Topology optimization design of the "Beam Shaping Assembly" of an AB-BNCT facility - application to the case of glioblastoma treatment

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Abstract.
Objective. This study aims to determine the optimal structure of the Beam Shaping Assembly (BSA) for an AB-BNCT (Accelerator-Based Boron Neutron Capture Therapy) facility. The aim is to maximize the possible depth of treatment for glioblastoma while ensuring that a treatment time constraint is not exceeded.
Approach. To achieve this goal, we utilize a new optimization procedure known as topology optimization. This technique can accurately identify the most optimal structure of a nuclear device, in this case a BSA, to be identified among 9×10^{1206} possible structures for the example given in this study. The exploration of such a vast space of configurations is inaccessible to any other method available to date.
Main results. The topology optimization generated Air-AlF_3-LiF-LiFPE BSA has an original structure that differs significantly from the structures previously tested by the BNCT community. This structure generates unprecedented treatment depths, with a Treatable Depth TD = 10.08 cm and an Advantage Depth AD = 12.76 cm (for 15 ppm of Boron-10 in blood, with a 3.5 tumor-to-blood Boron-10 concentration ratio), or TD = 10.61 cm and AD = 13.14 cm (for 18 ppm of Boron-10), much greater than any other design proposed to date by the community.
Significance. The findings of this study indicate that topological optimization procedures are highly beneficial for the design of BSAs, resulting in a significant qualitative improvement.

Key words: Boron Neutron Capture Therapy, beam shaping assembly, topology optimization.

1. Introduction

1.1. Study context

BNCT (Boron Neutron Capture Therapy) is a vector radiotherapy technique, during which a patient is exposed to a high flux neutron field, higher than 10^9 n/sec at the tumor level. The patient receives a Boron-10 vector, such as Borofalan (^{10}B-BPA), a couple of hours before treatment. This vector attaches itself mainly to cancer cells [1]. When the Boron-10 nuclei undergo neutron capture reactions, $^{10}B(n, \alpha)^7Li$, they emit two nuclei, alpha and Lithium-7, which have high linear energy transfer. These nuclei release their kinetic energy primarily in the cancerous cells. This radiotherapy was limited by a few intense neutron sources, usually nuclear research reactors with limited access. Recently, with the deployment of Compact Accelerator-based Neutron Sources (CANS), this approach, now called AB-BNCT (Accelerator-Based BNCT), can be used in hospitals, making it more accessible to a larger number of patients.

However, scientific and technological challenges remain, the resolution of which requires an international effort [1]. Among the main challenges to be met are: (i) the development of accelerators with low downtime rates, and targets capable of enduring the high beam power necessary to reduce the treatment time to acceptable levels; (ii) the development of Beam Shaping Assemblies (BSA), which shape the neutron field generated by the source to maximize dose deposition in cancerous tissues while minimizing damage to healthy tissues; (iii) monitoring the state of the target and the neutron field; (iv) the precise calculation and

monitoring of doses deposited in the patient's tissues; (v) the development of more selective ^{10}B vectors, to achieve a higher tumor/blood Boron-10 concentration ratio [1]. These challenges are also coupled with regulatory challenges and standardization challenges.

1.2. The challenges to be met in this study

Our study concerns point (ii), the development of a BSA to be placed between the CANS and the patient. To date, the neutron sources identified as promising for AB-BNCT, mainly $^{9}Be(d,n)$ and $^{7}Li(p,n)$, cf. [1], can generate neutron fields, certainly intense, but whose energies reach a few hundred keV to a few MeV. At these energies, neutrons cause excessive damage to the patient's tissues, and they should therefore be moderated before use. To achieve this, it is essential to place a device between the source and the patient. This device is constructed using carefully selected and positioned materials, and is designed to convert the high-energy spectrum of the source neutrons into a more epithermal spectrum, with energies ranging from a fraction of eV to a few tens of keV [1].

The design of such a BSA nevertheless poses several challenges: (i) neutron moderation must be done in a small volume, compatible with a hospital installation. However, fast neutrons have a large mean free path in most materials; (ii) under-moderation, or conversely, over-moderation of neutrons, leads to overexposure of the patient's healthy tissues, particularly since these also contain Boron-10; (iii) neutrons and gammas coming out of BSA propagate in the installation and become a radiological risk, for patients and staff, which must be limited; (iv) neutron moderation should not excessively reduce the output field intensity, keeping it high to minimize treatment time to less than one hour. These multiple constraints make optimizing a BSA for an AB-BNCT facility an interesting challenge, partly explaining the large number of studies published on this subject. These studies, some of which have resulted in designs that have been built, all use the same optimization method, called parametric optimization, and therefore all share the same limitations.

In a parametric optimization study, the structure of the device to be optimized, here an AB-BNCT BSA, is described by a set of parameters, in small numbers, e.g. the thicknesses and radii of the components, the list of materials to be used for each of them, etc., cf. e.g. [2-6]. The method then consists of varying these parameters, then simulating the performance of the device for each configuration thus created, to identify the best of them. This parametric approach, however, has two main limitations:

(i) Suppose that we use 10 parameters in total to describe the entire structure of the BSA (radii, thicknesses, angles, etc.), which is not many. Let us take only 10 possible values for each of these parameters. For this modest parametric study, the number of configurations to simulate is already 10^{10}. But, a simulation of a BSA takes between a few minutes for a deterministic code (e.g. with CBZ [6]) to a few hours for a Monte-Carlo code (e.g. with MCNP, PHITS, GEANT, etc.). Assuming that we have access to a powerful computation farm, which makes it possible to reduce this calculation time to 1 minute per configuration and run 100 simulations simultaneously, it would still require ~200 years in real time to complete this small parametric study. Thus, because of technological constraints (e.g. computing power in progress but not unlimited) and scientific constraints (e.g. long resolution time of the Boltzmann equation which governs the transport of neutrons in matter), a parametric optimization can only manage a tiny number of parameters, and therefore can only explore a tiny portion of the space of possible BSA configurations, even

when assisted by artificial intelligence, cf. e.g. [3, 7]. As a result, the BNCT community is likely missing out on the best performing designs.

(ii) The very choice of these parameters is guided by intuition and historical precedent, which leads the community to explore similar design paths, which can sometimes be counter-productive. A good counter-example will be given in section 3, with the shape of the OptTop collimator, until now always envisioned with a disk section.

