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Optimal heavy water neutron moderators for an AB-BNCT treatment unit

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Abstract. In this study, we use a topology optimization algorithm, developed at the CNRS LPSC, to design a heavy-water neutron moderator for a BNCT treatment unit. The solutions generated by this algorithm are compact yet succeed in limiting the exposure of patient's healthy tissues to levels below recommended limits. They present subtle, original geometries inaccessible to standard design techniques. The versatility of this novel approach makes it possible to automate the moderator design, and fit it to the configuration of the BNCT unit considered, e.g. the neutron source and materials it uses or the room it occupies, as well as to the biological parameters of its patients, e.g. the volume and depth of the tumor to be treated or the characteristics of the targeted organs.

Key words: boron neutron capture therapy, neutron moderator, topology optimization.

1. Introduction

Context. Boron Neutron Capture Therapy (BNCT) is a radiotherapy technique that uses a flux of epithermal neutrons to treat deep and/or diffuse tumors [1]. In the early days, these fluxes were generated by nuclear reactor cores, limiting the use of this approach to a small number of sites, the number of which is also declining with the decommissioning of a growing number of research reactors. The development of compact accelerator-based neutron sources that can be deployed in a hospital environment is removing this limitation, leading to renewed interest in this approach, renamed Accelerator-Based BNCT (AB-BNCT). Concretely, a patient absorbs before treatment a boron-10 delivery agent, which targets preferentially cancer cells [1]. Boron-10 captures neutrons with a high cross-section (~ 3800 barns at 0.025 eV) and splits into 2 nuclei, ^4He and ^7Li , with a probability of 94% both carrying 2.3 MeV of kinetic energy and 6% carrying 2.78 MeV. These heavy charged particles stop after a short track ($\sim 5\text{-}8\ \mu\text{m}$) through tissue, depositing most of their energies in the cancerous cells, destroying them. Some amount of boron-10, however, remains in the patient's blood, leading to unwanted exposure of healthy tissue subjected to the neutron flux. In addition, the primary and secondary particles that propagate in the treatment unit and in the patient induce potentially damaging exposure, which should be kept to a minimum [2]. For these reasons, the AB-BNCT neutron sources, which emit mostly epithermal to fast neutrons, must be assisted by moderators, which lower the energies of neutrons to levels less risky for healthy tissue, $< \sim 10$ keV [1]. The scientific and technological challenges that must be addressed to make AB-BNCT available, efficient and safe, therefore include (1) the development of intense compact neutron sources, (2) the development of targets that can withstand a high beam power ($\sim 30\text{-}75$ kW), necessary to reduce the treatment time to the order of one hour; (3) the synthesis of boron delivery agents allowing a higher contrast between the concentration in ^{10}B in the tumor and the blood; (4) improving knowledge on neutron and photon transport, and on the calculation of deposited doses and their biological effects; (5) high-accuracy monitoring of the doses delivered to patients; (6) the development of compact neutron moderators capable of adjusting their energies and directions to target a tumor while best preserving healthy tissue. The present study addresses this last issue (6).

Aim of the study. The design of BNCT moderators currently relies on parametric approaches. First, a set of potential configurations is assembled, by varying the composition and dimensions of their components. The choice of these configurations is based in part on the analysis of

1 neutron-matter interaction cross-sections, in part on human intuition and experience. For each
2 possible configuration, a simulation of the treatment unit is then performed, using Monte-Carlo
3 codes nowadays. Moderator configurations that offer interesting compromises between chosen
4 therapeutic and economic objectives are thus identified, and possibly refined. These parametric
5 studies yield interesting, multi-material design solutions, which deliver high tumor doses while
6 keeping the doses deposited in healthy tissues under control [3-5]. However, being constrained
7 by human creativity, they can only explore a small fraction of the solution space, and may thus
8 miss out on more efficient but unintuitive designs. For intermediate to deep-seated tumors e.g.,
9 parametric based designs cannot yet prevent the deposition of large doses in upstream tissues,
10 in particular in the scalp during the treatment of glioblastoma. Therefore, an approach that
11 would allow the space of possible configurations to be explored with little to zero human bias
12 could provide the BNCT community with innovative design solutions. For this purpose, we will
13 leave in this study the determination of the design of a heavy-water neutron moderator in the
14 hands of a topology optimization (TOPOPT) algorithm, the principle of which will be described
15 in section 3.1. Examples of successful applications of this TOPOPT approach will be presented
16 in sections 3.2 and 3.3. Finally, we will conduct in section 4 a set of sensitivity studies required
17 to evaluate the robustness of the TOPOPT computations, before concluding in section 5.

18
19 *Computation means.* The simulations carried out for this study were run on servers with 24
20 modern CPUs (+24 virtual), dating from the end of the 2010s, at the rate of one simulation per
21 server. The computation times mentioned in the rest of this study correspond without exception
22 to the durations of the computations launched on these machines.

23 24 25 **2. Modeling of the treatment unit**

26
27 In this section are presented the models, data and codes used for computing the structure of a
28 BNCT neutron moderator and its performances, for a specific configuration described below.

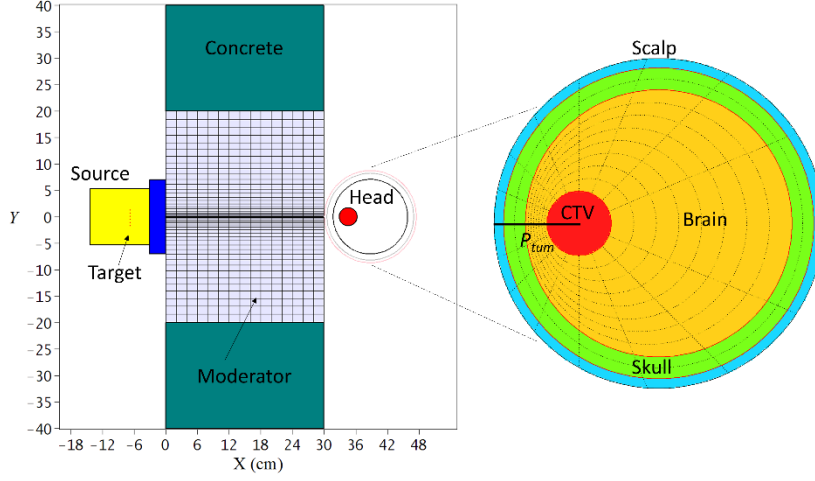
29
30 *Neutron source.* For this study, we consider one of the main neutron sources envisaged for an
31 AB-BNCT treatment unit, which makes use of the ${}^9\text{Be}(d(1.45\text{ MeV}), n)$ reaction. This reaction
32 produces neutrons with good efficiency, 3.3×10^{11} neutrons/mC, with a not too hard energy
33 spectrum, and its manufacture and operation at high power are considered less challenging than
34 ${}^7\text{Li}(p,n)$ sources [4]. The deuteron beam, here parallel to the Y axis, is assumed to be uniformly
35 distributed over the surface of the ${}^9\text{Be}$ target, a 10 cm^2 disc visible fig. 1 at $x = -6.7\text{ cm}$. Such a
36 surface is considered necessary to dissipate the high power deposited by the beam, expected to
37 be around 40 kW. The ${}^9\text{Be}$ deposit is assumed to be homogeneous. Therefore, in our
38 simulations, the neutron emission coordinates are sampled uniformly across the surface of the
39 target disk. The energy and angle distribution of the generated neutrons was measured by
40 Capoulat et al. [6]. It is rigorously implemented in the transport code used for this study, MCNP
41 6, by using the functionalities of its SDEF card [7]. The target casing model, simplified for
42 study purposes, is an aluminum and graphite structure, in yellow fig. 1. Between the casing and
43 the moderator is inserted a layer of lead, in blue fig. 1, to reduce the fluence of primary gamma
44 rays.

45
46 *Neutron moderator.* A ${}^9\text{Be}(d(1.45\text{ MeV}), n)$ source generates neutrons of $\sim 2\text{ MeV}$ in average,
47 which must be slowed down to the desired energies for a BNCT treatment, $< \sim 10\text{ keV}$, in order
48 to reduce the neutron dose in the healthy tissues. This moderation must be carried out in a device
49 with a low footprint, compatible with use in a hospital environment. Such a moderator must
50 therefore be manufactured mainly using materials having light nuclei, e.g. ${}^1\text{H}$ (water, plastics),

1 ^2H (heavy water), Be, C, F (inelastic diffusion), etc. For this study, we will optimize the
 2 structure of a moderator made of heavy water, 99% atomic pure. Heavy water is an interesting
 3 material for several reasons: (i) it has excellent neutron moderating power, ^2H having a low
 4 nucleus mass, close to that of the neutron; (ii) ^2H has a low neutron capture cross-section, which
 5 increases the output neutron fluence and reduces the production of dosing capture gamma rays.
 6 This material has already been used as a moderator in BNCT installations, at the JRR-4 reactor
 7 for example [8]. Its use was recently studied by Hervé et al., who showed during a parametric
 8 study that a hemispherical moderator made of heavy water presented the best tumor dose over
 9 brain dose ratios for most of the parameters they explored (composition and radius of the
 10 moderator, depth of the tumor) [5]. This moderator, with a maximum radius of 20 cm and a
 11 length of ~ 30 cm (variable), is inserted into a heavy concrete wall, in green fig. 1, which serves
 12 as biological protection. In order to limit the computation time, this moderator has an axis of
 13 symmetry, coinciding with the axis of the beam. Unless otherwise stated, the moderator will be
 14 segmented into $N = 375$ voxels $\Theta_j = 1 \dots N$ (25 steps in length, 15 in radius). These voxels, drawn
 15 in fig. 1, are cylindrical crowns with axis that of the beam, each containing a density ρ_j of heavy
 16 water varying between 0 and 1.11 g/cm^3 , the natural density of heavy water. The objective of
 17 the study is to find the densities ρ_j that optimize the BNCT treatment quality, using a topology
 18 optimization algorithm.

19
 20 *Patient's modeling.* For this study, we will consider the case of the treatment of glioblastoma.
 21 We will only model the patient's head, simplifying its composition. Only the brain, skull and
 22 scalp are modeled, using spheres with radii 7.05 cm, 8.21 cm and 8.71 cm, visible in fig. 1.
 23 These average radii, consistent with anatomical data for a standard adult human [9, 10], give
 24 volumes of brain, skull and scalp equal to those of Snyder's model [11]. The Clinical Target
 25 Volume (CTV) containing the tumor is modeled by a sphere of volume 20 cm^3 , represented in
 26 red fig. 1. This sphere is positioned at a depth P_{tum} , defined as being the smallest distance
 27 between the center of the CTV and the surface of the patient's head, cf. fig. 1. Its center is on
 28 the axis of the beam. The center of the patient's head is also on the axis of the beam, at a distance
 29 chosen so that the minimum distance between the surface of the head and the right side of the
 30 moderator is equal to 1 mm, cf. fig. 1 (quasi contact to minimize neutron losses). The patient's
 31 head is subdivided into $M = 89$ voxels $\Delta_i = 0 \dots 88$: 1 voxel Δ_0 for the tumor, 88 others for healthy
 32 tissues (64 for the brain, 16 for the skull, 8 for the scalp). These 88 voxels are delimited by: (i)
 33 cones whose vertices are the center of the CTV and whose opening angles vary between 0° and
 34 180° ; (ii) and ellipsoids of revolution, whose axes of symmetry coincide with that of the beam,
 35 and whose ends are chosen to regularly pave the patient's head. This paving is presented in fig.
 36 1 (right). The choice of this head model is motivated by several constraints: (i) *the computation*
 37 *time*: the time required for the optimization algorithm to converge increases with the number M
 38 of voxels used to pave the head, in $\sim 4M$ for M small. For $M \gg 1$, this time is expected to increase
 39 exponentially with M . Thus, for 89 voxels Δ_i for the head and 375 voxels Θ_j for the moderator,
 40 it takes 2 months of computation on a modern 24 CPUs server to determine the optimal structure
 41 of the moderator, a long time but which remains humanly compatible. Without axial symmetry,
 42 it would be necessary to add a discretization in angle φ around the axis of symmetry, by cutting
 43 the structure using planes containing the axis of the beam. By taking for example 10 angles φ ,
 44 the number M of voxels would increase to 881, and the computation time to ~ 20 months; (ii)
 45 *uncertainty on the volume of tissue concerned by a peak dose*: axial symmetry eliminates the
 46 uncertainty on the volume of tissue affected by a peak dose, most often not provided in the
 47 literature. Indeed, by cutting the model of the patient's head using planes containing the axis of
 48 symmetry, again, we can subdivide each voxel Δ_i into an arbitrarily large number of sub-voxels,
 49 of arbitrarily small volumes but nevertheless all exposed to the same dose; (iii) *sensitivity to*
 50 *morphological variability*: analytical models, e.g. of the Snyder type, are quite rigid, and their

1 representativeness for all patients may raise debate. In order to study the impact of the
 2 morphological variability of patients on the quality of their treatments, the head model
 3 considered in this study can be of interest. This sensitivity study will be conducted in section
 4 4.3.



6
 7
 8 **Figure 1.** (Left) simplified models of the neutron source (yellow), the biological protection (blue), the concrete
 9 wall (green), the moderator and its voxelization (gray), the patient's head and the CTV (red) ; (right) simplified
 10 model of the patient's head, with its voxelization: CTV (red), healthy brain (orange), skull (green), scalp (blue).

