines are still challenged by the three key issues of BNCT: firstly, finding a non-toxic $^{10}\text{B}$ carrier compound, which brings the isotope only into the cancerous cells or at least significantly more than in the healthy tissue. Secondly, a treatment beam has to be designed and constructed that delivers the optimal neutrons at the right location while minimizing the dose to healthy tissue. Thirdly, developing treatment planning (TP) programs in order to predict the dose and/or particle fluxes given to the patients. Since most BNCT treatment beams are reactor-based, the treatment planner has not only to determine the dose induced by neutrons but also from gammas. Most of the gammas already present in the beam are originating from the reactor core. Neutrons induce a dose in tissue due to reactions with $^{10}\text{B}$, hydrogen (giving recoiling protons and gammas) and nitrogen (producing protons). Thus in total there are four dose components.

Since neutrons are involved, the most experienced method of calculating the doses and fluxes in complex geometries from patients is based on the Monte Carlo technique. This paper will discuss the Monte Carlo based TP systems which are used and/or developed at the BNCT facility of the Institute for Energy, Joint Research Centre (JRC) of the European Commission in Petten, The Netherlands. In this facility a phase I clinical trial took place on 26 patients suffering from Glioblastoma Multiforme (GM) which is one of many life-threatening types of brain cancer. An important outcome of this study is that BNCT is a safe treatment modality and no toxicity was observed but the given doses are now considered to have been too low to cause a complete tumoridal effect. In a second trial, patients are treated who have Metastases of Melanoma (MM) in the brain. Although in the few patients treated it is observed that the growth in size of tumour lesions was halted, if not reduced, it is absolutely too early to draw conclusions since the number of treated patients is too low.
As well as discussing the Monte Carlo TP programs used in BNCT Petten, in Section 3 some accompanying studies are discussed which are closely related to this matter.

2. Description of BNCT TP systems

What follows is an overview with descriptions of all Monte Carlo based radiotherapy TP software developed, used and applied in the BNCT Petten facility.

2.1. BNCT_Rtpe

A project was started at the INEEL (Idaho National Engineering and Environmental Laboratory) in 1988 to develop a special-purpose medical image based Monte Carlo system optimised specifically for radiotherapy with epithermal neutron BNCT as the first application. This initial effort led to the collaboration with the University of Utah Department of Computer Science. The outcome of this collaboration was the BNCT.Edit system [3]. In 1994 BNCT.Edit was replaced by an improved system, BNCT.Rtpe (BNCT Radiation Treatment Planning Environment) [4]. BNCT.Rtpe was developed by the INEEL in collaboration with the Montana State University (MSU) Department of Computer Science. This code inherited the experience gained with BNCT.Edit. In addition, new sophisticated characteristics have been implemented, such as the Non-Uniform Rational B-spline (NURBS) approach to image-modality-independent reconstruction of patient geometry from medical images [5]. BNCT.Rtpe is the official TP System for the treatment of GM affected patients in Petten. All the treatments of the patients in the first trial (in all 4 cohorts) have been planned through the use of BNCT.Rtpe. This TPS is able to reconstruct the human head from the CT (or MRI) scans of the patient. The code Bnct_rtpe [6] provides a Graphical Unit Interface (GUI), which helps the user to construct the B-splines related to a number of “bodies”, identified on the image slices. After loading the image data, the bodies are identified by hand (skin, brain and several organs at risk, like eyes, pituitary and salivary glands, optic chiasm). Then, considering the medical prescriptions, the target is identified also on the slices. The GUI provides also the possibility to represent automatically the B-splines generated. In particular, it is possible to represent the bodies produced as separately as in the whole structure. Figure 2 represents all the bodies as plotted in the reconstruction window of Bnct_rtpe. The material composition for the previous bodies is selected from a standard library.

An input file (.input extension), ready to be processed by the transport calculation code connected to this TPS, the rtt_MC, is written, containing the information on the type of beam used (spectrum, flux, and so on). Therefore, this part constitutes the pre-processor of the Monte Carlo transport calculation. After the rtt_MC calculation, the results are presented using three different support programs: XCONTOURS, DOSE and EXCEL. XCONTOURS furnishes also the isodose curves related to the rtt_MC calculation, superimposing them on the CT slice images. The default coordinate reference system used in BNCT.Rtpe is made with the X and Y axis on the CT plane and the Z axis entering the view.