The challenge in this study is to go beyond parametric optimizations by proposing a method capable of exploring a much larger part of the space of possible BSA configurations. The goal is to identify, if they exist, innovative designs that could exhibit higher levels of performance. This challenge will be met using a new design strategy, called topology optimization (TopOpt) [8-10]. This TopOpt procedure will be presented in section 2.5 and successfully applied in section 3.

1.3. Objectives and methodology of the study

In this study, we will use the aforementioned TopOpt approach to calculate the best possible structure of a BSA suitable for the treatment of glioblastoma-like brain cancers. This particular therapeutic target is omnipresent in the BNCT literature, to the point of having become a sort of standard model, rightly or wrongly. There are certainly studies that optimize BSAs on other therapeutic targets, mainly cylindrical or parallelepiped phantoms in tissue equivalent or water, e.g. [4], but they are in the minority. The choice of the therapeutic target is also fundamentally related to questions of hospital strategy: should the AB-BNCT facility have a single treatment room, with a single BSA, to be used for all possible types of treatment (deep brain cancer, superficial melanoma, H&N, etc.)? This BSA, which cannot therefore be optimal for treating all types of tumors, could nevertheless be slightly modified between uses, for example by changing the geometry of the collimator [11-13]. Or would it, on the contrary, be more interesting to have several treatment rooms, in the same installation - the particle beam then being split between the different rooms -, or in a network of installations? Each could then be dedicated to the treatment of one specific class of pathology, and have a specific BSA.

The aim of this publication is not to resolve these questions. For this study, we had to make a choice - to optimize the performance of the treatment of a glioblastoma. This will allow for easy comparison of the results presented in section 3 with those of the majority of publications. It's important to note that the topology optimization procedure used in this study enables the automated design of the BSA and its adjustment to any therapeutic target as close as possible.

Section 2, we will detail the models and data used in this study, as well as the TopOpt procedure. Section 3, we will apply this TopOpt procedure to the design of an Air-AlF_3-LiF-LiFPE BSA optimized for the treatment of glioblastoma, coupled to a ^{7}Li(p(2.5 MeV), n) source. The resulting TopOpt BSA will present unprecedented levels of performance, in terms of treatment depth, well beyond the best designs published to date. This success illustrates the potential of the TopOpt approach to calculating BSAs, which was already foreshadowed in a previous publication, where we were interested in the topology optimization of modular BSAs in D_2O, with a longer-term objective, exploring the feasibility of a personalized AB-BNCT treatment, adjusted as close as possible to the morphology of each patient and tumor to be treated [10].

2. Models, data, methods

2.1. Modeling

As is customary in the literature, we will use the modified Snyder model to model the patient's head [14]. In this model, the patient's head is subdivided into three regions, skin, skull and brain, modeled by ellipsoids. The MCNP file describing this reference phantom, as well as the data to use it (Kerma functions, tissue compositions, etc.), can be downloaded from a LANL site [14]. The calculations carried out in this study will use data from this file, by adding as recommended the reference ^{10}B concentrations to the tissue compositions, by changing the neutron source, and by removing the air-filled cells upstream of the phantom. The doses deposited in the patient's healthy and cancerous tissues will be calculated, in Gy-Eq, with the usual formula: $D = (\mathrm{CBE})D_B + (\mathrm{RBE})_N D_N + (\mathrm{RBE})_f D_f + (\mathrm{RBE})_\gamma D_\gamma$ [1]. In this study, we will use the biological parameters recommended for the treatment of glioblastoma with BPA as Boron vector: (i) a mass concentration of ^{10}B in the brain and skull of 15 ppm, 22.5 ppm in the skin, 52.5 ppm in tumorous tissues; (ii) CBE = 3.8 in tumorous tissues, 1.3 in healthy tissues; (iii) $\mathrm{RBE}_N = \mathrm{RBE}_f = 3.2$, $\mathrm{RBE}_\gamma = 1$, cf. e.g. [2-4, 15, 16, etc.]. The D_B, D_N, D_f, and D_γ doses, due respectively to neutron captures on ^{10}B, to thermal neutrons, to other neutrons, and to gammas, are calculated using the Kerma functions given in the MCNP file [14].

2.2. Design objectives and constraints

To characterize the performance of AB-BNCT BSAs, and implicitly be able to compare the different designs proposed by the numerous teams working or having worked on this subject, several dosimetric FOMs have been proposed. The most used are the Treatable Depth (TD), the Advantage Depth (AD), and the Advantage Depth Dose Rate (ADDR). The AD, resp. the TD, is the depth in the phantom where the dose deposited in the cancerous tissues is equal to 1 time, resp. 2 times, the maximum dose deposited in healthy tissues. The ADDR is the maximum dose rate to healthy tissues. In this study, we chose to calculate BSA designs that optimize the TD. This FOM in fact represents better than the AD the therapeutic objective of the treatment of a glioblastoma, where it is generally wished to achieve at least 30 Gy-Eq in cancerous tissues without exceeding 12.5 Gy-Eq in healthy tissues [2, 16].

The calculation of AD and TD requires the calculation of the doses (see section 2.1) deposited in healthy and cancerous tissues, as a function of the depth in the phantom. This calculation therefore requires paving of the patient's head. In this study, we will use the paving of the reference file [14], made up of parallelepipeds of volume ~1 cm^3 (the dose limits not to be exceeded are given per cm^3 of healthy tissue), with sections of 1.6×1.6 cm^2 and thicknesses of 0.4 cm, centered on the axis of the beam, visible in Figure 1. This paving implicitly assumes that the maxima of doses deposited in the tissues, used for the calculations of AD and TD, are on the axis of the beam. However, as we observed in this study, or even more simply when the patient is positioned at an angle relative to the axis of the beam, this hypothesis is not necessarily verified. In this study, we therefore extended the paving of the reference file [14], i.e. cells of 1.6×1.6×0.4 cm^3 ≈ 1 cm^3, to the entire volume of the patient's brain, cf. Figure 6.

2.3. Formulation of the problem to be solved

As indicated in section 2.2, we want to design a BSA that maximizes the treatable depth, TD, subject to design constraints. These constraints, in arbitrary number, can be e.g. a material cost limit not to be exceeded, and/or a weight limit not to be exceeded, and/or a patient treatment

time not to be exceeded, etc. Finding an optimal BSA, in the mathematical sense of the term, therefore requires solving an optimization problem under constraints, very complex because the densities of particles that propagate in the installation, which obey the Boltzmann equation, vary non-linearly with the structure of the BSA, and are long to calculate [8].