11
 12 *Biological dose.* To evaluate the biological doses deposited in each voxel of the head, we will
 13 use the ICRU 46 compositions and densities of the tissues, recalled in Table 1 [11]. The
 14 composition of the tumor will differ from that of the brain only in its higher concentration of
 15 ¹⁰B. The ¹⁰B delivery agent considered is BPA, the corresponding ¹⁰B concentrations C_B are
 16 given in Table 2 for each tissue (factor 1 brain/blood, 3.5 tumor/blood, 1.5 scalp/blood) [4]. In
 17 this study, we will use a standard definition of the total biological dose, $D = w_\gamma D_\gamma + w_n D_n +$
 18 $w_p D_p + w_B D_B$, where $D_{\gamma,n,p,B}$ are the gamma, neutron, proton and boron doses, and $w_{\gamma,n,p,B}$ the
 19 corresponding biological weighting factors, given in Table 2 for each tissue [2]. To evaluate
 20 each dose component $D_{\gamma,n,p,B}$, we will use kerma factors for each tissue. The supplementary
 21 material of Ref. [11] contains files which allow to reconstruct the neutron kerma, $K_n(E)$, using
 22 the elementary neutron kerma given Ref. [12, 13], for each tissue. These kerma factors notably
 23 take into account the contributions of the ¹⁴N(n,p) or ^{nat}Cl(n,p) reactions. The K_n curves obtained
 24 are presented in fig. 2. The K_γ photon kerma are reconstituted for each tissue using Ref. [14]
 25 and log-log fits for the missing energy intervals. We checked fig. 3 (left) that this approach
 26 returns the photon kerma for the brain provided in Ref. [15]. The photon kerma obtained for
 27 each tissue are shown fig. 3 (right). Finally, the K_B boron kerma comes from [11], and is given
 28 in fig. 2 per ppm of ¹⁰B in tissue. The neutron kerma $K_n(E)$ including the contributions of (n, p)
 29 reactions, and the Coderre coefficients w_n and w_p being equal, the contributions D_n and D_p will
 30 be combined in a single dose, D_n . The equation for the total biological dose D_i in each voxel Δ_i
 31 of the patient's head is then written:

$$\begin{aligned}
 D_i &= w_{B,i} D_{B,i} + w_{n,i} D_{n,i} + w_{\gamma,i} D_{\gamma,i} \\
 &= \int_E \left[(w_{B,i} K_{B,i}(E) + w_{n,i} K_{n,i}(E)) \phi_{n,i}(E) + w_{\gamma,i} K_{\gamma,i}(E) \phi_{\gamma,i}(E) \right] dE \quad (1)
 \end{aligned}$$

34
 35 where $\phi_{n,i}(E)$ and $\phi_{\gamma,i}(E)$ are the neutron and photon fluences per unit of energy in the voxel Δ_i .
 36

	Brain	Skull	Scalp
H	107	50	100
C	145	212	204
N	22	40	42
O	712	435	645
Na	2	1	2
Mg	0	2	0
P	4	81	1
S	2	3	2
Cl	3	0	3
K	3	0	1
Ca	0	176	0
Density (g/cm ³)	1.04	1.61	1.09

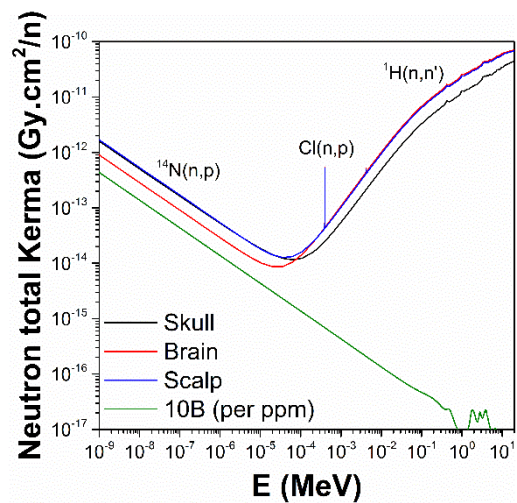
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Table 1. Chemical compositions (in mg/g) and densities (in g/cm³) in head tissues [11].

Tissue	w_B	w_n	w_p	w_γ	C_B (μg/g)
tumor	3.8	3.2	3.2	1	52.5
brain	1.3	3.2	3.2	1	15.0
skull	1.3	3.2	3.2	1	15.0
scalp	2.5	3.2	3.2	1	22.5

4
5
6

Table 2. Biological weighting factors w and ¹⁰B concentrations C_B (in μg/g) in head tissues.



7
8
9
10
11

Figure 2. Neutron kerma $K_n(E)$ in Gy.cm²/neutron(n) in the brain, the skull and the scalp; boron kerma, in Gy.cm²/neutron(n), per ppm of ¹⁰B in a tissue.

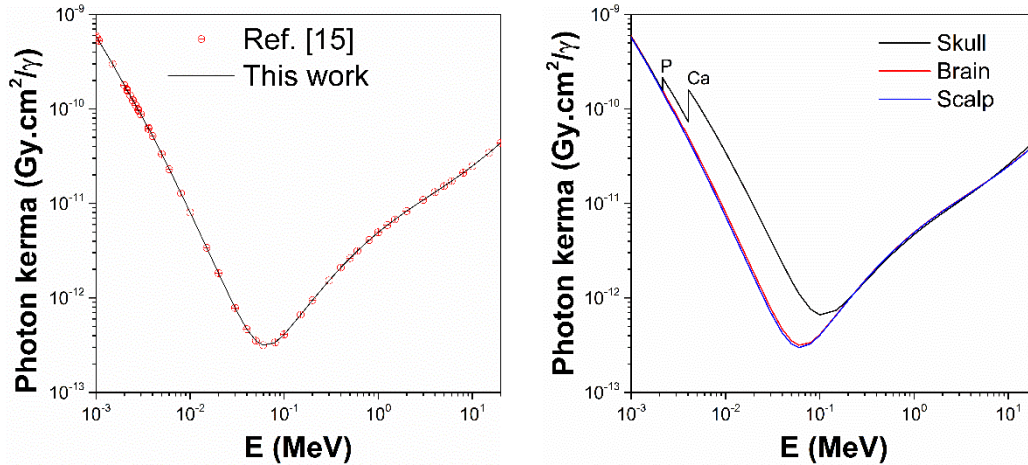


Figure 3. (Left) comparison of a reconstituted photon kerma in healthy brain with data of Ref. [15]; (right) photon kerma, $K_\gamma(E)$, in $\text{Gy}\cdot\text{cm}^2/\text{gamma}(\text{g})$, for brain, skull and scalp.

Peak doses. The values of the peak doses not to be exceeded locally, available in the literature for the brain, skull or scalp, vary significantly from one study to another, and rarely mention the volume of tissue concerned. Rubin recommends $L = 15\text{-}25$ Gy (brain), > 30 Gy (skull) and $15\text{-}20$ Gy (skin) [16]. Torres-Sánchez et al. used $L = 12.5$ Gy-Eq (brain) and 24 Gy-Eq (scalp), without justification nor indication of the volume concerned [3]. Capoulat et al. used $L = 11$ Gy-Eq (brain) and 16.7 Gy-Eq (scalp), also without justification nor indication of the volume concerned [4]. An average peak dose for the whole brain, 7 Gy-Eq, is however mentioned there. Hervé et al. used $L = 14.1 \pm 1.8$ Gy-Eq per cm^3 of brain [5]. This value comes from a study by Coderre et al., which showed that exposure of 14.1 Gy-Eq in 1 cm^3 of brain induces in 50% of treated patients a somnolence syndrome [2]. This proportion is reduced to 5% for $L = 11$ Gy-Eq (1 cm^3 of brain) [2], a more acceptable proportion if BNCT were to develop, which is the value used by Capoulat et al. [4]. The values $L = 16.7$ and 24 Gy-Eq respectively used by Capoulat et al. and Torres-Sánchez et al. for the scalp are consistent with the findings of a study by Menéndez et al., which shows that doses to the skin between 16.5 and 24 Gy-Eq have manageable toxicities [17]. The study by Menéndez et al. however concerns a small number of patients, whose area treated with BNCT was not the scalp but various leg skins. The transposition of the results of [17] to the determination of L (scalp) is therefore not immediate. In conclusion, as a precaution, we will use in this study the most conservative L values proposed in the literature, i.e. 11 Gy-Eq (brain), 30 Gy-Eq (skull) and 16.7 Gy-Eq (scalp). These conservative values pose an interesting challenge to the design of the moderator, which should ensure a high contrast between the tumor dose and the doses deposited in healthy tissues.

Transport code and nuclear data. The simulations carried out for this study were performed with the transport code MCNP 6 [7], simultaneously propagating neutrons and photons. With the exception of the results presented in section 4.2, the neutron and photon transport data used come from the ENDF/B-VII.0 database (/B-VI.6 for ^1H and ^{138}Ba). All cross-sections, including $S(\alpha,\beta)$ data, are taken at room temperature. With the exception of calculations performed with $N = 150$, all MCNP simulations performed in this study were run using 5×10^9 source neutrons.

3. Topology optimization of the moderator

In this section, we will let a topology optimization algorithm determine the structure of an AB-BNCT heavy water neutron moderator, with a level of human intervention as low as possible.

1 Still, choices will have to be made, which like any human choice are debatable, and amendable
 2 if necessary. We will choose to optimize the structure of a D₂O moderator, favoring, over all
 3 other considerations, the cleanliness of the treatment, i.e. the ability of the AB-BNCT unit: (i)
 4 to generate a high dose in the tumor; (ii) while ensuring that the doses deposited in the patient's
 5 head do not exceed the local peak doses, or exceeds them as little as possible if this goal proves
 6 untenable. This choice, which gives priority to the therapeutic objective over the economic
 7 objective, will lead to moderator configurations that will not necessarily maximize the dose rate
 8 deposited in the tumor, and therefore will not minimize the treatment time. This choice is
 9 present in the watermark in many studies of moderator design, cf. e.g. [3-5]. In part because
 10 treatment time is function of the maximum beam power, which itself depends on manufacturing
 11 processes and technological innovations not all off the shelf. Partly also because there is no
 12 rigid guideline on this treatment time. Some recommend it to be less than 60 min, but what
 13 about the possibility of multi-fractionating the treatment for example. In the absence of certainty
 14 on this subject, the choice made in section 3 seems reasonable. It is however important to note
 15 that an optimization of the moderator design with a different objective, e.g. an objective of
 16 minimizing the treatment time, can be carried out using the same methodology than that
 17 presented in section 3.1, by simply replacing the F_{PEN} function in Eq. (2) by the treatment time.

19 3.1. Formalization and resolution of the optimization problem

21 We want to determine the optimal composition of a D₂O moderator, i.e. the densities ρ_j of heavy
 22 water contained in each voxel Θ_j , allowing a D_{obj} dose to be deposited in the tumor while
 23 minimizing the exposure of healthy tissues. To achieve these goals, we must ensure that each
 24 dose D_i , given Eq. (1), deposited in each voxel Δ_i of the patient's head does not exceed the
 25 corresponding peak dose L_i . As a reminder, $L_i = 11$ Gy-Eq $\forall \Delta_i \in$ brain, 30 Gy-Eq $\forall \Delta_i \in$ skull
 26 and 16.7 Gy-Eq $\forall \Delta_i \in$ scalp. This problem can be formalized as follows:

$$\min_{\underline{\rho}} F_{PEN}(\underline{\rho}) = \sum_{i=1}^M \alpha_i \left(D_i(\underline{\rho}) / L_i \right)^n, \quad \alpha_i = \frac{V_i}{V_{head}}$$

$$28 \quad D_i(\underline{\rho}) = \frac{1}{V_i} \int_{E=0}^{+\infty} \int_{\underline{\Omega} \in 4\pi} \int_{\underline{r} \in \Delta_i} \left[\begin{array}{l} w_B(\underline{r}) K_B(\underline{r}, E) \\ + w_n(\underline{r}) K_n(\underline{r}, E) \\ + w_\gamma(\underline{r}) K_\gamma(\underline{r}, E) \end{array} \right] \varphi_n(\underline{r}, E, \underline{\Omega}, \underline{\rho}) d\underline{r} dE d\underline{\Omega} \quad (2)$$

$$\text{s.t. } B_n(\underline{\rho}) \varphi_n = Q_n \quad (C_1), \quad B_\gamma(\underline{\rho}) \varphi_\gamma = Q_\gamma(\varphi_n) \quad (C_2)$$

$$D_0(\underline{\rho}) = D_{obj} \quad (C_3) \quad \rho_j \leq \rho_{max} \forall j \quad (C_4)$$

29
 30 The problem (2) consists in finding the densities $\underline{\rho} = (\rho_1, \dots, \rho_N)$ in D₂O of the moderator voxels
 31 which minimize a penalization function F_{PEN} , while respecting 4 constraints: (C₁) the neutron
 32 transport must obey the Boltzmann equation, $B_n(\underline{\rho}) \varphi_n = Q_n$, where B_n is the Boltzmann operator,
 33 a function of the physicochemical characteristics of the materials crossed, therefore of the
 34 densities $\underline{\rho}$. Function $\varphi_n(\underline{r}, E, \underline{\Omega}, \underline{\rho})$ is the angular fluence of neutrons at position $\underline{r} = (x, y, z)$, of
 35 energies E and directions $\underline{\Omega}$. The Q_n term is the distribution in positions, energies and directions
 36 of the neutrons generated by the source, as a reminder ${}^9\text{Be}(d(1.45 \text{ MeV}), n)$ for this study; (C₂)
 37 photon transport must also obey a Boltzmann equation, with a source term Q_γ depending on the
 38 neutron fluence (production of gammas by neutron captures); (C₃) the dose D_0 deposited in the
 39 tumor must be equal to D_{obj} , equal to 30 Gy-Eq for a single-fraction glioblastoma treatment, cf.
 40 pp 201 of [1]; (C₄) the D₂O densities $\underline{\rho}$ can vary between 0 and $\rho_{max} = 1.11 \text{ g/cm}^3$, the natural

1 D₂O density. The F_{PEN} penalization function in problem (2) quantifies the cleanliness of the
 2 treatment: the lower its value, the more the treatment respects the peak doses in healthy tissues.
 3 Concretely, for each voxel $\Delta_i > 0$ of the patient's head, F_{PEN} is incremented by a quantity $(D_i/L_i)^n$
 4 weighted by the volume V_i of the voxel, V_{head} being the volume of the head. By taking a number
 5 $n \gg 1$, F_{PEN} is therefore incremented by a small quantity if $D_i < L_i$, since $x^n \rightarrow 0$ if $x < 1$, $n \rightarrow +\infty$,
 6 and on the contrary by a quantity high if $D_i > L_i$, since $x^n \rightarrow +\infty$ if $x > 1$, $n \rightarrow +\infty$. We will take
 7 $n = 30$ in this study. An analysis of the impact of this choice is carried out in section 4.1.

