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Assessment of absorbed dose distribution for the *in vitro* setup at the VITA facility

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Received June 10, 2025
Revised October 13, 2025
Accepted October 13, 2025

In this study, the spatial distribution of an absorbed dose and its components were assessed for the in vitro setup of the VITA accelerator-based neutron source, operating at the Budker Institute of Nuclear Physics, Siberian Branch of the Russian Academy of Sciences. Namely, the total and boron doses were obtained for cryovials placed at different distances from the neutron field axis. The cryovials contained a cell suspension doped with the realistic concentration of ^{10}B isotope. Additionally, the dependence of the quantities on the neutron moderator chemical composition and thickness was investigated.

Keywords: boron neutron capture therapy, absorbed dose, *in vitro* setup, Monte Carlo simulation.

DOI: 10.61011/TPL.2026.02.63042.20404

Boron neutron capture therapy (BNCT) [1,2] is a promising method for treating a number of malignant tumors that are resistant to traditional methods. BNCT is a binary form of radiotherapy based on selective destruction of tumor cells by heavy charged particles with high linear energy transfer that are produced in the interaction of thermal neutrons and a therapeutic drug containing ^{10}B isotope atoms. The absorption of a thermal neutron by a ^{10}B nucleus leads to prompt nuclear reaction $^{10}\mathrm{B}(n,\alpha)^{7}\mathrm{Li}$ with a cross section of 3837 b. This reaction proceeds with the release of 2.79 MeV of energy. In 6.1 % of all cases, it is distributed between a lithium nucleus (1.01 MeV) and an α particle (1.78 MeV); in the remaining 93.9 % of cases, the lithium nucleus escapes in an excited state and emits a γ- quantum with an energy of 0.48 MeV. Typical ranges of lithium ions and α particles in biological tissue do not exceed 12 μm, which is comparable to the size of a single cell. Thus, the ^{10}B isotope accumulated in tumor cells becomes an effective means of tumor destruction in a thermal neutron field.

Two main types of neutron sources are used to implement BNCT: nuclear reactors and charged particle accelerators with neutron-generating targets. Accelerator neutron sources are regarded as the most promising technical solution for BNCT, since they are safer in operation and more compact than nuclear reactors [1]. The VITA accelerator neutron source has been constructed and is operating at the Budker Institute of Nuclear Physics in Novosibirsk. It consists of a tandem electrostatic charged particle accelerator of an original design, a lithium target for generating neutrons in the $^{7}\mathrm{Li}(p,n)^{7}\mathrm{Be}$ reaction, and various neutron beam formation systems. This source provides an intense stationary monochromatic beam of protons or deuterons with an energy ranging from 0.1 to 2.3 MeV and a current of 0.5–10 mA and allows one to generate a flux of epithermal neutrons with an intensity up to $2 \cdot 10^{12}\,\mathrm{s}^{-1}$ [3].

The effectiveness of BNCT depends on the interaction of boron-containing drugs with biological tissues at the cellular level [1,4]. *In vitro* studies allow one to examine the selectivity of accumulation of boron-containing drugs in tumor cells, determine optimum concentrations of boron-containing compounds, and investigate the influence of various irradiation parameters on the therapeutic effect. One important factor influencing the reproducibility and reliability of *in vitro* studies is the accuracy of determination of the physical absorbed dose in an irradiated volume [5]. In BNCT, the primary contribution to the total absorbed dose is made by the absorbed boron dose associated with the energy release in nuclear reaction $^{10}\mathrm{B}(n,\alpha)^{7}\mathrm{Li}$. Direct determination of the absorbed boron dose is a complex experimental problem, which may be solved using prompt γ spectroscopy [3]. Numerical modeling of transfer of neutrons and their interaction with a cell suspension and a boron-containing drug may serve as an indirect method for determining the absorbed dose. This approach allows one to obtain reliable data on the distribution of absorbed dose components without direct measurements, simplifying significantly the preparation and performance of experiments.