Figure 2. Reconstruction window in Bnct_rtpe.

Figure 3. Boron isodose curves

Figure 4. All components (weighted) isodose curves
Figures 3 and 4 show some examples of the isodose curves related to the physical boron dose and the total weighted dose respectively.

The DOSE program permits to represent the depth-dose curves (weighted and physical doses) related to the centreline of the beam and the dose-volume histograms related to all the regions of the model. The DOSE utility program scans the output file of rtt_MC (.out file); the same file is scanned by EXCEL in order to acquire useful data for further calculations. In fact the dose rate data are inserted manually from rtt_MC into the TP Spreadsheet for the predefined positions (organs at risk). The spreadsheet calculates the irradiation time and the doses for all beam components given a prescribed physical dose at the prescription point.

Another important feature, also present in the other TPSs, is the evaluation of the doses delivered to the so called organs at risk, such as the pituitary gland, the salivary glands, the eyes, the optic chiasm, the inner ears and the thalamus. The positions of the organs at risk are defined by the user during the pre-processing phase. Afterwards, the system calculates the doses and fluences in these check points. Although BNCT_rtpe proved to be a useful and relatively efficient clinical research tool, there was still the need to reduce the computational time further. Accordingly, INEEL and MSU made some studies in the late 90s in order to achieve a significant breakthrough in execution speed reformulating totally the mathematical algorithms. The result of this effort was the development of the completely new SERA TP System in 1998.

2.2. SERA

The SERA (Simulation Environment for Radiotherapy Applications) TP system consists of seven modules that can be run independently. From the first module, which converts a set of CT or MRI images into a specific internal format, to the last one, which displays the computed doses, the SERA system is a stand-alone package. The SERA software can be divided into three main parts, that are:

1. Modelling of the patient’s geometry using manual and semi-automated tools from CT and MRI images.
2. Computation of the dose within the geometric model with SeraMC, the Monte-Carlo-based radiation transport code developed by the INEEL. Actually, this is a subset of routines taken from the old Morse Monte Carlo code.
3. Contouring and display of the computed doses onto the original set of medical images.

SeraModel is the image editor that allows the user to determine either manually or semi-automatically regions of interest through the whole set of medical images. The reconstruction technique used is based on a pixel-by-pixel uniform volume element, named “univel” [7]. The resolution of the model is therefore limited to that of the original medical image, allowing very accurate representation of the patient’s geometry that usual analytical surface representations cannot afford. A list of predefined bodies such as brain, skull, tumour, ventricles, etc. is available and refers to files that contain all the information required for radiation transport (elemental composition, RBE factors of the various dose components, etc.). Several editing modules are available in seraModel for making the completion of this task easier either manually or automatically [8].

A single module, seraCalc, is implemented in the core of the TP system for computing the radiation transport of each field into the univels geometry created from the modules described previously. This interface allows the user to input parameters for creating an input file to the Monte Carlo calculation tool, seraMC.

An important option in seraCalc is the parameter delw, which represents the side of each calculation (or edit, in SERA terminology) mesh cells. By default, SERA assigns to delw the value of 1 cm. The user could, in theory, arrives at the physical size of the CT pixel. However, preliminary calculations done for a validation exercise have shown no visible differences between the coarse (1 cm) and the fine resolution (5 mm), even in the calculation time.

The remaining modules of SERA system deal with the editing and display of the dose components computed by seraMC (also called post-processing phase). seraPlan allows the user to statistically combine up to four fields and/or up to six fractions from several independent seraMC calculations in
order to produce single effective doses. The dose combination is performed by weighting each
specified field dose component by the appropriate weighting factor, source strength, boron
concentration and exposure. The calculated doses, normalised to unit exposure, unit source strength
and unit boron concentration are then edited. seraDose is the dose contouring utility that displays the
two-dimensional isodose curves edited by seraPlan superimposed over the original set of medical
images.

A limitation in the dose representation is that the user cannot see the boron distribution normalized
to the boron dose maximum. On the other hand, the normalization can be referred to the point where the
thermal neutron fluence reaches the maximum. This is important especially in the case of a highly
heterogeneous boron distribution, where there should be no coupling between the boron dose and
thermal neutron fluence.