8 Problem (2) is a constrained optimization problem of which we can see the extreme complexity.
 9 The F_{PEN} function is a non-linear functional of the angular fluences of neutrons and photons,
 10 themselves non-linear, highly complex functionals of the densities ρ of the moderator. The
 11 space of solutions to be explored is also gigantic: for 375 voxels, each containing a density
 12 varying between 0 and ρ_{max} , say by small step $\delta\rho = \rho_{max}/50$, the number of possible moderator
 13 configurations is worth $50^{375} = 1.3 \times 10^{637}$, that is to say a numerical infinity. Despite this
 14 extreme complexity, it is now possible to solve problem (2) in a humanly compatible time using
 15 the topology optimization (TOPOPT) algorithm presented in Ref. [18, 19]. This algorithm
 16 solves the Lagrangian equations associated with the optimization problem, given Eq. (3), using
 17 an iterative procedure. Starting from a uniform configuration of densities, $\rho_j = \rho_0 \forall j$, it gradually
 18 modifies, small step $\pm\delta\rho$ by small step, the densities ρ_j of the voxels Θ_j until reaching the
 19 solution of the optimization problem at convergence. The doses $D_{n,i}$, $D_{\gamma,i}$ and $D_{B,i}$ which make
 20 up each dose D_i , cf. Eq. (1), can be calculated with MCNP using its DE and DF cards [7]. The
 21 calculation of the derivatives $\partial F_{PEN}/\partial\rho_j$ involves $M \times N$ derivatives $\partial D_i/\partial\rho_j$, which can all be
 22 calculated in a single MCNP simulation using its PERT card [7] and the procedure described
 23 in section 1 of Ref. [18]. In this study, we will take $\delta\rho = \rho_{max}/50$ and $\rho_0 = 0.2 \text{ g/cm}^3$.

$$L = F_{PEN} - \lambda.C$$

$$\frac{\partial L}{\partial \rho} = 0, \quad \frac{\partial L}{\partial \lambda} = 0 \quad (3)$$

3.2. Example of application of the TOPOPT approach

29 To illustrate the operation of this TOPOPT algorithm, we propose to determine in this section
 30 the optimal composition of a D₂O moderator for a 20 cm³ CTV at a depth $P_{tum} = 4.5 \text{ cm}$, cf.
 31 section 2. We will take for this calculation $N = 375$ voxels for the moderator and $M = 89$ voxels
 32 for the patient's head. The thickness H of the moderator and the heavy concrete wall is set at 30
 33 cm, cf. fig. 1. For this configuration, the algorithm converges in 95 iterations, which required 2
 34 months of calculation. Fig. 4 (left), we present in the XY plane some moderator configurations
 35 obtained before and after convergence for iteration numbers NUMITER ranging from 0
 36 (starting configuration, $\rho_j = 0.2 \text{ g/cm}^3 \forall j$) to 95 (convergence). The 3D structure of the
 37 moderator is generated by rotating these graphs around the $Y = 0$ axis of symmetry. The gray
 38 scales in fig. 4 (left) give the densities ρ_j in D₂O, in g/cm^3 , in the voxels Θ_j of the moderator.
 39 Fig. 4 (center), we present the maps of the total doses D_i associated with these moderators,
 40 deposited in each voxel Δ_i of the patient's head. The color scales in fig. 4 (center) give the values
 41 of the D_i doses in Gy-Eq. Finally, fig. 4 (right), we present the values of the dose excesses, E_i
 42 $= (D_i - L_i)/L_i$, in each voxel of the head, where L_i is as a reminder the value of the peak dose in
 43 the voxel Δ_i . The color scale in fig. 4 (right) gives the values of E_i in percent. For $E_i < 0$, the
 44 objective of the moderator optimization, the voxel is colored white. So, in summary, the more
 45 white and blue in these maps, the cleaner the treatment. These figures show how the TOPOPT
 46 algorithm improves iteration after iteration the structure of the moderator to improve the
 47 treatment cleanliness.

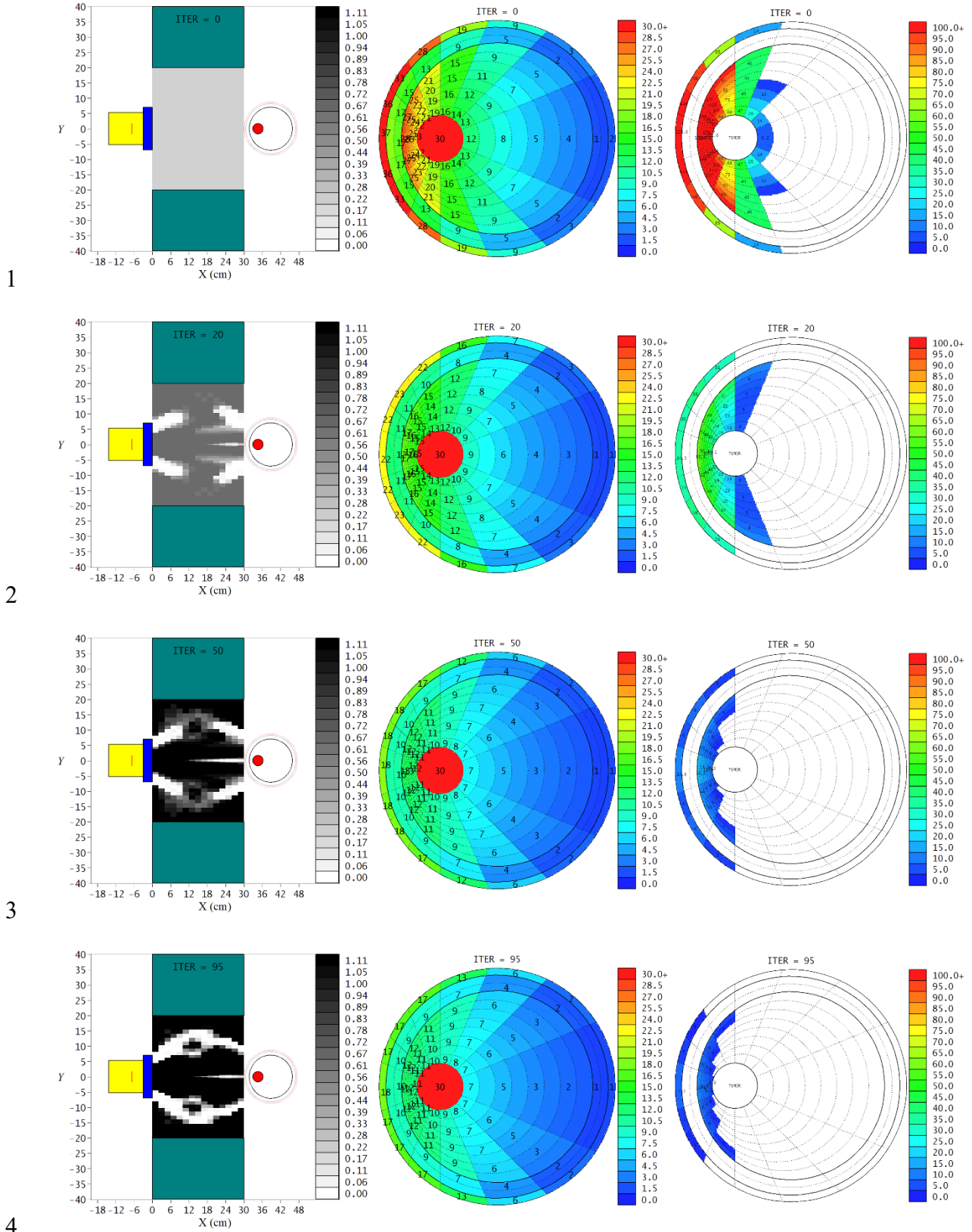
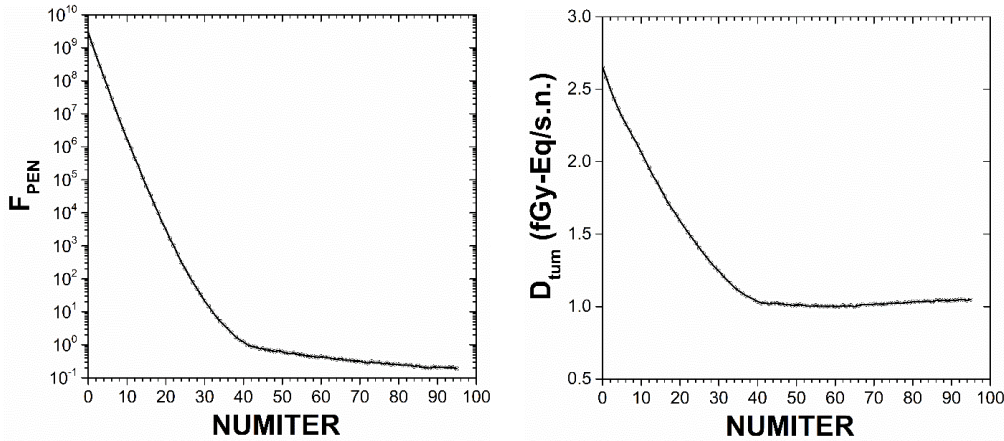


Figure 4. (Left) D₂O moderator configurations obtained for $N = 375$ voxels, $P_{tum} = 4.5$ cm, $H = 30$ cm and NUMITER = 0, 20, 50 and 95; (center) corresponding maps of the total doses, D_i , in Gy-Eq deposited in the patient's head; (right) corresponding maps of the dose excesses, E_i , in percent.

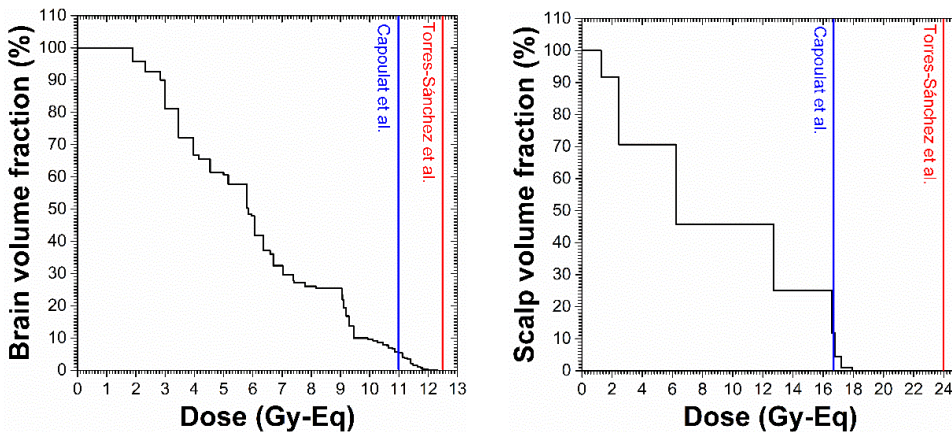
1 To complete this information, we show fig. 5 the evolution of F_{PEN} (left) and of the total dose
 2 rate D_{tum} deposited in the tumor, expressed in fGy-Eq/source neutron (s.n.) (right), as a function
 3 of the iteration number NUMITER. At convergence, $D_{tum} = 1.05$ fGy-Eq/s.n.. The efficiency of
 4 a ${}^9\text{Be}(d(1.45 \text{ MeV}), n)$ source being 3.3×10^{11} neutrons/mC [4], for a beam intensity of 30 mA
 5 [4], the treatment time necessary to deposit 30 Gy-Eq in the tumor will be 48 min. This time
 6 could be further reduced by adding to the simplified model of the unit treatment shown fig. 4 a
 7 reflector around the source at $x < 0$ cm. Indeed, a fraction of the source neutrons are emitted at
 8 angles greater than 90° , and are therefore artificially lost.
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Figure 5. Evolutions of F_{PEN} (left) and D_{tum} (right) with NUMITER, for $P_{tum} = 4.5$ cm, $N = 375$ and $H = 30$ cm.

Fig. 6, we plot for the optimal configuration of the moderator obtained at NUMITER = 95 (cf.
 fig. 4 or 7) the dose-volume histograms in healthy brain (left) and scalp (right), indicating the
 peak brain and scalp doses used by Capoulat et al. and Torres-Sánchez et al. [3, 4] described in
 section 2. For a dose to the tumor of 30 Gy-Eq and a CTV of intermediate depth, $P_{tum} = 4.5$ cm,
 we find that the doses deposited in healthy tissues remain mostly within the imposed limits.
 They exceed the peak values used by Capoulat et al. [4], 11 Gy-Eq (brain) and 16.7 Gy-Eq
 (scalp), only in a small volume of the brain (5.4%) and scalp (11.8%), and this by little in both
 cases. They nowhere exceed the peak values used by Torres-Sánchez et al., 12.5 Gy-Eq (brain)
 and 24 Gy-Eq (scalp), with a comfortable margin for the scalp. As for the skull, the maximum
 deposited dose is 9.9 Gy-Eq, well below its peak value, 30 Gy-Eq. In the end, the doses
 deposited exceed the peak doses of Capoulat et al. only in 4.8% of the head volume.

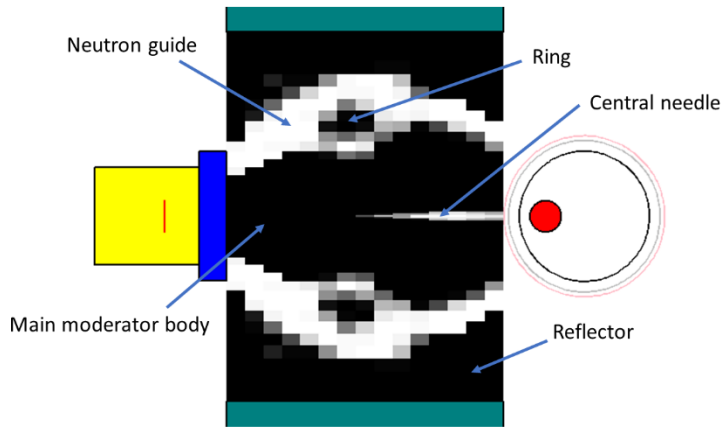


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Figure 6. Dose-volume histograms in healthy brain (left) and scalp (right), obtained for the TOPOPT moderator calculated for $P_{tum} = 4.5$ cm, $N = 375$ and $H = 30$ cm.