In the present study, we report the results of calculation of the spatial distribution of absorbed doses for the *in vitro* VITA setup and determine the contribution of the absorbed boron dose to the total dose absorbed within irradiated

objects. A model of the neutron-generating system of the VITA facility in a configuration designed for *in vitro* studies was developed in Geant4 (version 11.2.1) in order to perform computational studies. The main parts of the system model used (including the high-energy proton beam transport path, the target unit, and the moderator) were described in detail in our study [6]. The obtained calculated spatial and energy distributions of the neutron flux intensity provided an opportunity to verify the model by comparing the simulation results with the experimental data [6]. In the present work, the geometry of the model was supplemented with an *in vitro* setup, which is used for irradiating cryovials with a cell suspension and a boron-containing drug, and a new type of moderator.

Figure 1 presents the geometry of the modeled system, which uses moderators with different materials and geometric characteristics. Two types of moderators made of organic glass (polymethyl methacrylate, PMMA) and polyethylene with volumetric inclusions of bismuth (hereinafter referred to as Poly-Biz [7]) were examined. These moderators had a diameter of 200 and 160 mm, respectively. The developed model of the *in vitro* setup corresponds to its actual geometry and includes a horizontally located phantom made of 50-mm-thick organic glass with through holes, where cylindrical cryovials with a height of 50 mm and an external diameter of 16 mm are held. These vials are positioned at two radii relative to the center of the phantom (25 and 50 mm) and are fitted with caps 10 mm in height and 18 mm in diameter. Both the cryovials and their caps are made of polypropylene and have the same wall thickness of 1 mm. Each cryovial contained 1.5 ml of an evenly distributed mixture of water, which simulates a nutrient medium, cells, and ^{10}B isotope atoms with a given concentration. The total volume of cells was 0.4 % of the total volume of this suspension ($\sim 10^6$ cells). The distance between the surfaces of cryovial caps and the moderator in the experiment and models was 20 mm.

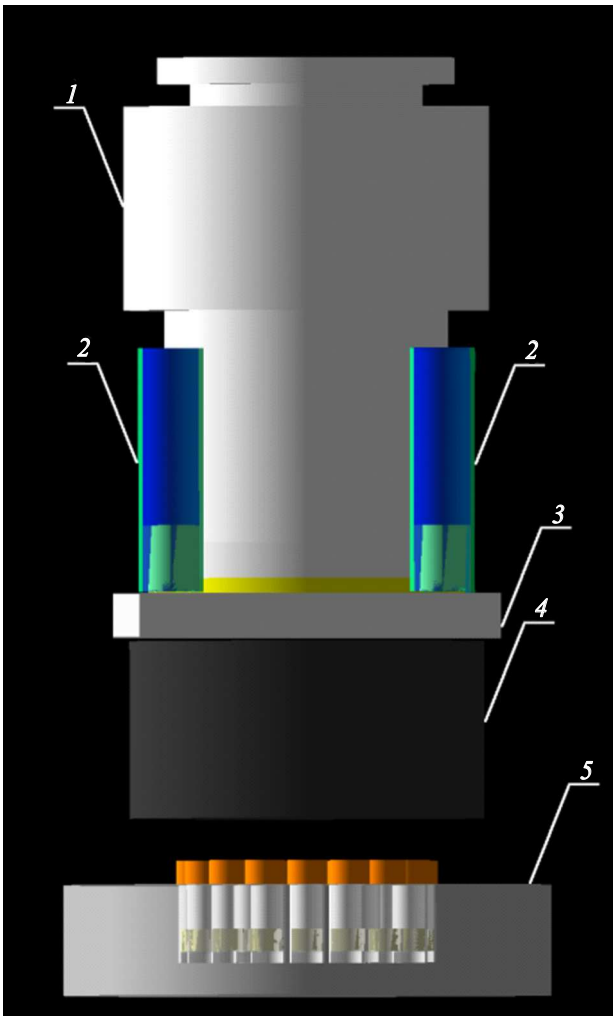


Figure 1. Geometry of the model of the neutron-generating system of the VITA facility in Geant4. *1* — High-energy proton beam transport path, *2* — polyvinyl chloride pipes of the target unit cooling system, *3* — target unit, *4* — PMMA or Poly-Biz moderator, and *5* — phantom with cryovials containing a suspension with cell cultures and the ^{10}B isotope.