This feature together with the fact that the isodose or isofluence curves are generated by SERA
based on the raw calculation data (before executing seraPlan), is a source of errors. This was
particularly evident in a validation setup, where the boron dose was zero in the point where the max
of the thermal neutron fluence has been recorded (DGIP). In this case, SERA shows a regular concentric
boron isodoses pattern even where there is no boron. This anomaly was discovered during the BDTPS
validation exercise, further described in paragraph 2.4. seraPlot provides integrated control of depth
dose curves and dose-volume histogram plotting utilities.

2.3. NCTPlan

This TP system is used for the patients in the clinical trial concerning melanoma metastases in the
brain. NCTPlan is the last version of a series of TPS designed and implemented at MIT since 1990 [9].
In 1996 MacNCTPlan [10] was released with many features that are still present in NCTPlan.
MacNCTPlan is an interactive TPS coupled to the MCNP4B Monte Carlo radiation transport code
[11]. It can be subdivided into two distinct parts: Part I provides the graphical environment for the
construction of 3D mathematical solid models from 2mm-slice medical images, while Part II furnishes
the environment for determining the dose patterns and for displaying the isodose contours
superimposed on the corresponding CT images of the patient’s head.

As the use of some MCNP features not involved in BNCT calculations increases the run time,
enhancements to the ordinary version of MCNP4B have been performed within collaborative work
between LANL and MIT/Harvard [12].

In the first part of MacNCTPlan, the 3D mathematical model of the patient’s head is created from a
set of 2D images, making use of the voxel reconstruction technique. In this method, each plane of
medical image data is partitioned into squares of regular size before being mathematically stacked to
construct a large 3D array of 11,025 cells of 1 cm$^3$ volume. A material file should be prepared for the
material assignment to each cells of the 3D model. To this purpose, two sets of 256x256x8 bits CT
images are required. The first set is done without the iodinated contrast agent (I- stack) and is used to
determine the tissue type that will make up the material of the 3D model for MCNP calculations. The
second set of images is performed with an iodinated agent (I+ stack) that causes the tumour and
oedema to be more visible on the computed images for the tumour outline process. Gd-enhanced MRI
images can also be used for identifying and locating the tumour and the oedema. This region is drawn
on the slices where it appears and saved in a separate text file to be used with the I- stack of images.

Once the target region has been defined, the user should select with a proper pointing option the region
of interest (ROI), which contains the tumour. The ROI should include areas of soft (tumourous and
healthy) tissue, skull and air. In fact, these are the four available elemental materials that fill the
irradiation volume for the radiation transport calculations. Special care is taken when assigning the
$^{10}$B concentration to the normal and cancerous soft tissue. This operation is called “test study” in the MIT-
Harvard protocol, where tissue samples are taken one week before the BNCT and 2-3 h after the boron
drug infusion. Venous blood samples are taken 10 times during 15 h after the infusion. The blood
samples are analysed through the PGRA, while the tissue samples are frozen in dry ice and analysed
through the alpha particle autoradiography technique. Blood samples are also taken just prior and after
the irradiation. Eventually the last blood measurements can help in properly scaling the blood boron-
time curve. This way, the $^{10}$B concentrations in the soft tissues are assigned, supposing that no boron is
gothing to concentrate in the bone and air.

The source definition is quite simple, as it consists of a virtual plane source in a fixed position in
reference to the 3D model. Therefore, once the user changes the orientation of the beam, the software
supposes that the 3D model remains in the same position, while the source plane definition is going to
be changed. This format imposed by the MacNCTPlan may cause some problems in some beam
configurations.

Once the 11025 cells model is created, a FORTRAN 77 program, called MPREP, provides the
MCNP input deck from a series of files. These files contain all the information required for computing
the doses in the irradiation volume such as the material file, the spatial, angular and energy
characteristics of the neutron and photon beams, the flux tallies and the flux-to-dose conversion
factors (based on the neutron KERMA factors for normal brain) [13] for each desired dose component.
In order to take into account the effect of the binding of individual nuclei on the interaction between
thermal neutrons and the considered materials, $S(\alpha,\beta)$ tables evaluated at 300K for hydrogen in light
water are included for all materials making up the patient’s head model.

MacNCTPlan part II provides the graphical environment for deriving the dose patterns from the results
of the radiation transport calculations performed by MCNP and displaying the results in one- or two-
or three-dimensional form.