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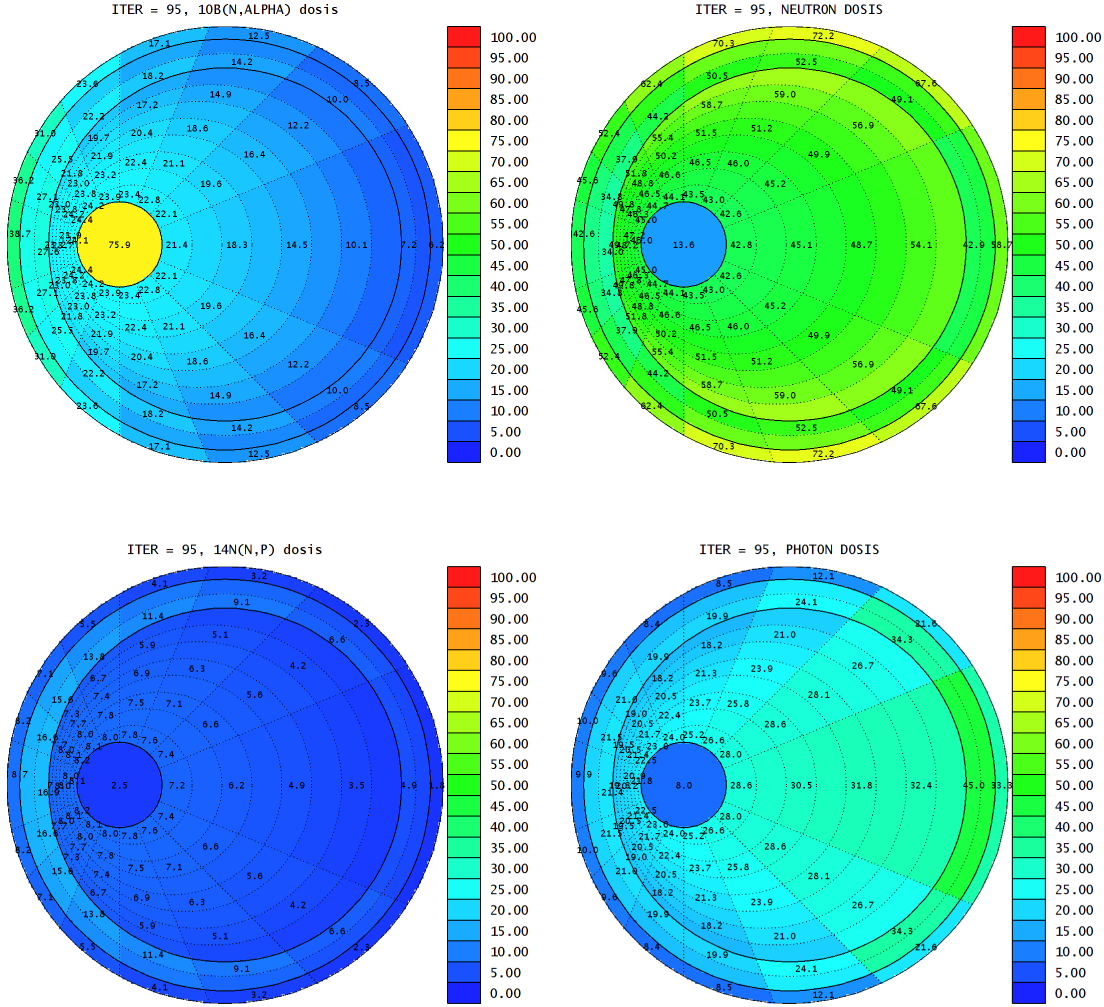
To achieve these conclusive results with a compact moderation volume, 0.04 m^3 (20 cm radius, 30 cm in length) despite the high energy, $\sim 2 \text{ MeV}$ in average, of the ${}^9\text{Be}(d,n)$ source neutrons, the TOPOPT algorithm generates a subtle device, visible fig. 4 iteration 95 or fig. 7 in more detail, composed of: (i) a neutron guide which drives the neutrons towards the tumor while slowing them down. This guide contains a heavy water ring, which scatters the neutron trajectories. At its exit, it recreates in an original way the equivalent of a multi-field treatment, which consists in simultaneously exposing a patient to several moderated neutron beams with different orientations [3]; (ii) a central needle, which acts as a small guide of moderated neutrons, and adds another directional exposure; (iii) and a main moderation body and a reflector. The details of this sophisticated structure are inaccessible to a parametric study, let alone to human intuition, thus illustrating the potential of the TOPOPT approach.



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Figure 7. Details of the TOPOPT moderator calculated for $N = 375$, $P_{tum} = 4.5 \text{ cm}$ and $H = 30 \text{ cm}$.

For the moderator obtained fig. 7, we give fig. 8, for each voxel Δ_i of the patient's head, the weights $w_{B,i}D_{B,i}/D_i$, $w_{n,i}D_{n,i}/D_i$ (all neutron contributions except ${}^{14}\text{N}(n,p)$), $w_{p,i}D_{p,i}/D_i$ (only ${}^{14}\text{N}(n,p)$) and $w_{\gamma,i}D_{\gamma,i}/D_i$, of each of the 4 components of the total dose D_i deposited, presented in section 2. The color scales of these figures give these weights in percent. We observe that: (i) the boron dose represents 76% of the total dose deposited in the tumor. Outside the tumor, however, it is only really important in areas of the scalp on the beam axis, where it matches the neutron dose contribution; (ii) the negligible nature of the ${}^{14}\text{N}(n,p)$ dose, except in the regions of the skull facing the moderator; (iii) the dominant character of the neutron dose, which accounts for $\sim 50\%$ of the total dose in all voxels except tumor, and which logically dominates in the areas of the scalp close to the exit of the neutron guide. The cleanness of the treatment thus strongly depends on the way in which the moderator slows down and focuses the neutrons on the head; (iv) the low relative contribution of gamma rays in the areas of the brain facing the moderator, which becomes important in its rear areas. This observation confirms the necessity to propagate neutrons and photons simultaneously in the simulations.



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4 **Figure 8.** Relative contributions, in %, to the total dose D_i of each of the 4 dose components presented section 2,
 5 $w_B D_B$, $w_n D_n$ (all reactions except $^{14}\text{N}(n,p)$), $w_p D_p$ (only $^{14}\text{N}(n,p)$) and $w_\gamma D_\gamma$, calculated for the TOPOPT moderator
 6 obtained for $N = 375$ voxels, $P_{tum} = 4.5$ cm and $H = 30$ cm (convergence at iteration 95) and shown fig. 7.

7

8 Fig. 9 (right), we give a representation of the energy spectra, $E \times N(E)/\Delta E \approx E \times \phi(E)$, of the
 9 neutrons (n) at the exit of the moderator, expressed in n/cm²/s.n., calculated for some positions,
 10 numbered from 1 to 4, shown in fig. 9 (left). Function $N(E)$ is the integral of the neutron fluence
 11 $\phi(E)$ per s.n. on the interval $[E, E+\Delta E]$, where the ΔE are the widths of the bins of the histograms
 12 fig. 9. We note that the moderator does not generate a ~ 10 keV mono-energetic, spatially
 13 homogeneous spectrum, contrary to what is sometimes recommended in the literature [1]. Its
 14 neutron guide (position 3) brings a contribution between 1 keV and 200 keV, visible fig. 9. The
 15 spectra generated by the central needle (position 1) and the moderation body (position 2) are
 16 epithermal from 1 eV to 100 keV, and contain a smaller proportion of neutrons of ~ 1 MeV. The
 17 spectrum emitted by the reflector (position 4) is a little harder, which makes it possible to
 18 compensate for the greater quantity of tissues to cross so that the neutrons arrive at the tumor
 19 with an energy favoring the captures on the ^{10}B . It is thus observed that the shape of the spectra
 20 at the exit of the moderator is coupled with the details of its structure. The TOPOPT algorithm
 21 cleverly adjusts the energies and directions of the neutrons exiting the moderator to minimize
 22 exposure of healthy tissue.

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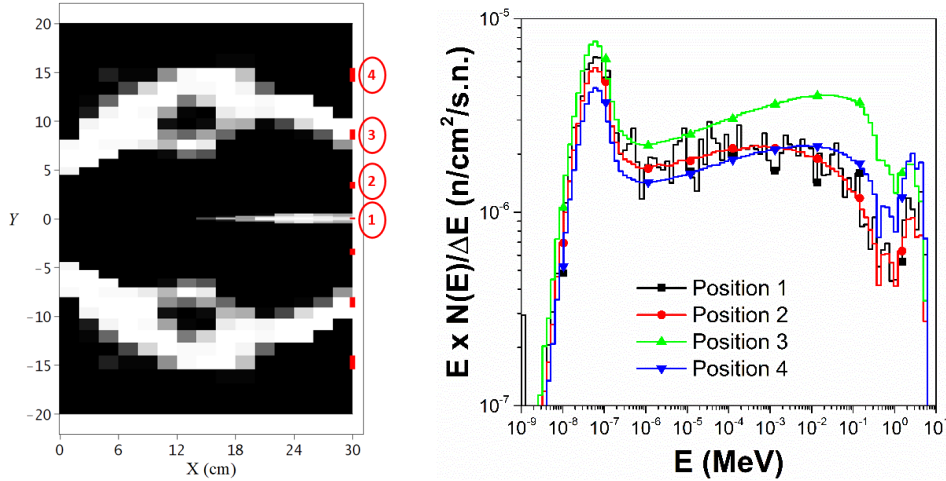


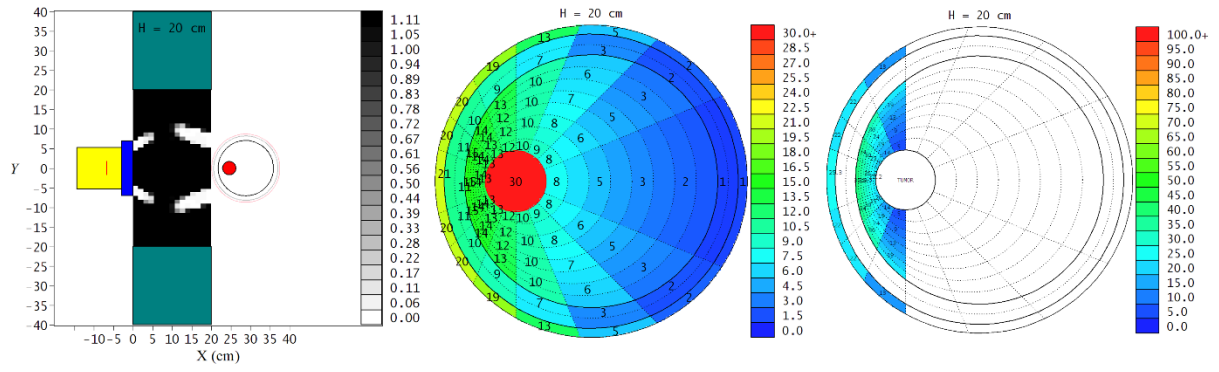
Figure 9. Energy spectra at the exit of the TOPOPT moderator obtained for $N = 375$, $P_{tum} = 4.5$ cm and $H = 30$ cm, at positions 1 to 4 indicated on the left.

3.3. Exploration of several parameters

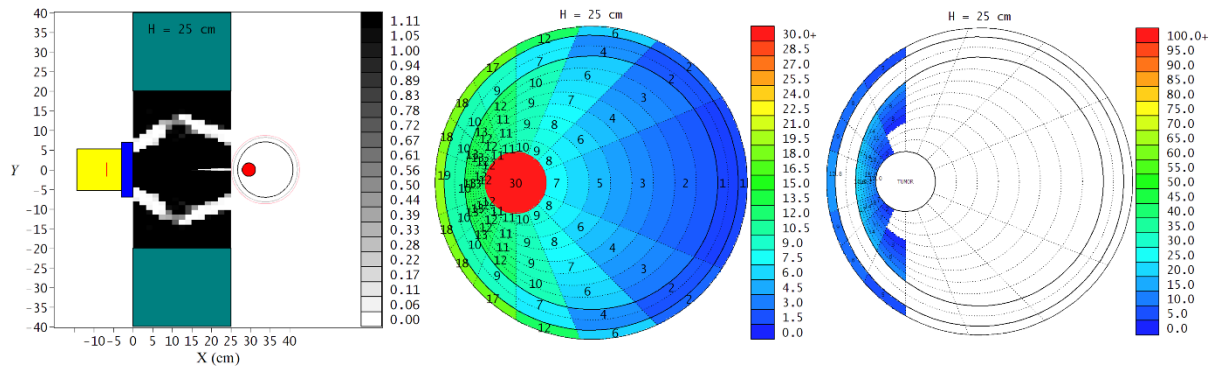
In this section, we will show how the shape of the moderator and the quality of treatment evolve with the maximum available thickness H or with the depth P_{tum} of the tumor. These studies will illustrate one of the strengths of the TOPOPT approach, which allows it to fit the design of the moderator to the various possible configurations of a BNCT treatment unit, as well as to the various biological parameters of its patients, including the nature of the neutron source used, the volume and the depth of the tumors to be treated, the structures of patients' heads, or the time and possible fractionation of the treatment, among many other parameters.