To solve a complex problem, the classic approach in science is to discretize it. Let us therefore start by subdividing the available volume of the BSA to be optimized into a large number, N, of smaller volumes, called voxels, $V_{i=1..N}$, each of which can thus contain a volume fraction χ_{ij} of M different materials, j=1 ...M. These voxels are illustrated in Figure 1. The objective of the study now becomes the calculation of the best possible distribution of material, $(\chi_{i=1..N,j=1..M})_{opt}$, in each of the voxels of the BSA.

In section 3, we will give an example of solving such an optimization problem for a classic constraint in AB-BNCT: MTT < 1 h. MTT refers to the maximum treatment time, defined as the time necessary to reach the dose limit for healthy tissues of the target organ. For the brain, this dose is worth ~12.5 Gy-Eq [2, 3]. It is recommended that MTT does not exceed one hour, for reasons related to patient comfort, the profitability of the treatment facility, and the fact that the concentration of ^{10}B-BPA in the patient's blood decreases over time [1].

In this context, the optimization problem to be solved is reformulated as follows:

$$\begin{aligned} &\max_{\chi_{i=1..N,\,j=1..M}} \; TD \\ &\text{subject to} \quad MTT < 1h \\ &\qquad \sum_{j=1}^{M} \chi_{i,j} = 1, \forall i \\ &\qquad \mathrm{B}_{n,\gamma}\varphi_{n,\gamma} = Q_{n,\gamma} \end{aligned} \tag{1}$$

In (1), “subject to” lists the constraints of the problem, here the constraint on MTT, a constraint of normalization to 1 of the χ_{ij} volume fractions in each voxel V_i by definition, as well as a constraint on the angular fluxes $\varphi_{n,\gamma}$ of neutrons and photons, which must obey the Boltzmann equation $\mathrm{B}_{n,\gamma}\varphi_{n,\gamma} = \mathrm{Q}_{n,\gamma}$, where $\mathrm{B}_{n,\gamma}$ is the Boltzmann operator and $\mathrm{Q}_{n,\gamma}$ the source of neutrons or photons [8, 9]. The neutron source used for this study is a ^{7}Li(p,n) metallic target, powered by a 10 mA beam. With ^{9}Be(d,n) and ^{13}C(d,n), this source is indeed considered one of the most promising in AB-BNCT [1]. The energy and angle distributions of the source neutrons were calculated using the TARGET code [17, 18]. The Q_{γ} source includes the photons resulting from the decay of ^{7}Be in the ^{7}Li(p,n) target as well as the gammas generated by neutron captures in the structure of the BSA and the patient's tissues. The coupled transport equations $\mathrm{B}_{n,\gamma}\varphi_{n,\gamma} = \mathrm{Q}_{n,\gamma}$ are solved using the Monte-Carlo code MCNP6 [19].

2.4. Choice of materials

The materials considered in this study will be: (1) air (1.22×10^{-3} g/cm^3), (2) ceramic AlF_3 (2.88 g/cm^3), (3) natural LiF (2.635 g/cm^3) and (4) LiFPE, a polyethylene (PE) enriched with natural LiF (1.13 g/cm^3), cf. [20]. The choice of air as a material may be surprising at first glance, but the results presented in reference [10] for modular heavy water BSAs, as well as those which will be presented in section 3 of this study, show that this choice is essential. Air is, in any case, a material implicitly present in the vast majority of design studies published to date by the

community, since it is notably present in and around the collimators that face the patient's head, cf. e.g. [2-4].

The 4 materials short-listed above are regularly used in AB-BNCT BSA design studies, for several reasons. Al, AlF_3 and their mixtures have low neutron capture cross sections and an interesting inelastic diffusion regime to slow down neutrons of ~1 MeV towards the epithermal range in a compact volume. PE and LiF are often used as radiological shields, to slow neutrons down to the thermal range and capture them. AlF_3 and LiF are sometimes combined into a single material by sintering, e.g. Fluental [21] or ALLIFLU [5]. Other fluorinated materials, such as MgF_2, PbF_2, CaF_2, etc., or even Teflon, can be used instead of AlF_3, cf. e.g. [1-6, 22, 23]. Replacing AlF_3 with one of these materials will not pose a problem for the TopOpt algorithm; this is an option we have studied and probably be built in the frame of a production of an epithermal neutron field of metrological reference.

2.5. Methodology for solving the optimization problem

In the example given in section 3, the structure of the BSA to be optimized will be contained in a cylinder of radius 50 cm and width L = 18 cm, the length L being counted from the exit face of the accelerator, visible in yellow Figure 1 (left). This cylinder will itself be inserted into a heavy concrete wall, visible in green Figure 1 (left), for the radiation protection of patients and staff. The patient's head, modeled by Snyder's phantom, is visible in Figure 1 (left) on the right, with the brain in pink. The volume of the BSA is subdivided into N = 230 voxels (cylindrical rings coaxial with the axis of the beam), the contours of which are visible in Figure 1 (left). The minimum distance between the patient's head and the exit face of the BSA is d = 5 cm (patient plane, see [1]).