MacNCTPlan calculates the dose rate for the whole CT volume. A 3D interpolation process is used
to interpolate the voxel-dose-rate to each pixel of the images, prior to any display [10]. This is due to
the fact that the 1cm$^3$ resolution of the MCNP model is far from the about 1mm$^3$ resolution of the MRI
(or CT) scanning. In this phase, also a Fourier Transformation and a ramp filter is applied to the 3D
dose matrix, in order to reduce the spatial dose gradients due to the Monte Carlo statistic fluctuations.
This adjustment process is quite diffused in the Positron Emission Tomography (PET) images
processing.

Cumulative-Dose-Volume Histograms (DVHs) for arbitrary tumour or normal tissue volumes can be
generated as well. A cumulative dose volume histogram is the distribution of the percent of tissue
volume exposed at or above a certain dose or dose rate within a region of interest.

An interesting feature of MacNCTPlan is the calculation of the maximum dose as a function of the $^{10}$B
concentration for each individual beam orientation. This information can be used for adjusting the
calculated dose rate with the actual $^{10}$B concentration during the irradiation.

MacNCTPlan provides also the effects of a multi-beam irradiation, linearly combining each individual
beam according to its weight (generally defined in function of the beams irradiation time difference).

NCTPlan is the new PC-based version of MacNCTPlan [14, 15]. The necessity to integrate the
entire process on one computing platform and requirements for upgrading the predecessor led to the
development of this code. The object-oriented programming offered several changes in the GUI
(multiple windows for modelling analysis and dose displays, etc.). In view of the integration
philosophy, MPREP has been integrated in NCTPlan. In addition, NCTPlan can superimpose isodose
contours on two orthogonal planes of the CT volume and update these in real-time as the orientation of
the planes changes.

Computational changes have been performed in the material assignment model, where the rounding
procedure not always guarantees that the total percentage of each cell adds up to 100%. In these rare
cases, MacNCTPlan assigns to the current cell, the last admissible mixture calculated, while NCTPlan
searches for the admissible mixture that minimizes the sum of the relative differences (in absolute
values).

Besides, since the image slices are 2 mm thick, 5 images comprise the material information in 1
$cm^3$. To assess which cells do not contain any tissue, MacNCTPlan analyses only the central image,
while NCTPlan inspects all of them. Also changes in the DVH calculating algorithm have been
performed, especially in order to reduce the errors due to the interpolation method. Further
comparisons between these two systems are reported in [16].
2.4. BDTPS

One of the BNCT problems, which still needs a final solution, is the proper definition of the $^{10}$B distribution in the cancerous, as well as in the healthy tissues. Recent research studies have demonstrated the possibility to acquire information on the boron distribution \textit{in vivo}, making use of sophisticated diagnostic machines, such as the 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.

However, the synthesis of $^{18}$F-$^{10}$B-FBPA, performed independently at the Prefectural University of Medicine in Kyoto [17] and at the University of Tennessee [18, 19] in 1996, should be really considered a milestone in BNCT research and allowed for starting a new field of research activities: the development of the BNCT TP system (TPS) based on the PET boron distribution data.

BDTPS (Boron Distribution Treatment Planning System) has been developed at the JRC-Petten (The Netherlands) in collaboration with the University of Pisa (Italy). During the TPS development a great care has been taken in order to include the main parameters necessary in a complete clinical TP. 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 also another important step in the TPS, because 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.

Apart from these features, which are almost standard and comprised in all the clinically oriented TP 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: 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 Petten GM trial). The pixel-based 3D model contains the regions to be evaluated during the Monte Carlo simulations. Like in SERA, each region is assigned its own unique identifier (ID), which serves as reference for the automatic reconstruction of the MC model. Therefore the MC model is also pixel-based. The big advantage of this approach is the best achievable preciseness, but, on the other hand, 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 the photon therapy, because the interactions of the photon in matter are regulated by physics definitely simpler than for neutrons. In particular, in BNCT four main nuclear reactions appear during the irradiation: the boron, the hydrogen and the nitrogen thermal neutron capture reaction and the proton recoil reaction, due to the neutrons 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 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.

The geometry in BDTPS is defined using a lattice grid, based on the regions IDs assignment, which is independent of the boron distribution acquired through the PET scanning. In fact, during the validation of BDTPS, it has been demonstrated that the boron concentration does not influence the neutron transport, even if 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.
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 MCNP model, because the combination of these two models provides in the post-processing the proper evaluation of the boron dose distribution, based on the real macroscopic \(^{10}\text{B}\) localization in the patient tissues.