3.3.1. Evolution of the structure and efficiency of a TOPOPT D₂O moderator with its thickness

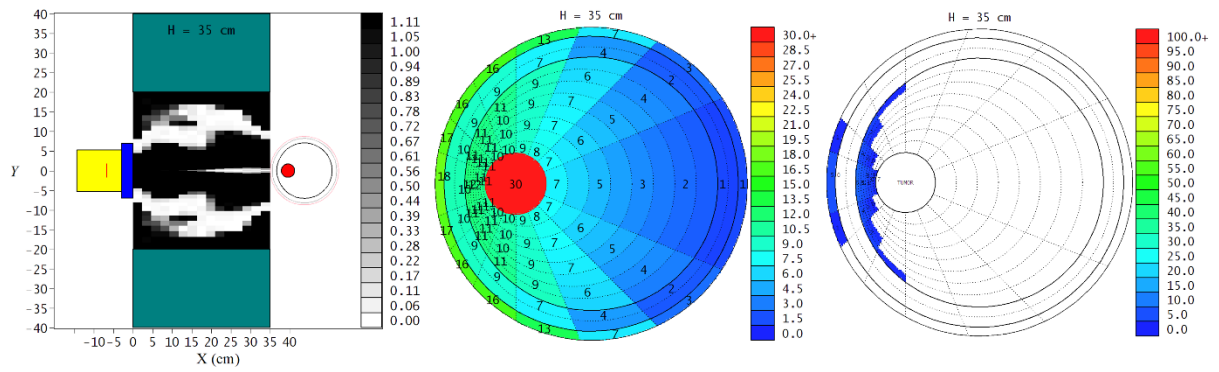
The calculations presented in section 3.2 were carried out for a thickness, $H = 30$ cm, of the moderator and concrete wall. This thickness has not been set arbitrarily: its order of magnitude comes from the work of Hervé et al. [5], who showed that a heavy water hemisphere of ~ 30 cm in radius moderates neutrons enough to deposit a high dose in the tumor while limiting the exposure of healthy brain tissue. However, one can wonder how the shape and performances of an optimal D₂O moderator evolve with thickness H . Fig. 10 (left), we present the TOPOPT configurations obtained for $N = 375$ voxels and $P_{tum} = 4.5$ cm, by varying H between 20 and 40 cm. The corresponding maps of the total doses D_i (resp. dose excesses E_i in each voxel of the head are presented in fig. 10 (center) (resp. right). We observe fig. 10 a foreseeable evolution of the optimal shape of the moderator with H . For low thicknesses, $H \leq 20$ cm, the too small available volume does not allow the algorithm to keep the central needle visible fig. 7, which is replaced in favor of a compact moderation body. Conversely, for high H values, there is more volume than necessary to slow down the neutrons. The algorithm has more room, and can create more complex and more efficient structures. In all cases, whatever the value of H , we observe that the algorithm systematically recreates a neutron guide similar to that shown fig. 7, which mimics a multi-field exposure.



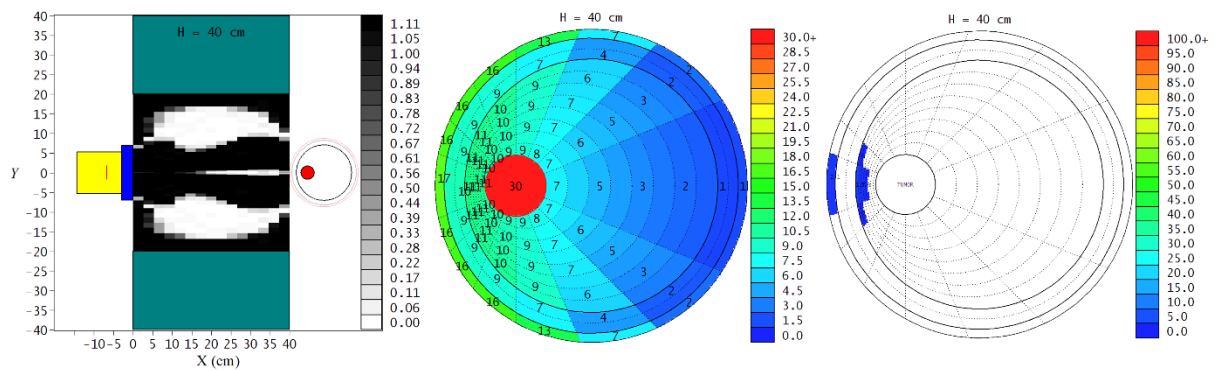
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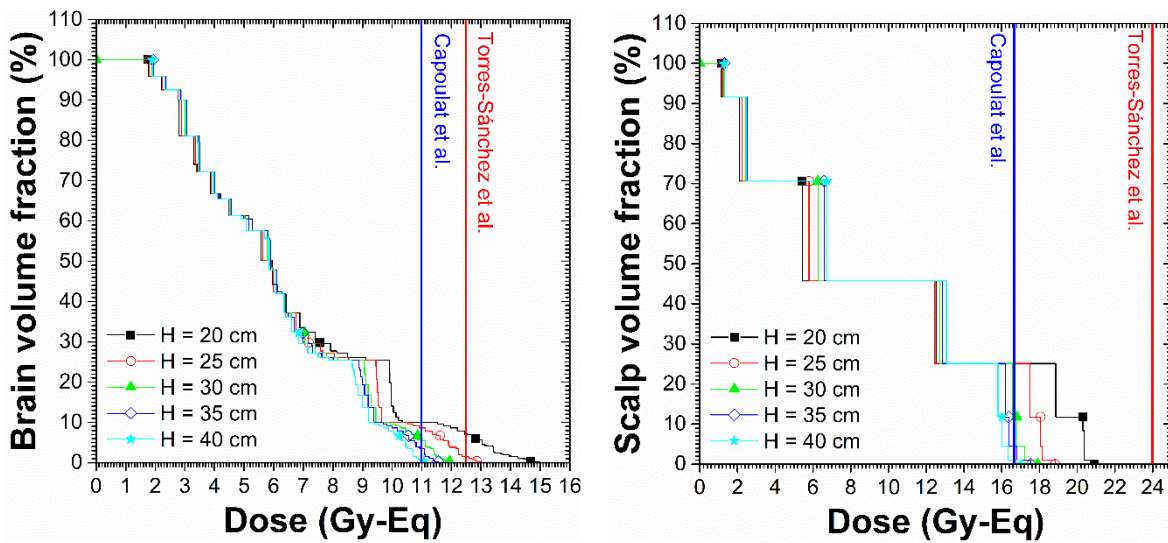
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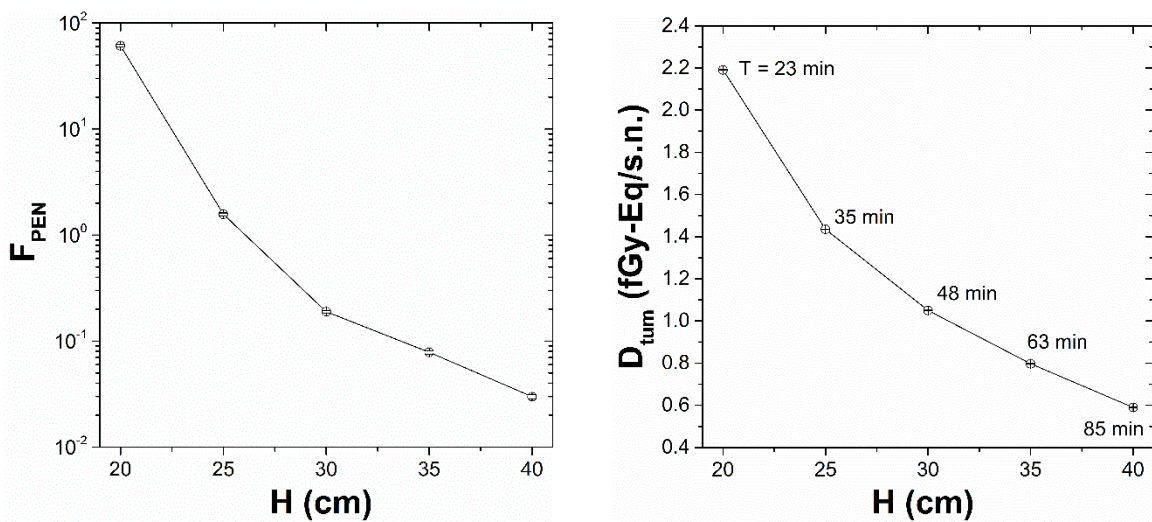
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Figure 10. (Left) configurations of the TOPTOP D₂O moderators obtained for $N = 375$ voxels, $P_{tum} = 4.5$ cm and $H = 20, 25, 35$ and 40 cm; (center) corresponding maps of the total doses, D_i , in Gy-Eq deposited in the patient's head; (right) corresponding maps of the dose excesses, E_i , in percent.

1 Fig. 11, we present the dose-volume histograms obtained in healthy brain (left) and scalp (right)
 2 as a function of H , for $N = 375$ voxels and $P_{tum} = 4.5$ cm. We note the cleanliness of the
 3 treatments obtained for $H \geq 30$ cm. For $H = 40$ cm e.g., the doses exceed the most conservative
 4 peak doses, 11 Gy-Eq (brain), 30 Gy-Eq (skull), 16.7 Gy-Eq (scalp), only in 0.41% of the
 5 volume of the patient's head, and this by little, +1-2% max. We also give fig. 12 the evolution
 6 of F_{PEN} (left) and D_{tum} (right) with H . The corresponding treatment times T , necessary to reach
 7 30 Gy-Eq in the tumor with 30 mA of beam intensity, are also indicated in fig. 12 (right). As
 8 one would expect, the more the thickness of the moderator increases, the better the neutrons are
 9 moderated and guided, the cleaner the treatment. But at the same time, the more H increases,
 10 the lower the neutron flux at the exit of the moderator, the longer the treatment. The choice of
 11 the thickness of the moderator will therefore require a compromise between the therapeutic
 12 objective (minimization of exposure to healthy tissues) and the economic objective
 13 (minimization of treatment time).



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 17 **Figure 11.** Dose-volume histograms in healthy brain (left) and scalp (right), obtained for the TOPOPT moderator
 18 calculated for $P_{tum} = 4.5$ cm, $N = 375$ voxels and $H = 20, 25, 30, 35, 40$ cm.



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 22 **Figure 12.** Evolution with H of F_{PEN} (left), D_{tum} (right) and T (right) at convergence, for $P_{tum} = 4.5$ cm and $N =$
 23 375 voxels.

1 3.3.2. Evolution of the structure and efficiency of a TOPOPT D₂O moderator with tumor depth

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 3 In this section, we will study how the optimal shape of the D₂O moderator and the associated
 4 treatment cleanliness evolve with the depth P_{tum} of the tumor. For this study, which is costly in
 5 computing power, we reduce the number N of voxels of the moderator to 150. As the volume
 6 of moderator voxels is subsequently increased, the MCNP simulations can be run with a lower
 7 number of source neutrons, here 2×10^9 . This reduction in the spatial resolution makes it possible
 8 to reduce the computation time per P_{tum} value to ~ 15 days, instead of 2 months beforehand. The
 9 considered P_{tum} depths vary from 3.5 cm (tumor in contact with the skull) to 8.5 cm (tumor at
 10 the center of the head). The thickness H of the moderator is set at 30 cm. The TOPOPT
 11 configurations obtained are presented in fig. 13-14 (left). For each configuration, the total doses
 12 D_i and the dose excesses E_i in the voxels of the head are presented fig. 13-14 (center and right).

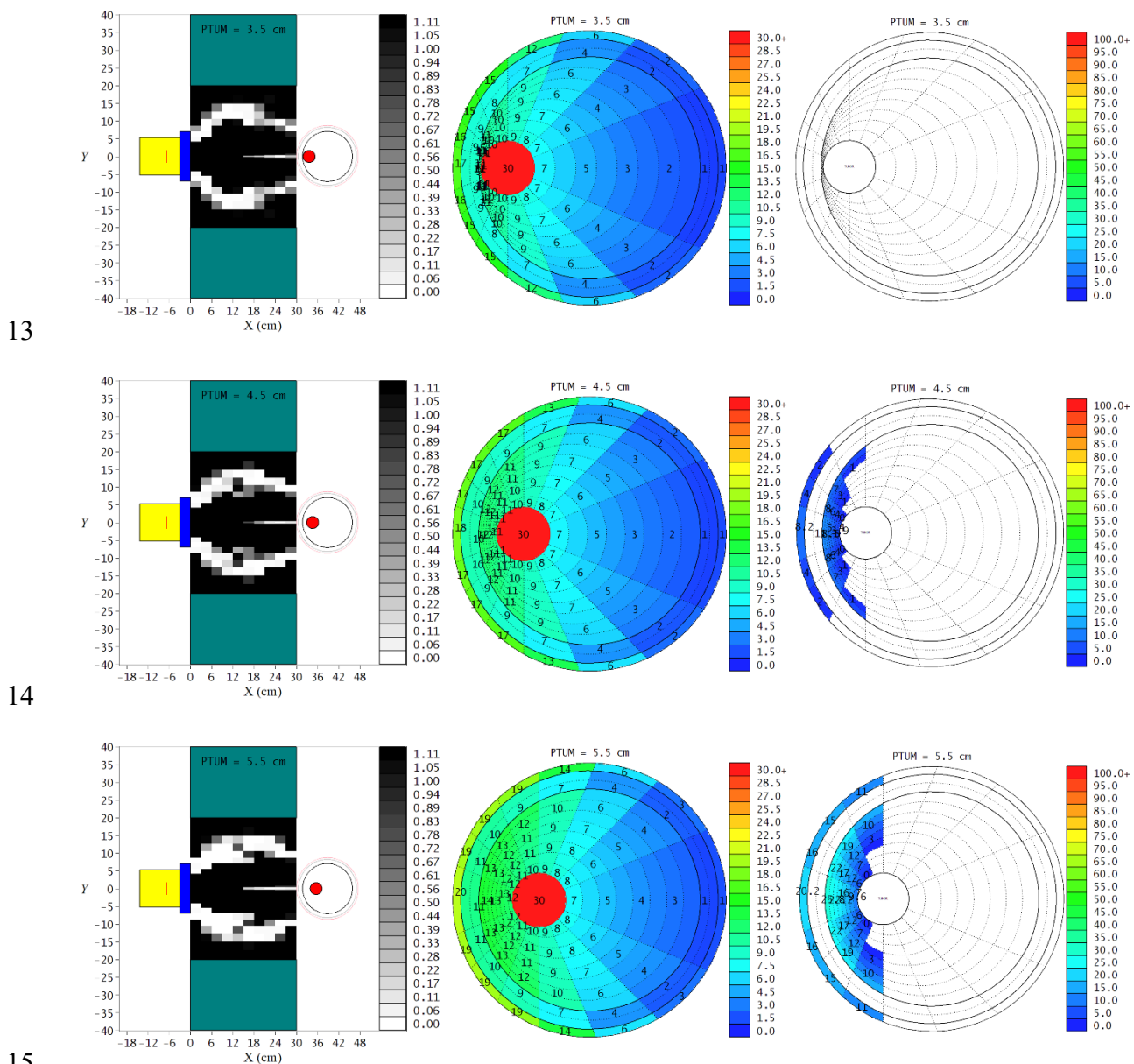


Figure 13. (Left) configurations of the TOPOPT D₂O moderators obtained for $N = 150$ voxels, $H = 30$ cm and $P_{tum} = 3.5, 4.5$ and 5.5 cm; (center) corresponding maps of the total doses, D_i , in Gy-Eq deposited in the patient's head; (right) corresponding maps of the dose excesses, E_i , in percent.