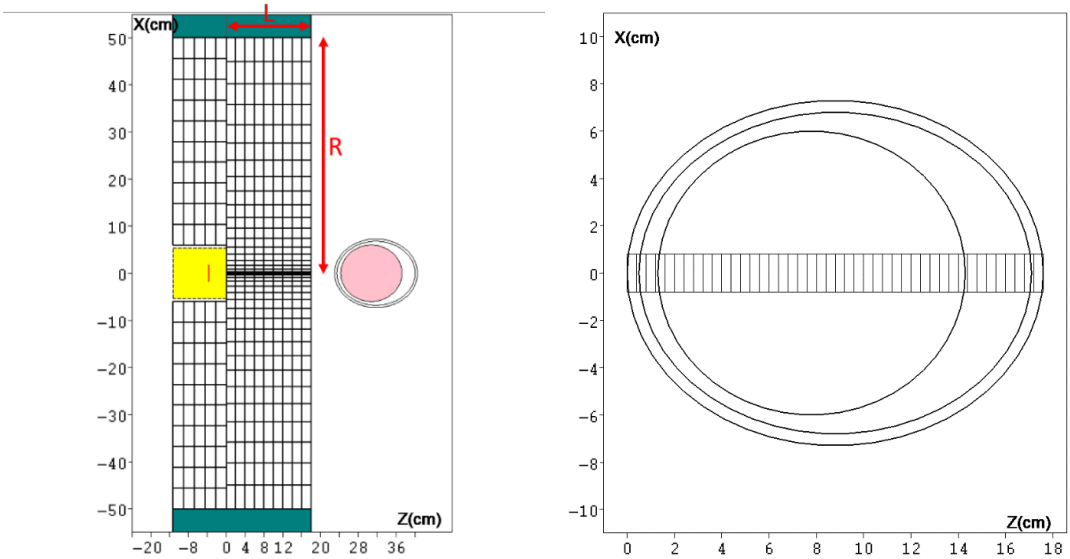

Figure 1. (Left) voxelization of the BSA, with the concrete wall (in green), Snyder's phantom (brain in pink) and the accelerator finger glove (in yellow), in the *XZ* plane; (right) standard paving used for the calculation of TD and AD, in the *XZ* plane, to be completed by the paving of the patient's brain visible in Figure 6.

As indicated in sections 2.3-2.4, each voxel can contain a variable proportion of 4 materials, air, AlF_3, LiF, LiFPE, to be optimized. By varying these proportions in steps of 1% e.g. (which will be the case in this study), taking into account the constraint of normalization to 1 of the χ_{ij}, cf. equation (1), there are therefore $C(100+4-1,4-1) = 176851$ possible material compositions per voxel, and therefore a total of $176851^{230} \approx 9\times10^{1206}$ possible BSA configurations to explore.

Operationally, this number is infinite; we can for example compare it to the number of atoms in the visible universe, estimated at 10^{82} atoms. There obviously does not exist, and there probably never will exist, any computer capable of exploring such configuration space by brute force. A parametric optimization, whose parameters would have been the $\chi_{i=1..230,j=1..4}$, is completely impossible here.

However, surprisingly, modern mathematics provides a way to solve problem (1), through an approach called topology optimization (TopOpt), developed at LPSC (CNRS-IN2P3, UGA, GINP) since 2018. This approach is described in references [8, 9], for the simplified case of devices made of one or two materials with a single design constraint. This tool is coupled to the Monte-Carlo MCNP6 code, in order to accurately simulate and jointly optimize the transport of neutrons and gammas in the device [19]. Since these first publications, this TopOpt procedure has been rewritten to handle an arbitrarily large number of materials and design constraints, the only limitation now being the memory of the server on which the calculations will run.

Without going into technical details, the multi-material and multi-constraint version of the TopOpt procedure requires the Lagrangian reformulation of problem (1), cf. [8-10]. This Lagrangian problem is now solved using a method similar to the KKT method [24, 25]. The Lagrangian perturbations necessary for the implementation of this method are calculated using the MCNP6 code [19]. The numerical resolution of the Lagrangian problem is carried out iteratively. At iteration 0, we feed the calculation with an arbitrary distribution of material in the BSA – for this study, 100% AlF_3 in the 230 voxels and 0% for the other materials, cf. Figure 2. Then, iteration after iteration, the TopOpt algorithm will simultaneously modify the material distributions in the N voxels of the BSA, small steps by small steps, in the right direction, until it converges towards the solution of problem (1). To limit the computational cost, other tricks are necessary to reduce the number of iterations, supplemented by automated use of the convergence acceleration tools made available in MCNP6 [19]. These multiple innovations make it possible to resolve a problem of type (1), although impossible on paper, in a humanly admissible time, ~80 days on a 48 CPU Intel Xeon Gold 5220R @ 2.2 GHz server for the example given in section 3.

3. Example of application of the TopOpt approach to the design of BSAs

3.1. Optimal structure of an Air-AlF_3-LiF-LiFPE BSA

In this section, we propose an example of application of the topology optimization procedure described in section 2.5 to design an optimal AB-BNCT BSA, solution of problem (1), in the context of treating a glioblastoma. The materials that have been chosen for the BSA are listed in section 2.4. The neutron source uses the ^{7}Li(p,n) nuclear reaction with a 2.5 MeV proton beam.

Figures 2 and 3 illustrate the convergence of the TopOpt algorithm, iteration after iteration, towards the optimal structure of the BSA, solution of (1). In Figures 2, which are sections of the BSA structure in the XZ plane, the gray scales give the volume fractions of each material in the 230 voxels. The black voxels thus contain 100% of the material considered, the white voxels 0%. The complete structure of the BSA is generated by rotation around the axis $X = 0$. The left and middle columns give the BSA structures at iterations 0 and 50 of the TopOpt algorithm. The right column gives the final structure of the BSA, solution of (1), obtained at iteration 145.