2.5. Comparison of the TP systems

After the description above, interesting questions are of course whether one of the described TP software provides 'better' results over the others and/or whether one TP program is more user-friendly. To start with the last question: As the reader noticed in the last sections describing the TP programs, the systems used in BNCT are not at a level of what it is expected from a commercial product; because it is rather at a pre-stage. Therefore there are still some bugs in the codes that may cause the computer to hang and which have to be solved. Fortunately, due to this developer/academic status, the source codes of most TP software, the user-interfaces and the program stream can be changed according to the demands of the user. A good example in this context is SERA from INEEL which is well supported. In Petten, the BNCT_rtp code is made more user-friendly by automating partly the sequence of separate programs that has to be started. Also a program is written to process the calculated data such it is immediately presented in the data sheet format as prescribed by the protocols. It is considered as an advantage that in NCTPlan a sequence of buttons positioned at the top level of the program’s window is the same as the sequence of steps that has to be followed in order to make a treatment plan. An advantage of BNCT_rtp, SERA and BDTPS is the possibility to view the geometries in 3D which is not possible with NCTPlan. This feature is useful when checking the direction of the treatment beam before the calculation is started.

Concerning the first part of the question mentioned at the beginning of this section, Albritton and Kiger [20] made a lot of effort to map out the differences in results among the calculation engines of the TP systems. Albritton and Kiger are colleagues from the BNCT group in the United Sates (Massachusetts Institute of Technology and Harvard Medical School) with whom the Petten group intensively collaborates in the MM trial. Compared with a reference, which is a validated MCNP5 [21] dose depth curve of the total biologically weighted dose, the BNCT_rtp and SERA results are up to 7\% larger. The NCTPlan results are based on MCNP4B which show an under dosage of up to 5\%. The BDTPS results are calculated using MCNPX which are equal to the reference within 2\%. The use of MCNP based calculation engines is considered as advantageous while there is a large community who improves the code and cross section data every day. The calculated over or under dosages are not affecting the dose descriptions as given to the patients in the trials. This is because the source descriptions in the codes are adjusted such that they provide the doses and reaction rates as obtained by measurements. The different physical models and/or cross section data in the affected codes are circumvented in this way.

The boron distribution can also affect the boron dose description: studies with a heterogeneous phantom indicated that SERA overestimates up 15\% the boron dose in vial containing 100 ppm of \(^{10}\text{B}\), compared to BDTPS [22].

Last but not least it is mentioned here that the speed of calculating one beam/field is for all calculation engines of the same order. A coarse translation of the computer power of the older Unix systems running BNCT_rtp and SERA to the newer computers running MCNP result in a figure of about 90 minutes per field with similar statistical uncertainty.

3. Applications in order to improve MC based BNCT treatment planning

Closely related to the matters discussed in this paper are the efforts to optimise and speed up the treatment planning for BNCT patients who need an irradiation of the whole brain. This is most often the case in the MM trial where tumour lesions are spread throughout the whole brain. For such plans
many combinations of beams have to be examined and optimised. This optimisation can be applied no matter what TP system is applied.

3.1. Plan optimisation by using linear programming

For BNCT of melanoma metastases in the brain, it has been necessary to calculate the dose distributions in the patient for dozens of possible neutron beams and then to combine manually the different beams by individually weighting and adding them. This time consuming approach eventually gave the required treatment plan, which satisfied the prescription dose. However, by linear optimisation with the Simplex method [23], the optimum weights for a set of beams can be determined mathematically. The objective function to maximise is the minimum averaged physical boron dose in one certain lesion for every set of beams. The maximisation of this objective function is performed under the constraints of certain maximum and minimum dose limits in the organs at risk (OAR) and lesions respectively and restricting the set of weighted beams to deliver an average total weighted dose of 7 Gy in the brain as written in the EORTC protocol 11011 [24]. After iteration, by using the constraint set for the minimum dose in the lesions as a variable and performed for all combinations of the neutron beams, the optimum beams and weights are found for each treatment [25].