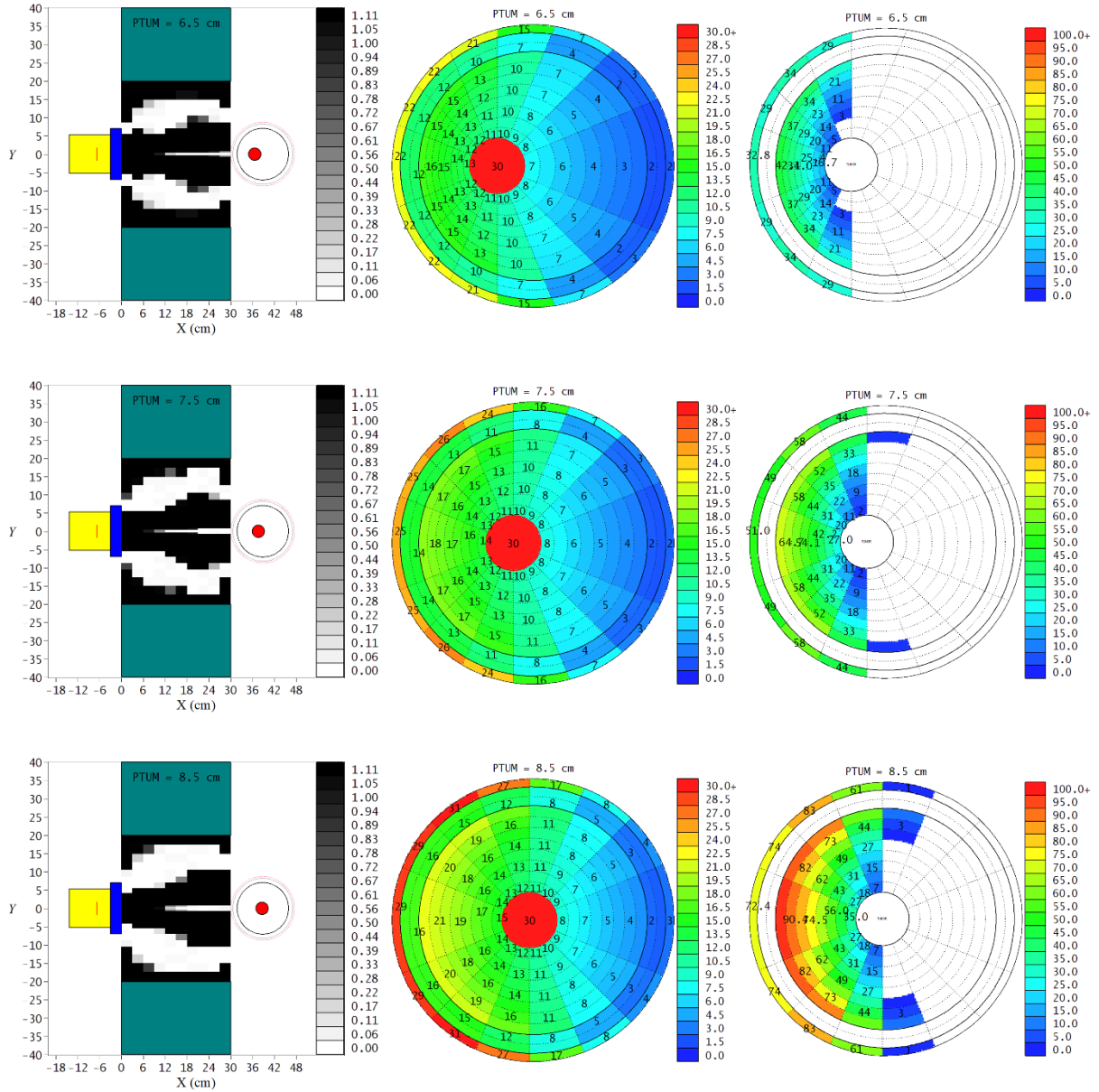
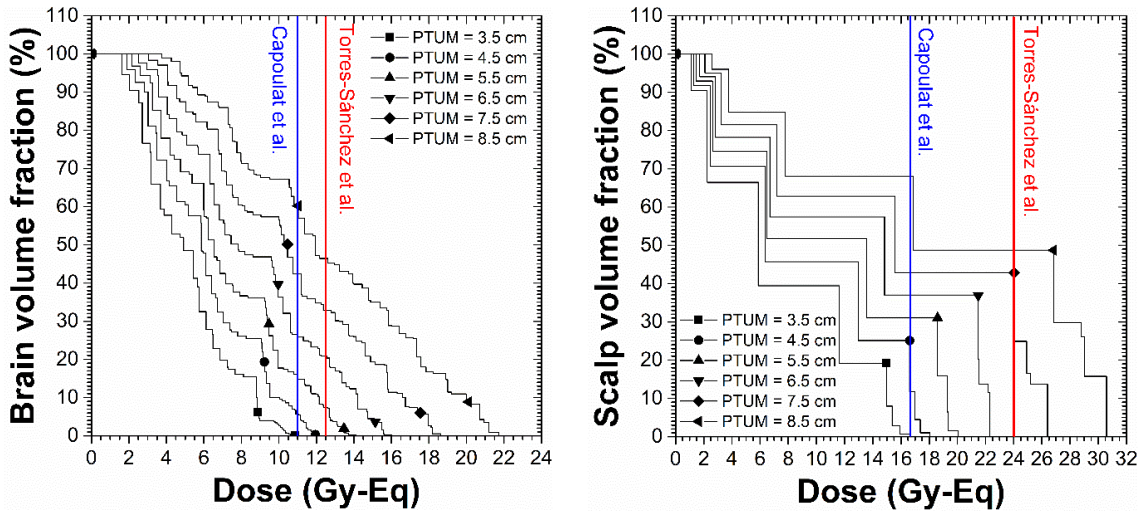


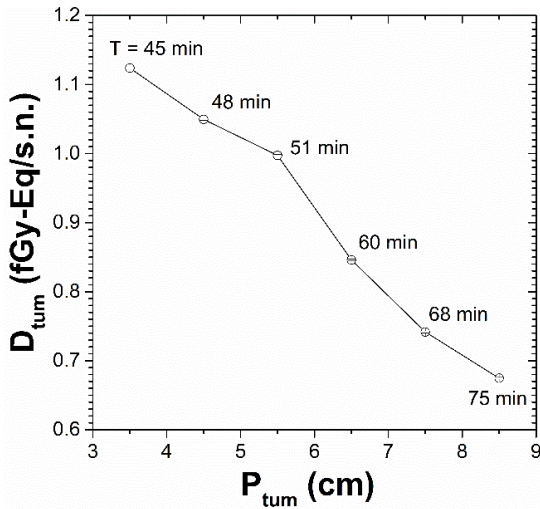
Figure 14. (Left) configurations of the TOPOPT D₂O moderators obtained for $N = 150$ voxels, $H = 30$ cm and $P_{tum} = 6.5, 7.5$ and 8.5 cm; (center) corresponding maps of the total doses, D_i , in Gy-Eq deposited in the patient's head; (right) corresponding maps of the dose excesses, E_i , in percent.

For $P_{tum} \leq 5.5$ cm, we observe fig. 13 that the algorithm recreates a moderation body, a reflector, a neutron guide and a central needle, as discussed in section 3.2. At 5.5 cm, however, a topology transition occurs; the moderator shape evolves to be closer to that of a moderated gun, whose moderation volume decreases as P_{tum} increases. Such a development is consistent with the fact that the deeper the tumor, the harder the neutron energy spectrum must be to reach it. For $P_{tum} \leq 5.5$ cm, the treatment maintains a good degree of cleanliness, with doses exceeding peak values only in a small volume of the patient's head, and by little. Beyond that, the quality of treatment deteriorates. This development is made clearly visible in fig. 15, where we present the dose-volume histograms obtained for healthy brain (left) and scalp (right) for each depth. For tumors deeper than 5.5 cm, it will probably be necessary to modify the thickness H and the radius (so far set at 20 cm) of the moderator, as suggested by the perhaps too small thickness of the reflectors visible in fig. 14. Materials other than heavy water will also have to be tested,

1 which may perform better at very high depths. This specific study will be conducted as part of
 2 a project currently being submitted. We give fig. 16 for information the evolution of the D_{tum}
 3 dose rate with P_{tum} . The corresponding treatment times T , necessary to reach 30 Gy-Eq in the
 4 tumor with 30 mA of beam intensity [4], are indicated.
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 8 **Figure 15.** Dose-volume histograms in healthy brain (left) and scalp (right), obtained for $N = 150$ voxels, $H =$
 9 30 cm and P_{tum} ranging from 3.5 to 8.5 cm.

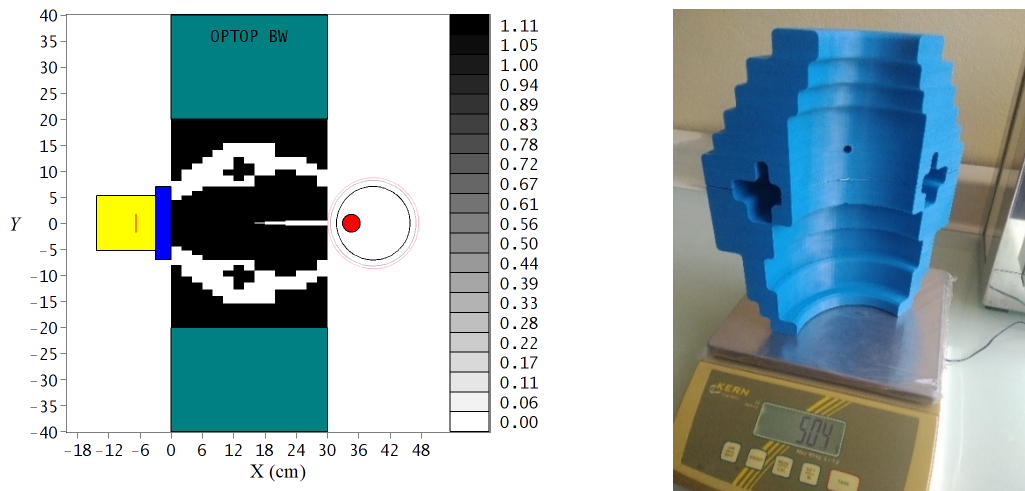


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 13 **Figure 16.** Evolution of D_{tum} and T with P_{tum} , at convergence, for $H = 30$ cm and $N = 150$ voxels.

14 3.4. Manufacture of a TOPOPT D2O moderator

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 17 The densities ρ_j of heavy water obtained by topology optimization in the voxels Θ_j of the
 18 moderator vary between 0 and ρ_{max} , the density of heavy water. Strictly compliant manufacture
 19 of a TOPOPT moderator will therefore require the use of porous materials, e.g. beads of varying
 20 sizes, or alveolar media manufactured by 3D printing. Such technologies exist, cf. e.g. [20, 21].
 21 However, a simplification of the design, of the binary type, where we force each moderator
 22 voxel to contain either 0% or 100% heavy water, would, at least initially, be easier to machine.
 23 Fig. 17 (left) presents the design obtained for $H = 30$ cm and $P_{tum} = 4.5$ cm by taking $\rho_j = \rho_{max}$
 24 if $\rho_j > \rho_{max}/2$, $\rho_j = 0$ otherwise. The F_{PEN} value obtained for this simplified configuration, called
 25 TOPOPT Black & White (BW) in the rest of this study, is equal to 0.1998 ± 0.0062 , against

1 0.1892 ± 0.0058 for the original TOPOPT configuration. These two values are statistically
 2 compatible, the simplification of the design does not lead to a significant deterioration in the
 3 quality of treatment. This result is consistent, since apart from a few border voxels, the TOPOPT
 4 design shown in fig. 7 is already predominantly binary.
 5 This simplification of the design facilitates the manufacturing of the TOPOPT moderator. One
 6 possible solution is to machine, e.g. from aluminum or steel, a cylindrical tank 20 cm in radius
 7 and 30 cm in length. The neutron guide and the central needle of the TOPOPT BW moderator
 8 can then be 3D printed and positioned in the tank, which is then filled with heavy water (32
 9 liters for the design in fig. 17). We give fig. 17 (right) a photo of a section of the neutron guide,
 10 printed in PLA using a RAISE3D machine from the CNRS LPSC printing platform. There is a
 11 small hole, made for the heavy water to fill the ring in the neutron guide visible in fig. 7 or 17.