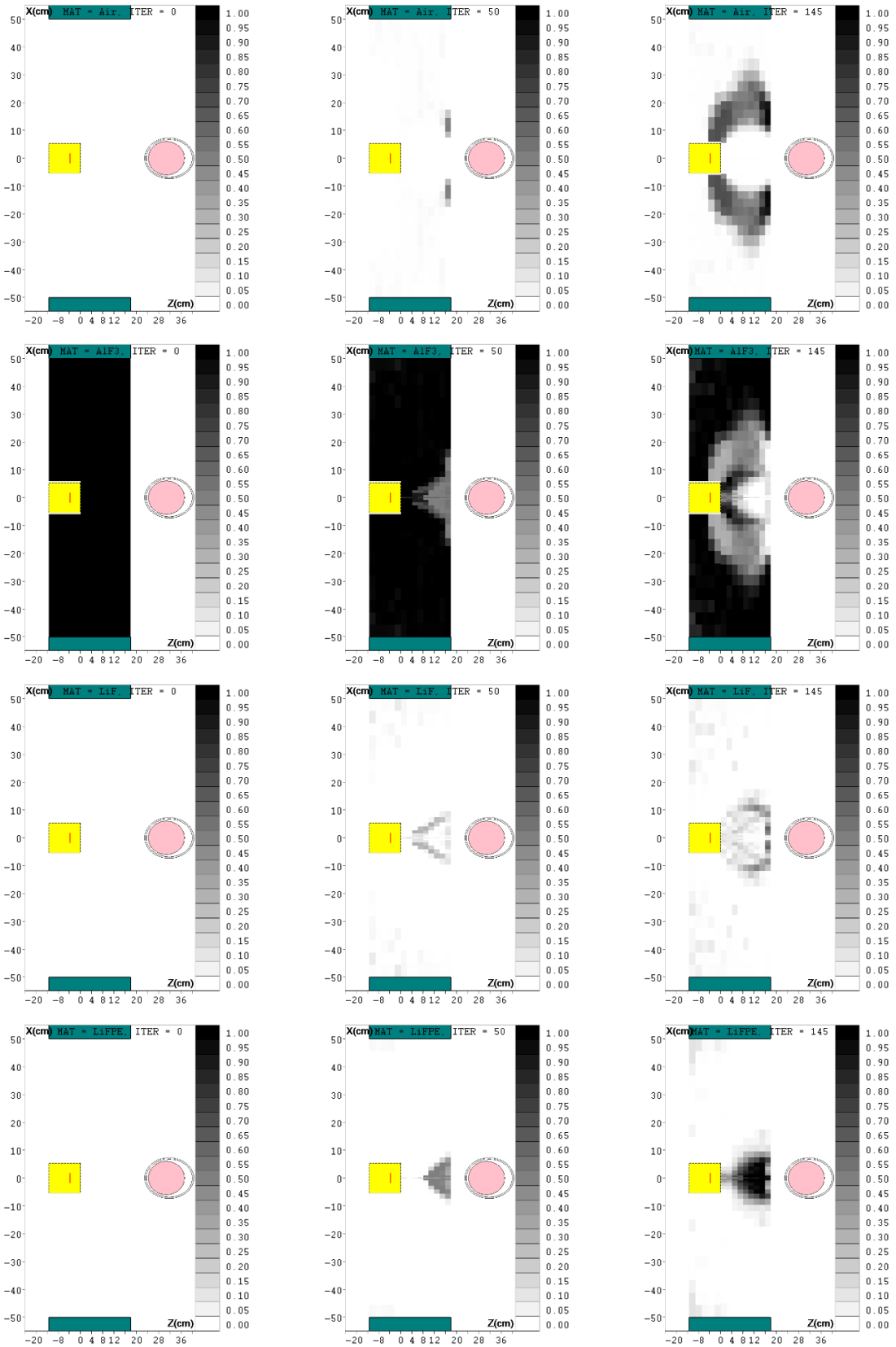

Figure 2. Convergence of the TopOpt algorithm towards the solution of problem (1) for an Air-AlF_3-LiF-LiFPE BSA, for L = 18 cm, R = 50 cm and a ^{7}Li (p(2.5 MeV),n) source. The figures in the left column give the BSA structure at iteration 0, those in the middle column give the structure at iteration 50, and those on the right column give the final structure, at convergence. The 1st line gives the volume fractions of air in the structure, the 2nd those of AlF_3, the 3rd those of LiF, and the 4th line those of LiFPE.

We note in Figure 2 that the TopOpt procedure generates a novel BSA structure, very different from those published to date by the community. Among the innovations concentrated in Figure 2, we note that the TopOpt procedure generates a moderation body in AlF_3, pierced by a tunnel of annular section, cf. air distribution in Figure 2. This tunnel, which surrounds a LiFPE cone lined with LiF, guides the neutrons towards the patient's head, playing the role of a collimator. The interest of this original collimator geometry - compared to other collimators proposed to date by the BNCT community, which all have a disc-shaped section facing the patient's head - will be discussed in more detail in section 3.2.

3.2. Performance of the TopOpt BSA

To date, except communications which would have escaped the attention of the authors, the best dosimetric FOMs values obtained by the BNCT community are TD ≈ 7.9 cm and AD ≈ 11 cm. Torres-Sánchez et al. obtained TD = 7.85 cm (and AD = 9.74 cm) with a BSA optimized using, as absolute design constraints, threshold values of 5 in-air FOMs of the neutron and gamma fields proposed in an IAEA report from 2001 [27], altogether with a Boron-10 concentration in blood of 18 ppm instead of the usual 15 ppm [2]. Studies have however shown that the threshold values of these in-air FOMs are too restrictive, and could paradoxically eliminate the BSA designs presenting the best therapeutic performances, cf. e.g. [1, 27, 28]. In the new 2023 IAEA report on BNCT, these in-air FOMs have therefore been re-evaluated and accompanied by a clear warning: (sic) “the reference values […] are specifically not suggested as 'requirements' or ' recommendations' that have to be achieved by a system provider or facility” [1]. It is possible that Torres-Sánchez et al. would have obtained better TD values with these 2023 threshold values, or by not using them as absolute constraints as it is now recommended. In this study, like other authors since 2001, we favored the dosimetric FOMs, TD, AD and MTT, for the optimization of the BSA [1]. Concerning AD, a value of 10.99 cm was obtained by a collaboration between the Xiamen Institute, the University of Pavia and the Nanjing University of Aeronautics and Astronautics, and presented at the ICNCT 19 conference [29]. To achieve AD = 10.99 cm, this team simulated the exposure of the patient's head, modeled by Snyder's phantom, to the combination of two mono-energetic and mono-directional neutron fields (both parallel to the axis of symmetry of the Snyder’s model), of 6 keV and 7 keV. This collaboration did not, however, present the nature of the source or the structure of the BSA capable of generating such mono-energetic and mono-directional neutron fields, certainly very complex to achieve with sufficient intensity given the diffusive nature of neutrons. In any case, it is unlikely that the BSA installed at the Xiamen BNCT Center would be capable of delivering such neutron fields [1].

Figures 3 and 4, we give the evolution of TD, AD and MTT with the iteration number of the TopOpt calculation, as well as the profiles of the doses deposited in the phantom, functions of the depth, obtained for the TopOpt solution, which under-tend these values (note: the maximum dose to healthy tissues at iteration 145 remains on the beam axis). We observe that the TopOpt design, presented in the right column in Figure 2, makes it possible to reach TD = 10.08 ± 0.02 cm, with AD = 12.76 ± 0.01 cm [1], ADDR = $2.19\times10^{-2} \pm 10^{-4}$ Gy-Eq/min/mA and MTT@10mA = 57.17 ± 0.23 min. These TD and AD values are unprecedented, much higher than the best values obtained to date, recalled above. Note that, with a TD that close to 10.3 cm, which is the maximum distance from the center of the patient's head to its surface (see Figure 6 in the *YZ* plane), virtually all tumors can be reached by changing the orientation of the patient's head regardless of their depth.