A neutron field was formed in modeling by irradiating a lithium target with a proton beam with an energy of 2.05 MeV and a diameter of 80 mm. Three thickness values were considered for each of the two moderator types: 62, 72, and 82 mm for PMMA and 70, 80, and 90 mm for Poly-Biz. The average energy release in one cryovial positioned at the inner or outer radius of the setup was calculated with ^{10}B isotope atoms lacking or present (100 ppm) in the suspension volume. Average energy release $\langle E_{\mathrm{BC}}\rangle$ due to reaction $^{10}\mathrm{B}(n,\alpha)^7\mathrm{Li}$ was calculated as $\langle E_{\mathrm{BC}}\rangle = \langle E_{\mathrm{B}}\rangle$ - $\langle E_{\mathrm{WB}}\rangle$, where $\langle E_{\mathrm{B}}\rangle$ is the energy release in a cryovial containing 100 ppm ^{10}B and $\langle E_{\mathrm{WB}}\rangle$ is the energy release in a cryovial without ^{10}B. The energy release values were then converted into absorbed doses per cryovial normalized to the integral accelerator current.

Figure 2 shows the values of average absorbed total and boron doses per one cryovial positioned at the inner or outer radius of the setup. These values were obtained by modeling for two types of moderators (PMMA, Poly-Biz) of different thicknesses and are normalized to an integral proton beam current of 1 mA · h. It should be noted that the routine practice in experimental *in vitro* and *in vivo* studies and therapy of tumors of domestic animals at the VITA facility is to use a PMMA moderator with a thickness of 72 mm or a Poly-Biz moderator with a thickness of 80 mm. For convenience, we refer to these values as „reference“ moderator thicknesses. It should also be emphasized that all irradiated cryovials were positioned at the inner radius (regardless of the type of moderator used) in earlier *in vitro* experiments carried out at the VITA accelerator neutron source [8,9]. The percentage ratios of the absorbed boron dose to the total dose corresponding to various configurations of moderators and radial positions of cryovials at the *in vitro* setup are listed in the table.

Analyzing the obtained results, one may conclude that the reference configuration of the Poly-Biz moderator provides a better ratio of the absorbed boron dose to the total