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 14 **Figure 17.** (Left) BW design of the TOPOPT moderator calculated for $N = 375$ voxels, $P_{lum} = 4.5$ cm and $H = 30$
 15 cm; (right) 3D printing in PLA of a section of the neutron guide of this moderator.
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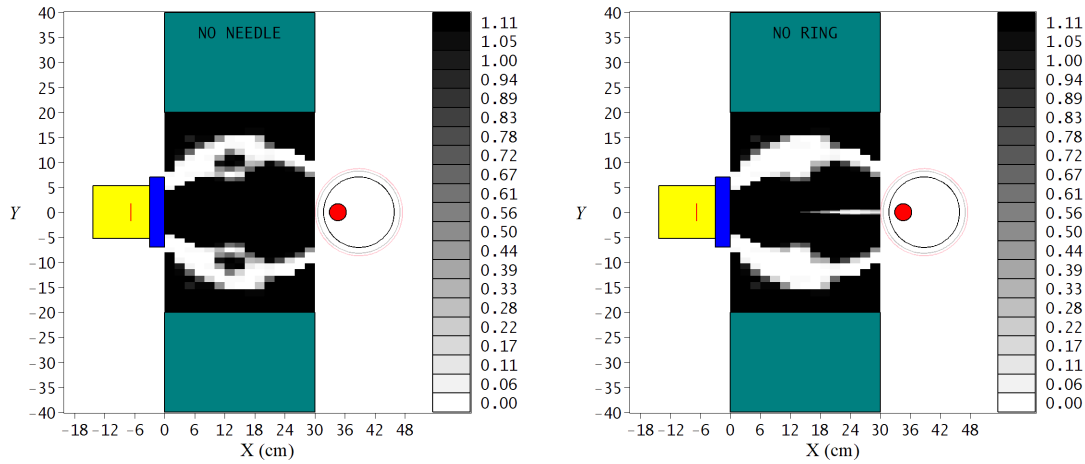
17 4. Robustness of the design of a moderator

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 20 In this section, we present a set of sensitivity studies, useful for evaluating the robustness of the
 21 TOPOPT calculations. We have explored the sensitivity of the quality of treatment to the details
 22 of the structure of a TOPOPT moderator, to the voxelization of the patient's head, to the
 23 parameterization of the F_{PEN} function, to the uncertainties on transport data and to the
 24 morphological diversity of the patients.
 25

26 4.1. Robustness of the topological optimization

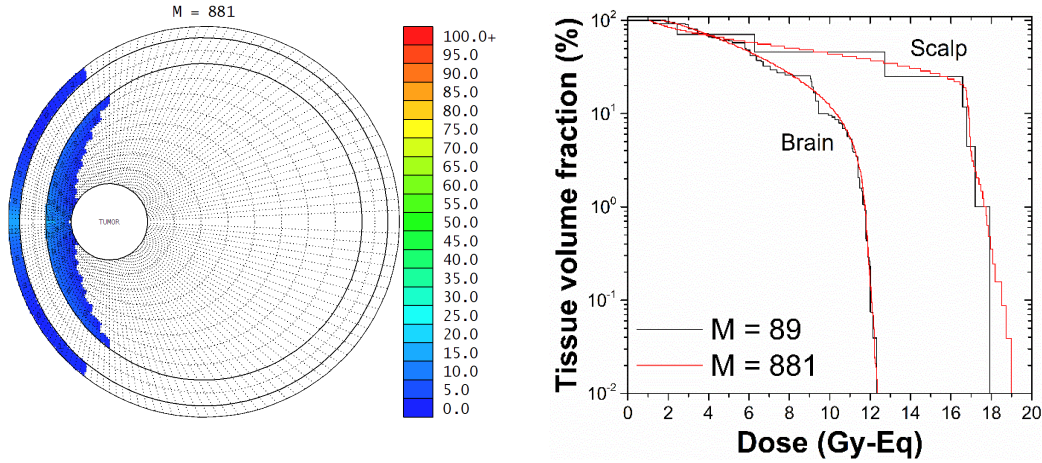
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 28 *Global or local optimum.* The moderator shapes computed in section 3 are complex but proved
 29 efficient. One can nevertheless legitimately wonder if each of these shapes really constitutes a
 30 global optimum of the optimization problem (2), and not a local optimum. Could there be even
 31 more efficient shapes? The TOPOPT algorithm is a complex iterative algorithm, and predicting
 32 the outcome of an iterative algorithm, even a very simple one, is in the vast majority of cases
 33 impossible, cf. Langton's ant or Syracuse conjecture. Nonetheless, there are arguments in favor
 34 of the global optimum. In Ref. [18], we verified, for several optimization problems constructed
 35 to have a solution obvious to a human or an analytical solution that the TOPOPT algorithm
 36 does indeed reach the global optimum. In addition, it is possible to test the robustness of the
 37 solutions found, e.g. the solution proposed in fig. 7, by modifying some geometry details, for

1 example by removing the D₂O ring or the central needle described in section 3.2, then by
 2 looking at the impact of these modifications on the treatment quality. The geometries of these
 3 modified moderators are presented in fig. 18. The F_{PEN} values obtained are 0.2030 ± 0.0063 (no
 4 needle) and 0.2202 ± 0.0067 (no ring), against 0.1892 ± 0.0058 for the TOPOPT moderator.
 5 We see a degradation in the cleanliness of the treatment, indicating that the intricacies of the
 6 structure of a TOPOPT moderator (at least this one) are not superfluous.



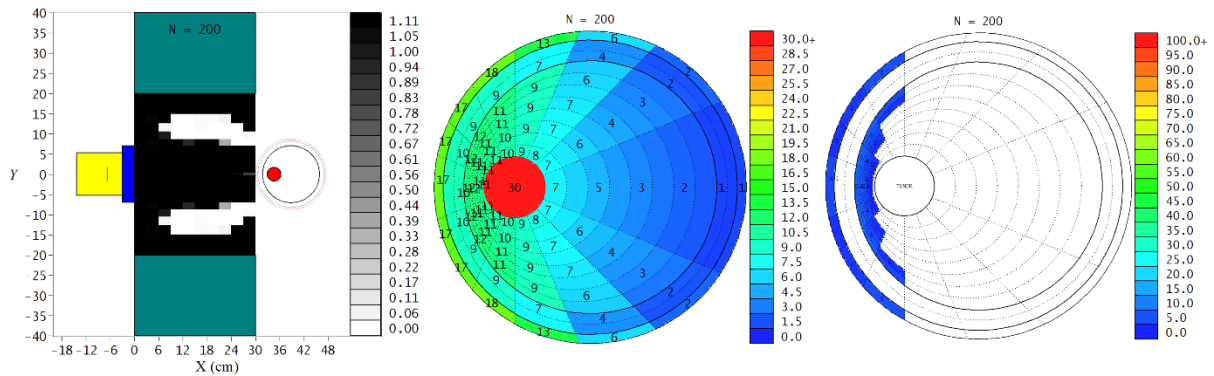
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 9 **Figure 18.** (Left) design obtained by removing the central needle in the TOPOPT moderator shown fig. 7; (right)
 10 design obtained by removing the D₂O ring in the neutron guide of the TOPOPT moderator shown fig. 7.

11
 12 *Existence of dose hot spots.* The head model used in this study, presented in section 2 and fig.
 13 1, is composed of $M = 89$ voxels: 1 for the tumor, 88 for the healthy tissues. Even if its axial
 14 symmetry eliminates the need for a discretization in angles around the axis, one can legitimately
 15 wonder if this small number of voxels can mask, by averaging it on the volume of a voxel, a
 16 (or several) local deposit of very high dose, of the hot spot type, in particular in tissues located
 17 near the exits of the moderators. To study this possibility, we took the TOPOPT moderator
 18 shown fig. 7, and recalculated with it the doses deposited in a head model comprising $M = 881$
 19 voxels, 1 for the tumor, 880 for the healthy tissues, drawn in fig. 19 (left). The resulting map of
 20 dose excesses is given fig. 19 (left). By comparing it with that obtained in fig. 4 for $M = 89$, we
 21 see no hot spot, only a slight increase in the dose delivered in the scalp in front of the central
 22 needle, cf. fig. 7. To complete the analysis, we plot fig. 19 (right) the dose-volume histograms
 23 in healthy brain and scalp obtained for $M = 89$ and 881. We again note a slightly higher dose
 24 deposition in an area encompassing 0.04% of the volume of the scalp, located in front of the
 25 central needle. We therefore retained $M = 89$ in this study, a value which ensures a compromise
 26 between the spatial resolution of the dose deposition and the large computation time (as a
 27 reminder, 2 months for a TOPOPT computation with $N = 375$ and $M = 89$, against ~ 20 months
 28 probably with $M = 881$).
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3 **Figure 19.** (Left) map of the dose excesses E_i , in %, obtained for the head model with $M = 881$ voxels and the
4 TOPOPT moderator shown fig. 7; (right) dose-volume histograms in healthy brain and scalp, obtained for $M = 89$
5 and 881 voxels.

6
7 *Sensitivity to optimization parameters.* The TOPOPT moderators presented in section 3 were
8 obtained by minimizing the F_{PEN} function formulated in Eq. (2). This formulation of F_{PEN} is a
9 human choice, reasoned, but which constitutes nonetheless a weak point. One can legitimately
10 wonder if the shapes and performance of moderators could be significantly improved with a
11 different formulation of F_{PEN} . Here again the question of the global character of the calculated
12 optima arises. Ideally, to answer this question, it would be necessary to propose a large number
13 (~ 100) of different yet credible F_{PEN} formulas, to compute for each of them the shape and the
14 properties of the TOPOPT moderator, then to conclude on the robustness of the design to the
15 choice of the formulation of the optimization problem. Such a study would however require a
16 gigantic computing power, which would amount in decades per 24 CPUs server. For the time
17 being, we therefore propose a less ambitious but more economical study, which consists in
18 keeping the formulation (2) of F_{PEN} , but by modifying the only parameter which is arbitrarily
19 chosen there, the number n . Indeed, the only condition on n is that it is $\gg 1$. To do this, we
20 recalculated the shape of the optimal moderator for $H = 30$ cm, $N = 150$ voxels, $P_{tum} = 4.5$ cm,
21 this time taking $n = 200$ instead of 30 so far. The configuration of the TOPOPT moderator thus
22 obtained is shown fig. 20 (left); the corresponding maps of doses and dose excesses in the head
23 voxels are presented in fig. 20 (center and right).



24
25
26 **Figure 20.** (Left) configuration of the TOPOPT D₂O moderator obtained for $N = 150$ voxels, $H = 30$ cm, $P_{tum} =$
27 4.5 cm and $n = 200$; (center) corresponding map of the total doses, D_i , in Gy-Eq deposited in the patient's head;
28 (right) corresponding map of the dose excesses, E_i , in percent.

1
2 Compared to the design shown fig. 13 for $n = 30$, we note an evolution in the shape of the
3 moderator, with a reduction in the length of the neutron guide and the central needle, both in
4 favor of a larger moderation volume. However, these design changes do not lead to a significant
5 change in the quality of treatment, as can be seen by comparing the maps of the dose excesses
6 fig. 13 for $n = 30$ and fig. 20 for $n = 200$. By recalculating F_{PEN} with $n = 30$ for the design
7 shown fig. 20, we get $F_{PEN} = 0.2367 \pm 0.0124$, against 0.2245 ± 0.0112 for the design shown
8 fig. 13, two values compatible in their error bars. The treatment quality therefore seems not
9 very sensitive to the choice of the number n , which constitutes a first element of response on
10 the robustness of the optimization to the formulation of F_{PEN} . However, we observe that the
11 D_{tum} dose rate obtained for the design shown fig. 20 is equal to 0.9468 ± 0.0016 fGy-Eq/s.n.,
12 against 1.0495 ± 0.0017 fGy-Eq/s.n. for the design shown fig. 13. The treatment time for the
13 TOPOPT design with $n = 200$ is therefore increased by 10% compared to the TOPOPT design
14 with $n = 30$. Taking a value of n that is too large is therefore counterproductive. Indeed, for
15 very large n values, function F_{PEN} varies considerably during convergence, over 70 orders of
16 magnitude for $n = 200$: $F_{PEN} = (2.6 \pm 1.4) \times 10^{74}$ at NUMITER = 0, $(9.7 \pm 3.9) \times 10^{51}$ at
17 NUMITER = 10, $(4.0 \pm 1.8) \times 10^3$ at convergence. Above all, its values are affected by very
18 large statistical errors, since they grow proportionally with n (derivative of F_{PEN}). Such
19 variations and stat. uncertainties alter the convergence of the TOPOPT algorithm, by penalizing
20 in a counterproductive way the transfers of matter between the voxels of the moderator which
21 would make it possible to exceed, even slightly, the peak doses at a place of the patient's head,
22 to significantly reduce exposure elsewhere. We therefore kept $n = 30$ throughout the study, a
23 reasonable value which satisfies the condition $n \gg 1$ while limiting the statistical error on F_{PEN}
24 at a few %.