[1] The topology optimization carried out in section 3 aimed to maximize TD, not AD, cf. (1). Therefore, the AD value reported here is not the best value that can be obtained with an Air-AlF_3-LiF-LiFPE BSA.

In several studies, cf. e.g. [1-3], Boron-10 concentrations in the blood of 18 ppm, instead of the standard 15 ppm, and 65 ppm instead of 52.5 ppm in tumorous tissues, are used. With these concentration values, the TopOpt design reaches TD = 10.61 cm, with AD = 13.14 cm, ADDR = $2.32\times10^{-2} \pm 10^{-4}$ Gy-Eq/min/mA and MTT@10mA = 53.80 min [(2)]. Finally, the Treatment Ratio (TR), ratio of the maximum dose delivered to cancerous tissues to the maximum dose delivered to healthy tissues, is TR = 4.74 for 15 ppm of Boron-10 in the blood, and TR = 5.40 for 18 ppm of Boron-10.

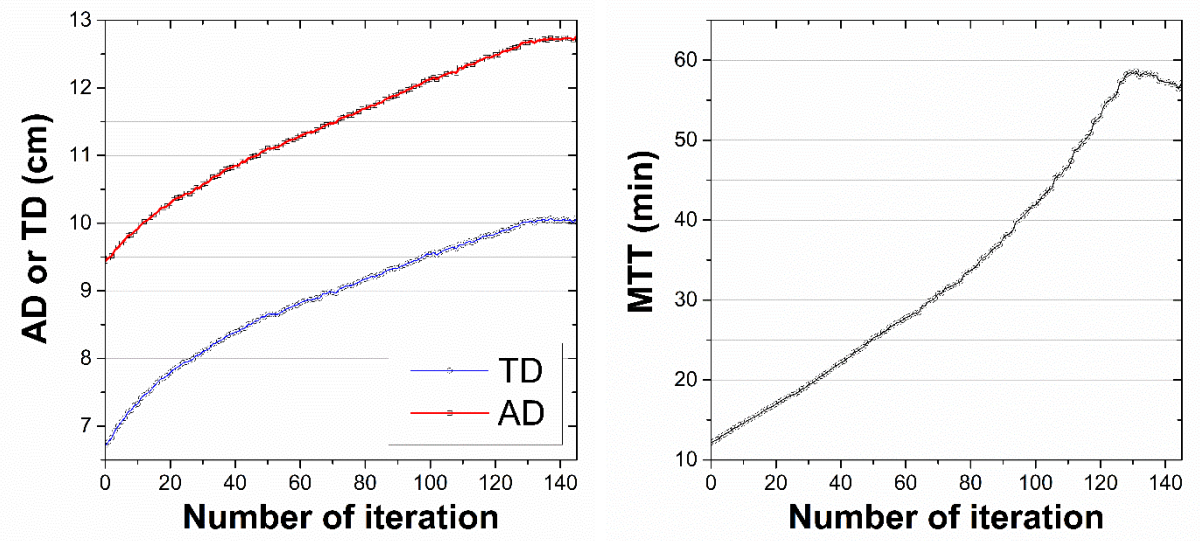

Figure 3. Convergence of TD and AD (left) and MTT (right) with the number of iterations of the TopOpt calculation, for 15 ppm of Boron 10 in the blood.

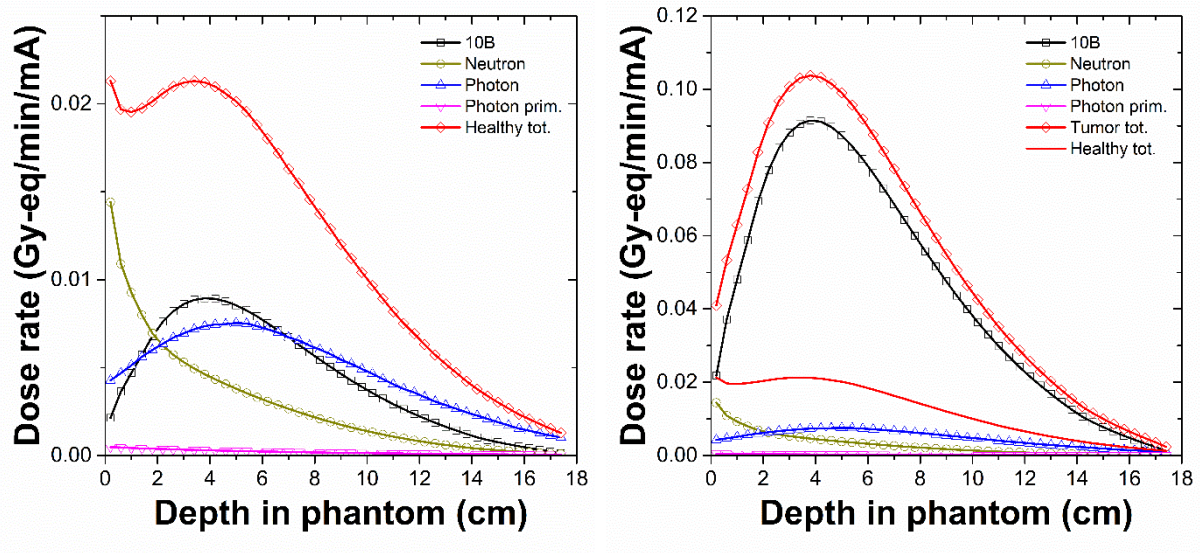

Figure 4. Evolutions of the dose to healthy (left) and cancerous (right) tissues with the depth in the phantom, obtained with the TopOpt configuration of the BSA given in Figure 2 iteration 145, for 15 ppm of Boron-10 in the blood. The respective contributions of ^{10}B doses, neutrons ($D_N + D_f$), photons and primary photons to the total doses are also provided.

[2] Likewise, these values are not the absolute optima of the problem, the TopOpt calculation having been carried out with standard concentrations of ^{10}B in blood and tumorous tissues, of 15 ppm and 52.5 ppm respectively.