3.2. Example set-up and preliminary result

The first attempt for optimising the treatment plan with linear programming was performed on a real case with all dose data of several beams provided by NCTPlan [10], exploited for another investigation at Petten which deals with the applicability of the code Scan2MCNP [26], and which can provide a finer structured geometric model of the patient in MCNP, the patient case mentioned above could be ‘translated’ into a fine structured voxalised MCNP model. Another motivation for this work stems from the fact that in NCTPlan, the report of all dose components relevant to every organ at risk (OAR) and every tumour lesion is also very time consuming. Consequently, as many of these dose values for a number of beams have to be known when starting the optimisation, it was chosen to use the new MCNP geometric model. All dose values in the lesions and OARs can be automatically read from the MCNP tally output file. Figures 5 and 6 show this MCNP model obtained with Scan2MCNP of the patient’s head with all OARs and tumour lesions defined.

![Figure 5. MCNP geometric model of real patient case with the organs at risk.](image1)

![Figure 6. MCNP geometric model of real patient case with the tumour lesions marked.](image2)

![Figure 7. The direction of the 18 beams in the Petten set-up.](image3)

Note that the MCNP model, although only shown in white in Figures 5 and 6, consists of skin tissue, brain tissue, soft tissue and cranium [13]. This specific patient had 21 lesions (Figure 6) of melanoma spread throughout the whole brain with a slight preference for the left side. Ten OARs, as defined in the protocol (e.g. eyes, inner ears, pituitary glands, etc.), are shown on the left in Figure 5. In this example, it was chosen to calculate with MCNP, 18 beam orientations around the head of the patient, positioned on his back; therefore no beam can be aimed at the back of the head in the Petten
facility. In this study, the method chosen to gather the optimum combination of beams with the appropriate beam weights is the Simplex method. The Simplex method is a method for solving problems in linear programming. This method, invented by G. Dantzig, tests adjacent vertices of the feasible set (which is a polytope, such as a point, line segment, polygon, polyhedron, etc.) in sequence; at each new vertex the objective function improves or is unchanged. The Simplex method is very efficient in practice and converges in expected polynomial time for certain distributions of random inputs [from mathworld.wolfram.com]. The whole scheme of object function, inequalities and equalities is solved with Matlab [27] using the optimisation toolbox. As a preliminary result, the total irradiation time decreased by more than 30%, which is advantageous regarding both the pharmacokinetics of the boron in the patient and patient comfort. Investigations are going on whether another definition of the objective function and constraints influences/improves the outcome.

4. Discussion and conclusion

Several Monte Carlo based treatment planning systems have been used, tested and/or developed at the BNCT Petten facility. They played an important role in the irradiation protocols, adopted in this research centre. In particular, BNCT_rtpe has been used in the GM protocol, while NCTPlan has been included in the MM protocol. Apart from the differences due to the specific mathematical implementation, all of them demonstrated to be very helpful within the decision-making process related to the choice of the proper irradiation beam identification. However, all of them are characterized by a long process, most of the time requiring a lot of effort and time from the treatment planner.

To find a good combination of beams manually and to optimise the beam weights is difficult when dealing with patients suffering from lesions spread throughout the whole brain. The advantage of the Simplex method is that the treatment planner can focus on the comparison of different sets of beams for which it is known that each combination is the best possible configuration concerning the beam times. Previously, most of the available treatment planning time was spent on weighting each beam correctly for a certain combination and only a few different sets of beams could be investigated. Future studies will deal with testing and applying other possible optimisation schemes and investigating how to calculate more quickly many different beam locations and orientations. Linear optimisation has provided useful beam combinations, which were never considered before. In comparison with treatment plans obtained earlier for patients with many lesions, a reduction of the total irradiation time of 30% can already be achieved. A shorter treatment time in BNCT is favourable, not only for the comfort of the patient but also for the fact that the boron concentration in the tumours decreases with time.

Finally, a specific TPS has been implemented at the JRC-Petten with the main aim to integrate the real $^{10}$B distribution into the Monte Carlo model. BDTPS has been validated with a specific phantom geometry containing heterogeneous $^{10}$B distribution. The irradiation of the phantom has been simulated with SERA and MCNP-4C. The main results of its validation [22] have shown that the thermal neutron flux along the centreline is evidently overestimated by SERA. This is probably due to the method used by SERA to take into account the geometric differences. For example, these are enhanced passing through two adjacent small zones with different materials.

In addition to that, differences appeared between BDTPS and SERA in the evaluation of the boron dose distribution, especially inside the small cups (vial) containing different boron concentrations in the validation geometry. 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 SERA.

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