25 26 4.2. Sensitivity to nuclear data

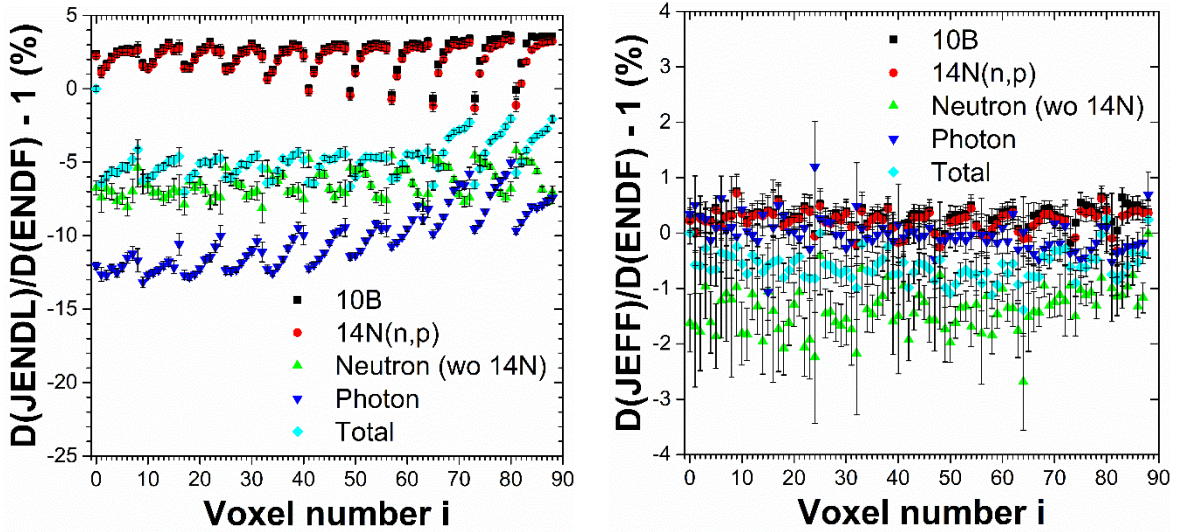
27
28 We will address here the question of the uncertainty on the calculated quality of treatment
29 induced by the uncertainties on the transport data. These transport data are produced through
30 models whose use or parameters can differ from one evaluator to another. They are affected by
31 statistical and systematic uncertainties, due to imperfections or unknowns in the experimental
32 devices used to measure them, to statistical fluctuations in measurements, to approximations in
33 modeling and analysis, etc. Carrying out such a sensitivity analysis & uncertainty quantification
34 study is a considerable work, which goes beyond the scope of this study. To address this
35 nonetheless important question, we propose here a simplified and common approach, which
36 consists in performing the calculations using several different databases, then in comparing the
37 results obtained.

38 For this study, we used the moderator shown fig. 7, obtained for $N = 375$ voxels and $P_{tum} = 4.5$
39 cm, using transport data from the ENDF/B-VII.0 database (/B-VI.6 for ^1H and ^{138}Ba), cf. section
40 2. We then recalculated the doses deposited in the patient's head, the F_{PEN} function, and the D_{tum}
41 dose rate in fGy-Eq/s.n., using two other databases, JEFF-3.1 and JENDL-3.3. This study
42 required some adjustments: (i) as JENDL-3.3 lacks the gamma-ray production cross-sections
43 for ^2H , ^{35}Cl , ^{37}Cl and ^{138}Ba (.42c), we used for these isotopes data from ENDF/B-VII.0 & /B-
44 VI.6 (.70c for ^2H , ^{35}Cl , ^{37}Cl , .66c for ^{138}Ba); (ii) same for ^{138}Ba in JEFF-3.1 (.03c), replaced by
45 ENDF/B-VI.6 (.66c); (iii) The $S(\alpha, \beta)$ thermal data were all taken from ENDF (hwtr.10t for the
46 moderator, grph.10t and al27.12t for the source casing, lwtr.10t for the head).

47 Fig. 21, we present, as a function of the voxel number i , the relative deviations, $D_i(x)/D_i(\text{ENDF})$
48 $- 1$, with $x = \text{JENDL-3.3}$ or JEFF-3.1 , between the ^{10}B , $^{14}\text{N}(n,p)$, neutron (without $^{14}\text{N}(n,p)$),
49 γ and total doses, calculated with ENDF/B-VII.0 & /B-VI.6, JEFF-3.1 and JENDL-3.3 (note:
50 these are doses expressed in Gy-Eq, obtained by setting the total dose $D_{i=0}$ deposited in the

1 tumor at 30 Gy-Eq, see fig. 21). We observe that, whatever the voxel $i > 0$ considered, the JEFF-
 2 3.1 and JENDL-3.3 total doses are systematically lower than the ENDF total doses, sometimes
 3 significantly (note: with the exception of voxels 80 and 88 for JEFF-3.1, where the deviations
 4 appear positive but are in fact consistent with 0 in the statistical error bars). It follows that the
 5 treatments predicted with JEFF-3.1 and JENDL-3.3 are cleaner than that predicted with ENDF,
 6 but also a little longer, as shown by the values of F_{PEN} and D_{tum} calculated for these 3 databases
 7 given table 3. It is probable that JENDL-3.3 underestimates the exposure of healthy tissues,
 8 because its data, particularly of gamma-ray production, are less complete. The difference
 9 between JENDL-3.3 and ENDF gamma doses is clearly visible in fig. 21 (left). Throughout our
 10 study, we adopted a conservative approach, consistently using the most unfavorable database,
 11 ENDF/B-VI.6 & VII.0, as it predicts a higher exposure to healthy tissues than JENDL-3.3 or
 12 JEFF-3.1.

13



14

15

16 **Figure 21.** Deviations in % between the ^{10}B , $^{14}\text{N}(n,p)$, neutron (w/o $^{14}\text{N}(n,p)$), γ and total doses, calculated for the
 17 TOPOPT moderator of fig. 7 with the ENDF/B-VI.6 & VII.0 and JENDL-3.3 databases (left), and with the
 18 ENDF/B-VI.6 & VII.0 and JEFF-3.1 databases (right). Note: the tumor voxel is the voxel $i = 0$, brain is $i = 1 \dots 64$,
 19 skull is $i = 65 \dots 80$, scalp is $i = 81 \dots 88$.

20

Database	F_{PEN}	D_{tum} (fGy-Eq/n.s.)
JENDL-3.3	0.0573 ± 0.0018	1.0089 ± 0.0010
JEFF-3.1	0.1595 ± 0.0049	1.0412 ± 0.0010
ENDF/B-VI.6&VII.0	0.1892 ± 0.0058	1.0499 ± 0.0010

21

22 **Table 3.** Values of F_{PEN} and D_{tum} obtained for the TOPOPT moderator shown fig. 7 ($N = 375$ voxels, $P_{tum} = 4.5$
 23 cm), computed with the JENDL-3.3, JEFF-3.1 or ENDF/B-VI.6&VII.0 databases.

24

25 4.3. Sensitivity to morphological parameters

26

27 The TOPOPT moderators obtained in the previous sections were computed using a simplified
 28 model of the patient's head, presented and discussed section 2. The shape and composition of a
 29 real human head are much more complex, so one can legitimately wonder what impact this
 30 simplification, common to any analytical or even voxelized model, can have on the quality of
 31 treatment. In addition, the morphology of a human head varies considerably from patient to
 32 patient. It is therefore interesting to study how (1) the modeling of the head and (2) the great
 33 morphological variability of patients can impact the design of the moderator and its associated

1 treatment quality. The TOPOPT procedure presented in this study may provide an element of
2 solution to these problems, thanks to its adaptability. In this section, for the time being, we
3 propose to provide an element of response to the problem (2).
4 To answer this, we generated 92 different patients' heads, by independently sampling for each
5 patient its brain radius R_b , its skull radius R_s and its head radius R_h , according to Gaussians of
6 centers $\langle R_b \rangle = 7.05$ cm, $\langle R_s \rangle = 8.21$ cm and $\langle R_h \rangle = 8.71$ cm, and 5.35% standard deviation.
7 These values comply with Ref. [9, 10], which give size distributions of adult heads. However,
8 since a variable distributed according to a Gaussian can take any value between $-\infty$ and $+\infty$, we
9 have prohibited values of R_h less than $0.899 \times \langle R_h \rangle$ (1st percentile) and greater than $1.115 \times \langle R_h \rangle$
10 (99th percentile) [10]. In the absence of data found on the minimum and maximum thicknesses
11 of skull and scalp, R_b and R_s radii are sampled freely, provided that $R_b < R_s < R_h$. These 92
12 generated head configurations all have different radii, and different brain, skull or scalp
13 volumes. For each of them, we have adapted the voxelization shown in fig. 1: 1 voxel for the
14 CTV ($i = 0$), 64 for healthy brain tissue ($i = 1 \dots 64$), 16 for the skull ($i = 65 \dots 80$), 8 for the scalp
15 ($i = 81 \dots 88$), 89 in total. Each patient is positioned at the exit of the TOPOPT BW moderator
16 shown fig. 17. The positions of the centers of the heads are adjusted so that the minimum
17 distance between the surface of the head and the exit of the moderator remains equal to 1 mm,
18 cf. section 2. The volume of the CTV is equal to 20 cm^3 , its depth P_{tum} equal to 4.5 cm.
19 Fig. 22, we plot the distributions of the dose-volume histograms obtained in healthy brain and
20 scalp for the 92 patients, indicating the 1st, 5th, 25th, 50th, 75th, 95th and 99th percentiles. We
21 find that the doses deposited in the brain exceed the peak dose used by Capoulat et al. [4], 11
22 Gy-Eq, only in a small fraction of the brain for all patients. Doses exceed the peak dose used
23 by Torres-Sánchez et al. [3], 12.5 Gy-Eq, in 25 out of 92 patients. However, for 23 of these 25
24 patients, the affected brain volume is negligible, less (or even much less) than 0.2%. For 2 out
25 of 92 patients, who thus stand out exceptionally, the volume of brain exposed to a dose higher
26 than 12.5 Gy-Eq reaches 4.7% for one, 4% for the other. These 2 patients have unusual
27 morphological parameters: (i) for the first, a small head, $R_h = 7.99$ cm (the 2nd smallest in the
28 sample), and thin thicknesses of skull and scalp, resp. 4.1 mm and 0.5 mm; (ii) for the second,
29 an abnormal skull thickness, 1.3 mm, and radiuses of brain, skull and head, 7.60 cm, 7.73 cm
30 and 8.30 cm, all quite far from the average values. The findings are similar for scalp. The doses
31 deposited in the scalp never exceed the peak dose used by Torres-Sánchez et al. [3], 24 Gy-Eq.
32 They remain below 18 Gy-Eq in the bulk of the scalp volume for all patients. These results are
33 important, and rarely presented in the literature. They show that, for a tumor of intermediate
34 depth, here 4.5 cm, reusing a moderator designed for a generic model patient, whose head has
35 the standard proportions, will most often have no major harmful impact on the healthy tissues
36 of a random patient, whatever its morphology of his head. However, for a fraction of patients,
37 of the order of a few percent, side effects are to be feared, either in the brain (somnolence
38 syndrome) or in the scalp.
39

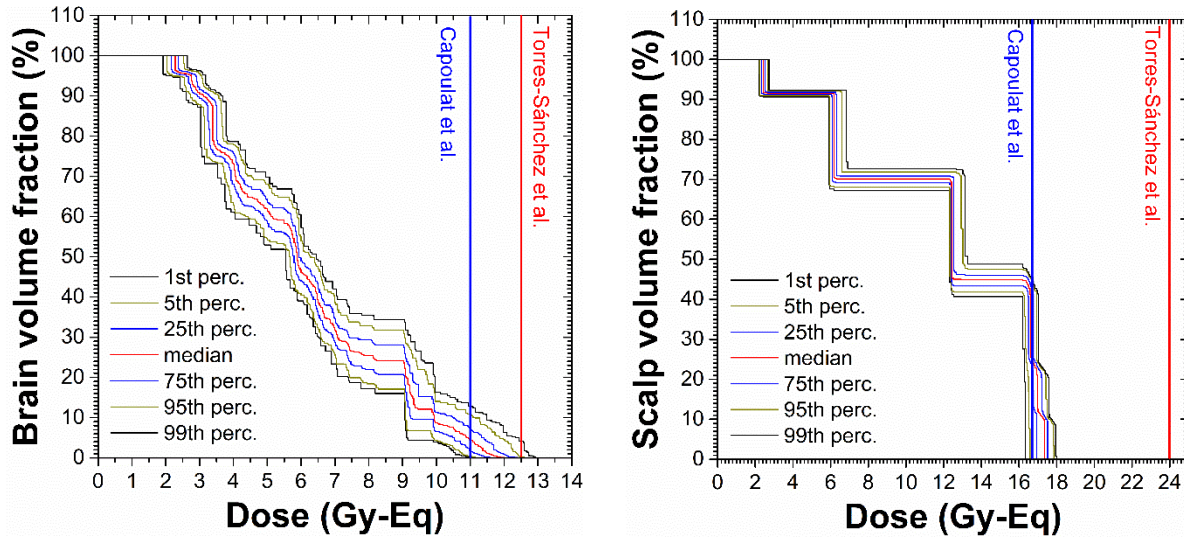


Figure 22. Distributions of the dose-volume histograms in healthy brain (left) and scalp (right) obtained for the 92 patients, using the TOPOPT BW moderator shown in fig. 17 for $P_{tum} = 4.5$ cm and $H = 30$ cm.

5. Conclusion and perspectives

In this study, we applied a topology optimization algorithm developed at the CNRS LPSC to compute the structure of a heavy water neutron moderator for an AB-BNCT unit, for various tumor depths or moderator thicknesses. Calculations performed for deep glioblastomas using a ${}^9\text{Be}(d(1.45 \text{ MeV}), n){}^{10}\text{B}$ source give convincing results. Despite the high energy, ~ 2 MeV in average, of the source neutrons, the TOPOPT moderators manage, in a compact volume, less than 0.04 m^3 , to deliver targeted doses, which reach 30 Gy-Eq in the tumor in a reasonable time while sparing healthy tissues. The local doses deposited in these tissues remain below the recommended limits, in almost the entire head volume, for tumor depths of up to 6 cm at this time. TOPOPT moderators have sophisticated structures, inaccessible in their detail to intuition or to previous parametric methods. They contain unexpected components, e.g. neutron guides mimicking multi-field treatments, the efficiency of which could inspire other designs. The progress made in manufacturing processes, 3D printing for example, now makes the machining of such components accessible to a small structure, laboratory or hospital unit. The versatility of the TOPOPT approach makes it possible to automatically fit the design of the moderator to the configuration of the BNCT treatment unit considered and to the biological parameters of the patients. However, despite these first promising results, progress remains to be made, on the computation time, on the head model, or on the maximum tumor depth that can be properly reached. As such, we plan to study, as part of a submitted project, materials other than heavy water that could be of therapeutic and economic interest. Heavy water is indeed an efficient material for slowing down neutrons in a compact volume without capturing them, but it remains expensive and is a special nuclear material.

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