To understand how the TopOpt structure makes it possible to reach high treatment depths, we give in Figure 5 a visualization of the neutron field generated in the air, at the output of the TopOpt BSA, as a function of the radial distance *R* to the axis of the beam and the distance *Z* to the exit plane of the BSA. We note that the structure of the TopOpt annular collimator creates an original neutron field, which combines directionality and moderation. The neutrons which take the tunnel visible in Figure 2 are partly directed toward the patient's head and are added there, see green zone Figure 5. The latter is exposed to a field that is both homogeneous and intense, despite the distance, 13.8 cm on average, between the head and the BSA. The flux map in Figure 5 also allows us to understand the role played by the LiFPE cone lined with LiF, visible in Figure 2, in the structure of the TopOpt BSA. We note in Figure 5 that this cone completely cuts the flux of neutrons emitted in the axis of the beam, facing the patient, thus avoiding the formation of a hot spot of dose deposited in healthy tissues upstream of the brain on this axis [(3)]. It is the combination of this filter cone and the annular collimator which makes it possible to achieve the high TD and AD values obtained in this study. We finally note that the TopOpt structure generated in Figure 2 closely resembles the structure of the modular heavy water AB-BNCT moderators generated by TopOpt in a previous study [10]. This convergence of designs - even though the objectives, constraints, or materials differ between these two studies - reinforces the relevance of the annular collimator solution found.

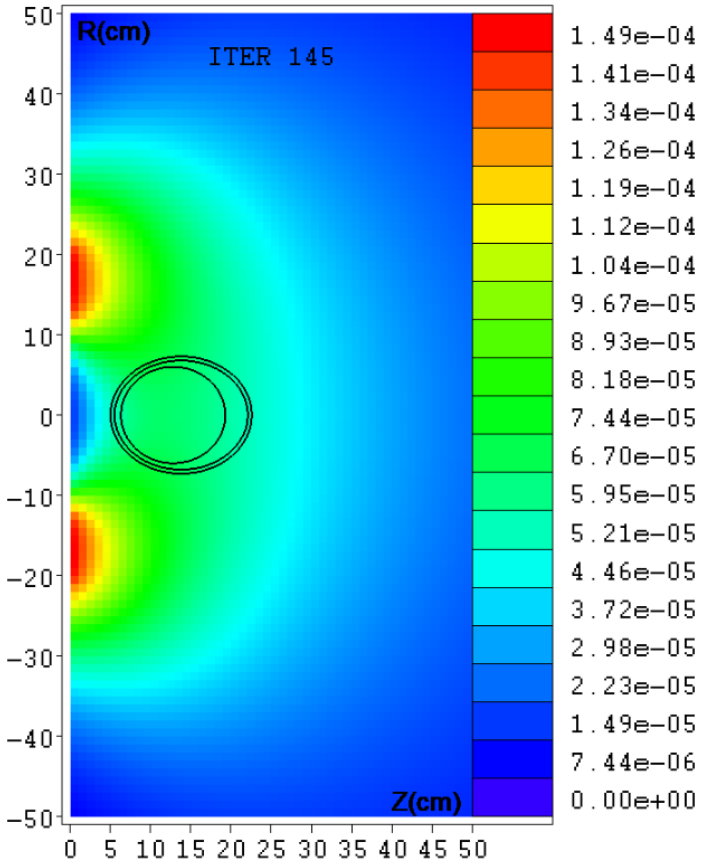

Figure 5. Neutron flux in air generated by the BSA, as a function of the distance *Z* to the BSA exit plane and the radial distance *R* to the beam axis. The color scale gives the flux values, in neutrons per cm^2 per source neutron, at points (*Z*, *R*). The patient's head, modeled by Snyder's phantom (whose tissues were replaced by air for this calculation), is also traced.

[3] Caution: in Figure 5, the areas of high flux (in red) and low flux (in blue) may both appear in black when the figure is printed in black and white; they may therefore be confused.

Still to better understand how the TopOpt design solution works, we give Figure 6 the maps of the doses it generates in cancerous tissues of the patient's brain. As a reminder, the patient's brain was paved using cells of 1 cm^3 volume, cf. section 2.2. We again observe that the TopOpt solution does not concentrate the dose in the first centimeters of the brain, unlike other designs published to date. It deposits it over an area of ~6 cm radius, deep, with a dose to cancerous tissues that exceeds 30 Gy-Eq, the therapeutic objective, in 61% of the patient's brain volume for an irradiation time equal to MTT, without exceeding anywhere the limit dose, 12.5 Gy-Eq, to healthy tissues (by definition of the MTT). This design, which in some way mimics a multi-directional AB-BNCT treatment (one direction per exit point of the annular collimator), makes it possible to avoid the creation of a dose hot spot along the axis of the beam. This results in the high TD treatable depth value achieved by the TopOpt design.