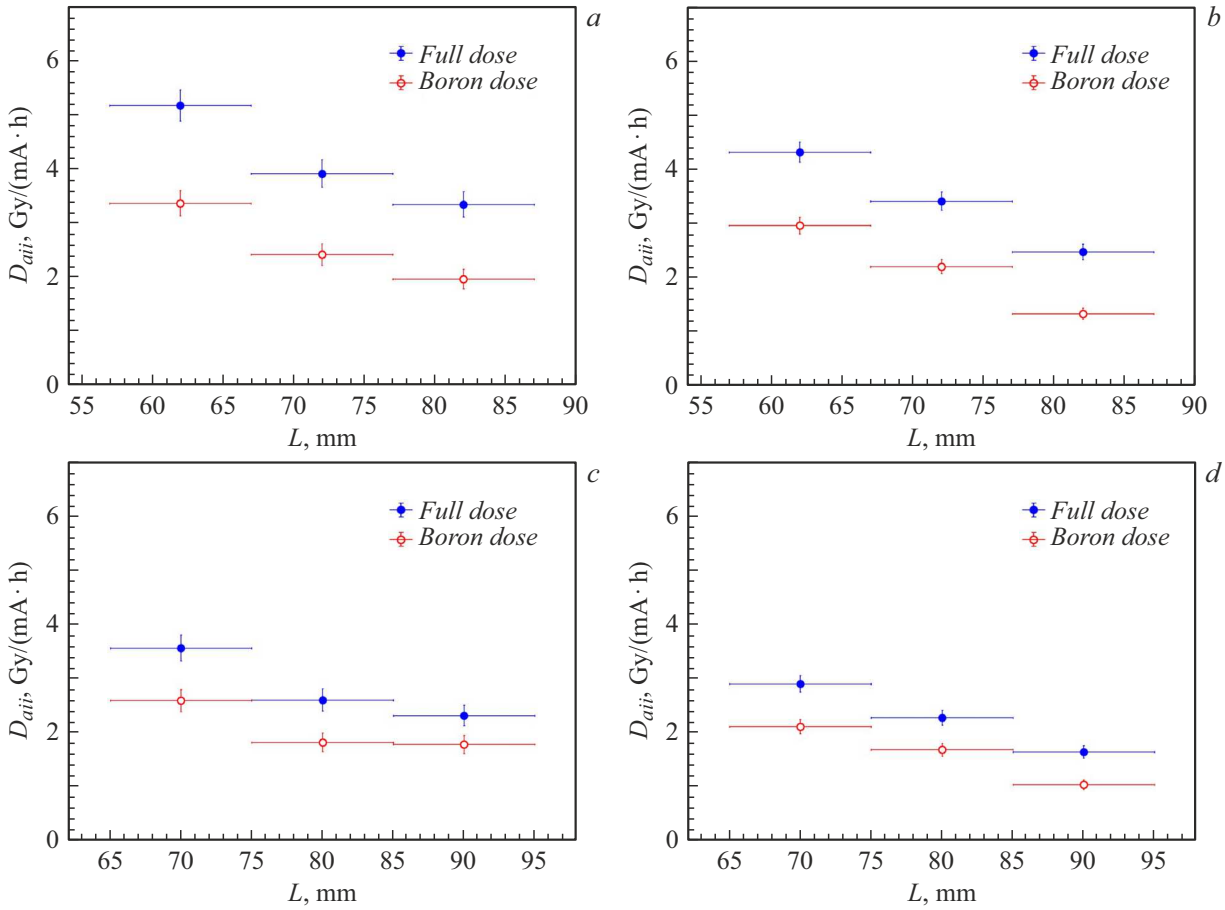


Figure 2. Dependences of the average absorbed total (filled circles) and boron (open circles) doses per one cryovial located on the inner or outer radii of the setup, which are normalized to an integral proton beam current of 1 mA · h, on the neutron moderator thickness. *a* — PMMA moderator, the vial position is at the inner radius; *b* — PMMA moderator, outer radius; *c* — Poly-Biz moderator, inner radius; *d* — Poly-Biz moderator, outer radius. Statistical errors are indicated.

Percentage ratios of the average absorbed boron dose to the total dose corresponding to different moderator configurations and cryovial positions (the statistical error for all percentage ratios is 1 %)

Moderator material	Cryovial positioning radius, mm	Neutron moderator thickness		
		−10 mm	Reference	+10 mm
PMMA	25 (inner)	65	62	59
	50 (outer)	68	64	54
Poly-Biz	25 (inner)	73	70	77
	50 (outer)	73	74	63

dose than the reference PMMA configuration. However, compared to Poly-Biz, the PMMA moderator provides an opportunity to reach total absorbed dose levels in a cryovial that are at least 30 % higher. In terms of uniformity of the distribution of the absorbed dose in cryovials at different radii, the reference configuration is the optimum one for both types of moderators. With an increase in thickness of the PMMA moderator, the absolute values of absorbed doses at the outer radius of the setup and the percentage ratio of the absorbed boron dose to the total dose decrease significantly. In the case of Poly-Biz, the percentage ratio of the absorbed boron dose to the total dose at the inner radius of the setup increases with increasing moderator thickness. However, the uneven distribution of absorbed doses at different cryovial positioning radii limits the applicability of both types of moderators in a configuration with increased thickness. When the thickness of both types of moderators is reduced, the absolute values of the absorbed total and boron doses increase significantly, which opens up the possibility of reducing the accelerator operating time in

in vitro irradiation studies. However, the distribution of the absorbed dose at different cryovial positioning radii does also become less uniform in this case, which limits the potential for simultaneous irradiation of cell cultures at both radii of the setup.

Thus, the first results of calculations of the spatial distribution of absorbed doses for the *in vitro* VITA facility setup, which were performed using Monte Carlo simulation in Geant4, were presented. It was found that the optimum configuration of the moderator should be determined based on the number of cryovials that need to be irradiated in an *in vitro* experiment. Specifically, if less than eight cryovials are to be processed, the optimum option is to use a moderator of a smaller thickness and irradiate cell cultures only at the inner radius of the *in vitro* setup. If the experiment requires a sample several times larger in size (9–24 cryovials), the optimum option is irradiation with a reference moderator thickness and positioning of cryovials with a cell suspension at both radii of the setup. The results of calculations and the developed detailed model of the *in vitro* setup should help optimize the procedure of planning of *in vitro* experiments at the VITA accelerator neutron source.

Funding

This study was supported by the Russian Science Foundation, grant No 24-62-00018 (https://rscf.ru/project/24-62-00018/).

Conflict of interest

The authors declare that they have no conflict of interest.

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Translated by D.Safin