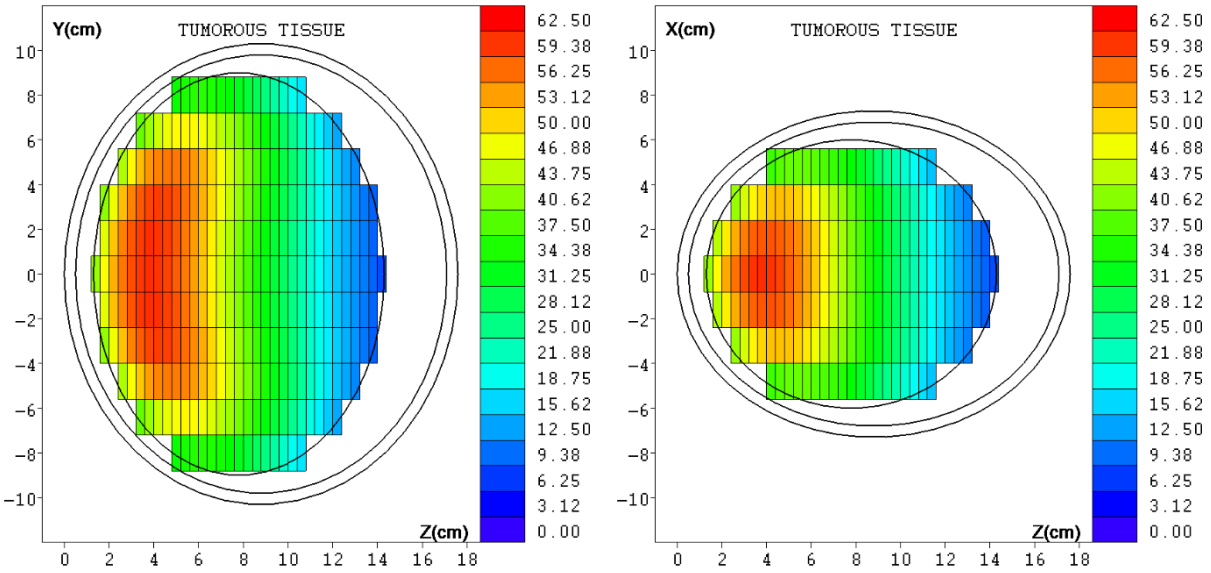

Figure 6. Doses deposited in cancerous tissues, in the *YZ* (left) and *XZ* (right) planes, obtained with the TopOpt design solution, for 15 ppm of Boron-10 in the blood and an irradiation time equal to the MTT. The axis of the beam is the axis $X = Y = 0$. The color scales give the dose values, in Gy-Eq, in each voxel of the brain.

Since the TopOpt structure sends the neutrons, so to speak, sideways at the patient's head, and not straight on, they have to travel a little further through the patient's head than other designs to reach the axis. The neutron energy spectrum generated by the TopOpt BSA, given in Figure 7, is therefore harder than the spectra usually presented in the literature. The average neutron energy here is 27.2 keV, with 1.1% of the flux below 0.5 eV, 51.9% between 0.5 eV and 10 keV, 15.0% between 10 keV and 20 keV, 15.4% between 20 keV and 50 keV, and 16.7% above 50 keV, without excessive impact on the dose in healthy tissues, which nowhere exceed the limit value of 12.5 Gy-Eq while at the same time the dose in tumorous tissues reaches 59.1 Gy-Eq (with 15 ppm of Boron-10 in the blood) or 67.3 Gy-Eq (with 18 ppm of Boron-10 in the blood) for an irradiation time equal to MTT. The fact that the topologically optimized spectrum retains such a large component between 10 and 50 keV shows again that, for a well-optimized BSA, neutrons of a few tens of keV can retain therapeutic interest for the treatment of deep cancers [1, 28]. The cutoff at 10 keV of the epithermal range, until recently considered as an energy limit not to be exceeded for BNCT neutron fields, appears here, a little more, as too restrictive. We also give in Figure 7 the energy spectrum of the source neutrons, calculated in Snyder's phantom when the BSA structure is removed and replaced by air. This additional data makes it possible to better visualize the shift in the energy spectrum carried out by the BSA.

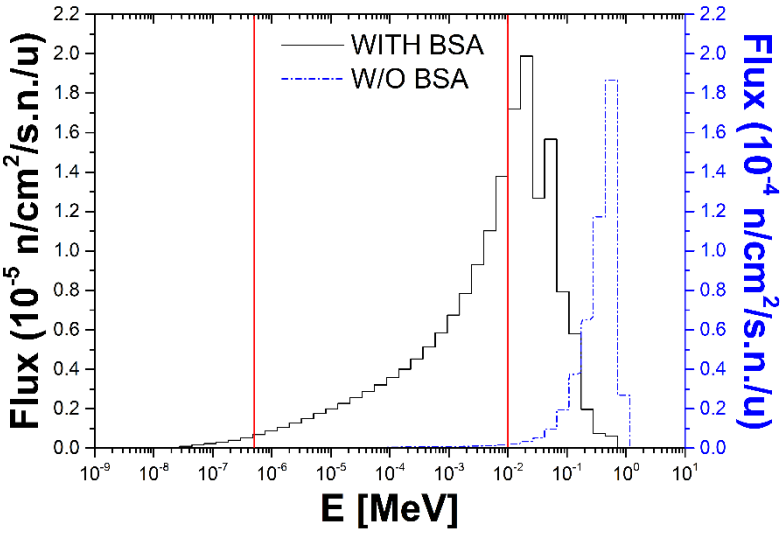

Figure 7. Energy spectra of neutrons per unit of lethargy, in neutrons (n) per cm^2 per source neutron (s.n.) per lethargy (u), generated in Snyder's phantom (whose tissues are replaced by air for these calculations) by the TopOpt BSA (in black), or when the structure of the BSA is removed and replaced by air (in blue). The limit of the epithermal zone, 0.5 eV – 10 keV, is indicated by vertical red bars.

We will conclude this section by emphasizing that the BSA structure calculated here has been optimized for the treatment of brain cancers. This structure may not be optimal for treating other cancers, especially shallow ones like melanomas, which require a more focused and thermalized neutron field. It would be interesting to conduct a dedicated TopOpt calculation for these cancers to potentially identify new innovative designs. We plan to carry out this study as part of the CHEMINS project continuation, as mentioned in the Acknowledgments section.

5. Conclusion

In this study, we used a topology optimization procedure (TopOpt), developed at LPSC (CNRS-IN2P3, UGA, GINP), to calculate the best possible structure of the Beam Shaping Assembly (BSA) of an AB-BNCT facility, which maximizes the depth of treatment of a glioblastoma under treatment time constraint. The Air-AlF_3-LiF-LiFPE TopOpt design of this BSA, coupled to a ^{7}Li(p(2.5 MeV,n) source, presents several innovative components, which radically differ from the previous design paths explored by the BNCT community. In particular, this design includes (i) an annular section neutron collimator, which directs moderated neutrons toward the patient's head by mimicking the effect of a multi-directional treatment, and (ii) a filter cone, which prevents the formation of a hot spot of dose deposited upstream of the cancerous tissues to be treated. This unique design makes it possible to achieve a record TD (Treatable Depth) value, 30% higher than the best result presented at this time. The result demonstrates the effectiveness of TopOpt's new approach to define the design. This approach allows for the quick identification of the best design solution from the nearly endless array of possible BSA configurations.

We emphasize that even greater treatable depths could probably be obtained by varying the maximum length of the BSA (here fixed at 18 cm), its radius (here fixed at 50 cm), the energy of the proton beam (here set at 2.5 MeV), or by testing other materials. However, at the rate of ~80 days per TopOpt calculation on a modern server, cf. section 2.5, this promising study will require very significant computing power. It will be the subject of a specific investment in the continuation of the CHEMINS project (see Acknowledgments section).

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